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Stereochemische Untersuchungen, 77[1]. – Gesättigte Heterocyclen, 64[1]

# Synthese von gesättigten Methylen-überbrückten 1,3-Benzoxazinen

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Aus dem Cycloaddukt **4** von Norbornen (**1**) und Trichloracetylisocyanat wurde der Aminoalkohol **3** hergestellt und daraus das tricyclische 1,3-Oxazin-2-on **7**, bzw. 1,3-Oxazin-2-thion **8** und die 1,3-Oxazin-Derivate **2a – d** synthetisiert. Die mit Norbornan anellierten *exo-exo*- (**10** und **12**) bzw. *endo-endo*-1,3-Oxazin-4-one (**11** und **13**) wurden aus den 3-Hydroxy-2-carboxamiden **5** und **9** erhalten. Die Struktur der tricyclischen kondensierten Systeme mit starrem Gerüst wurde durch $^1$H- und $^{13}$C-NMR-Spektroskopie bewiesen.

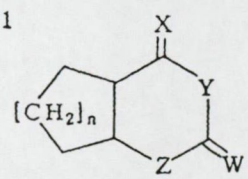
**Stereochemical Studies, 77[1]. – Saturated Heterocycles, 64[1]**

**Synthesis of Saturated Methylene-Bridged 1,3-Benzoxazines**

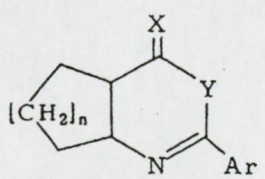
The aminomethylbicyclanol **3**, obtained from the cycloadduct **4** of norbornene (**1**) and trichloroacetyl isocyanate, furnished the 1,3-oxazin-2-one **7**, 1,3-oxazine-2-thione **8** and 1,3-oxazines **2a – d**. The *exo-exo*- (**10**, **12**) and *endo-endo*-1,3-oxazin-4-ones (**11**, **13**) were prepared from the 3-hydroxy-2-carboxamides **5** and **9**. Structure of these rigid tricyclic systems were proved by $^1$H and $^{13}$C NMR spectroscopy.

In früheren Arbeiten haben wir kondensierte bicyclische gesättigte 1,3-Oxazine[2,3], 1,3-Oxazin-2-one[4-6], 1,3-Oxazin-4-one[7,8] und verwandte kondensierte Pyrimidinone[9,10] dargestellt (Schema 1). Diese Substanzklassen dienten als Modelle für systematische stereochemische und pharmakologische Untersuchungen[8,9]. Im Falle der einheitlichen stereoisomeren Homologen untersuchten wir einerseits den Einfluß der zum Heteroring *cis*- und *trans*-anellierten Carbocyclen auf die Konformation des Heterocyclus und andererseits den Einfluß des Heterocyclus auf die Konformation des Carboringes. Vergleichende Konformationsuntersuchungen wurden mittels Röntgenstrukturanalyse[5,11-18] bzw. $^1$H- und $^{13}$C-NMR-Spektroskopie[2-6] durchgeführt.

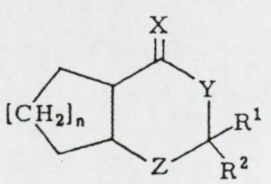
Schema 1




n = 1, 2, 3, 4
*cis, trans*




X, W = O, S, $H_2$
Y = O, NH, NR
Z = O, S, NH, NR




$R^1$, $R^2$, = Alkyl
$R^1$ = H; $R^2$ = Alkyl
$R^1$,= H; $R^2$ = Ar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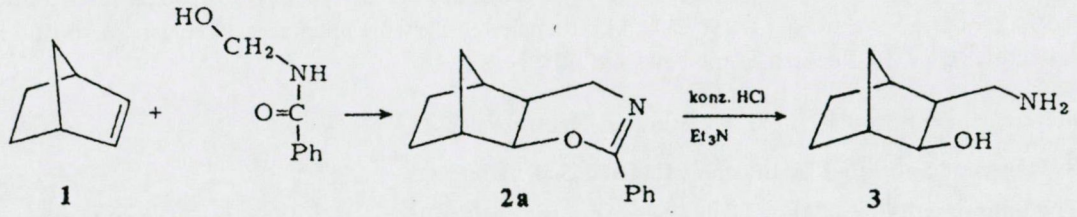
In Fortführung dieser Arbeiten synthetisierten wir Tetra- und Hexahydro-3,1-benzoxazine[19,20], die als tricyclische Homologe der von uns früher dargestellten *cis*-Trimethylen-1,3-oxazine[7] mit Ethylen- bzw. Vinylenbrücken im Cyclopentanring betrachtet werden können.

In der vorliegenden Arbeit berichten wir über Isomere mit vertauschten Sauerstoff- und Stickstoff-Positionen. Der Sauerstoff ist jetzt an den Carbobicyclus gebunden. Diese Stellungsisomeren wurden einerseits für pharmakologische Untersuchungen, andererseits als Modelle für $^1$H-NMR-Studien dargestellt, um sie mit den früher hergestellten Substanzen[20] spektroskopisch zu vergleichen.

## Synthese

Wir versuchten zunächst, *cis-exo*-3-(Aminomethyl)bicyclo[2.2.1]heptan-2-ol (**3**) durch Säurehydrolyse des Adduktes **2a** von Norbornen (**1**) und *N*-(Hydroxymethyl)-benzamid[21-23] darzustellen (Schema 2). Da die Ausbeute zu niedrig war, verwendeten wir dann Trichloracetylisocyanat als Additionspartner[24], wobei der Aminoalkohol **3** mit günstiger Ausbeute gewonnen wurde. Das dabei auftretende Zwischenprodukt **5** ist ein geeigneter Reaktionspartner zur Darstellung der tricyclischen 1,3-Oxazin-4-one **10** und **12**.

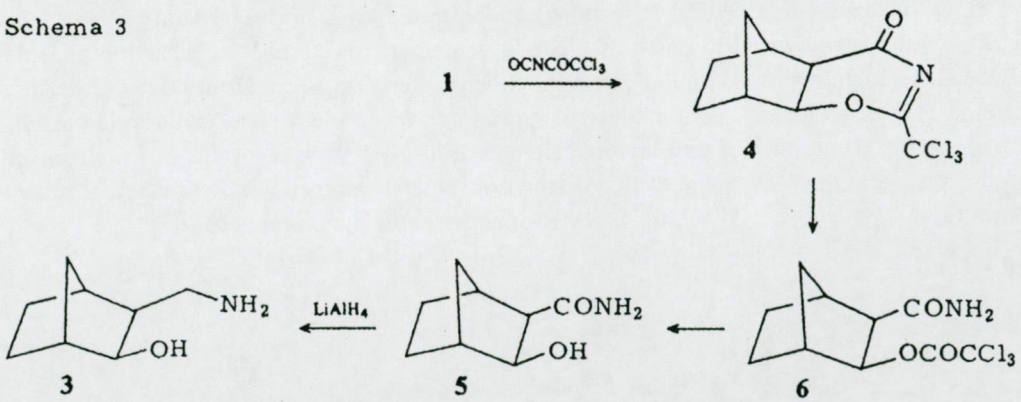
Schema 2




**1** **2a** **3**

Die Hydrolyse des aus **1** mit Trichloracetylisocyanat erhaltenen *r*-4a,*c*-5,6,7,*c*-8,*c*-8a-Hexahydro-2-(trichlormethyl)-5,8-methano-4*H*-1,3-benzoxazin-4-ons[20] (**4**) ergibt 3-(Trichloracetoxy)bicyclo[2.2.1]heptan-2-carboxamid (**6**) (Schema 3). Die basische Entacylierung von **6** führt zu **5**, das bei Reduktion mit $LiAlH_4$ den Aminoalkohol **3** liefert (Gesamtausbeute, auf Norbornen bezogen, 45%).

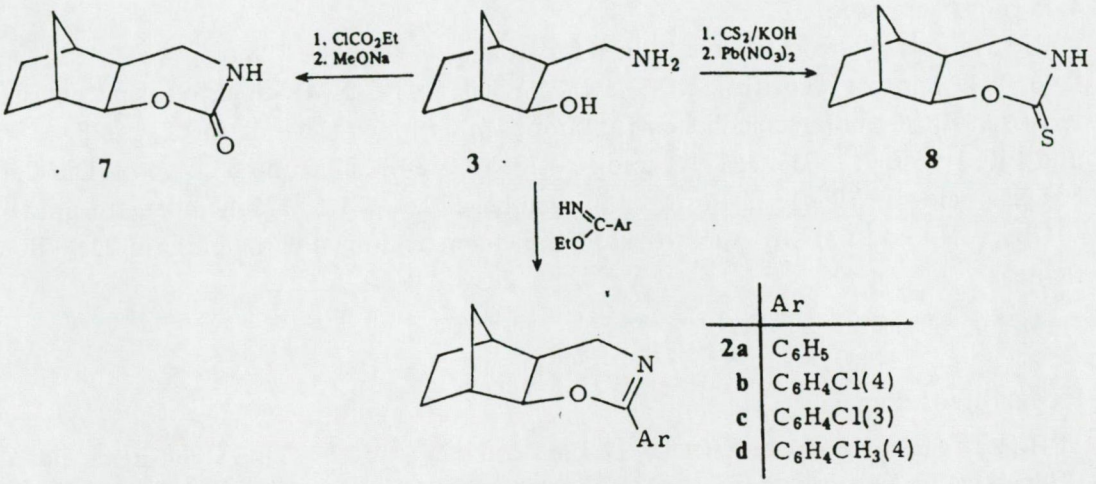
Schema 3




Aus dem Aminoalkohol **3** wird mit Chlorameisensäure-ethylester das Carbamat hergestellt, das mit Natriummethylat zu *r*-4a,*c*-5,6,7,*c*-8,*c*-8a-Hexahydro-5,8-methano-

4*H*-1,3-benzoxazin-2(3*H*)-on (**7**) cyclisiert wird (Schema 4). Das entsprechende Thion **8** wird durch Ringschluß des aus **3** mit $CS_2$ erhaltenen Dithiocarbamats mit $Pb(NO_3)_2$ gewonnen. Aus **3** werden mit substituierten aromatischen Imidsäureestern die 2-Aryl-*r*-4a,*c*-5,6,7,*c*-8,*c*-8a-hexahydro-5,8-methano-4*H*-1,3-benzoxazine **2a–d** dargestellt. Das so gewonnene **2a** stimmte mit dem durch Cycloaddition erhaltenen Produkt[21] überein.

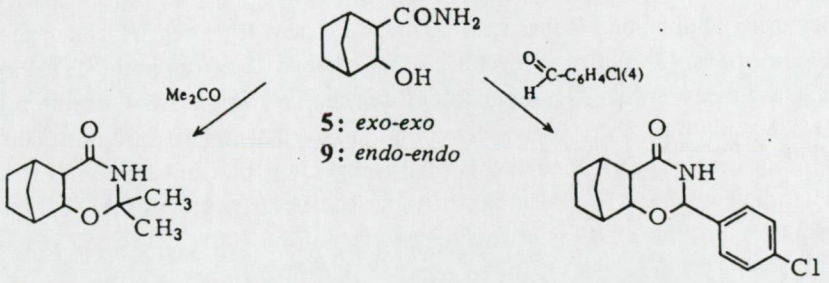
Schema 4




| | Ar |
|---|---|
| **2a** | $C_6H_5$ |
| **b** | $C_6H_4Cl(4)$ |
| **c** | $C_6H_4Cl(3)$ |
| **d** | $C_6H_4CH_3(4)$ |

**5** wird auf bekannte Weise zum 3-Oxobicyclo[2.2.1]heptan-*endo*-2-carboxamid oxidiert und anschließend mit $NaBH_4$ zum *endo*-3-Hydroxybicyclo[2.2.1]heptan-*endo*-2-carboxamid-Epimeren **9** reduziert[24]. **5** und **9** ergeben mit Aceton die tricyclischen *cis-exo*- (**10**) und *cis-endo*-1,3-Oxazin-4-one (**11**). Mit 4-Chlorbenzaldehyd werden das *cis-exo*- (**12**) und das *cis-endo*-(**13**)-Isomerenpaar gewonnen (Schema 5).

Schema 5




**5**: *exo-exo*
**9**: *endo-endo*

**10**: *cis-exo*
**11**: *cis-endo*

**12**: *cis-exo*
**13**: *cis-endo*

## Spektroskopische Untersuchungen

Im IR-Spektrum sind die Carbonylbanden der Urethangruppe von **7** bei 1700 $cm^{-1}$, die Amid-I-Banden der Verbindungen **10–13** bei 1650–1645 $cm^{-1}$ zu finden. Die νNH-Frequenzen dieser Gruppen liegen im Intervall von 3450–2750 $cm^{-1}$. Verbindung **8** besitzt scharfe νNH-Banden um 3170 $cm^{-1}$. Im Falle von **2a–d** sind die νC=N-Frequenzen bei 1645–1640 $cm^{-1}$ zu beobachten.

Die Dublettaufspaltung des 6-H-$^1$H-NMR-Signals ($J$ = 7 Hz) beweist die Di-*exo*-Anellierung der Verbindungen **2a–d**, **7**, **8**, **10** und **12**. Da die vicinale Proton-Proton-Kopplung der Wasserstoffatome 6 und 7 einem Torsionswinkel von ≈ 90° entsprechend klein ist, wird das 6-H-Signal allein durch die 5-H/6-H-Wechselwirkung aufgespalten. Das 6-H-Signal der Di-*endo*-Verbindungen **11** und **13** ist dagegen ein Doppeldublett mit Kopplungskonstanten von 9.5 und 4.5 Hz. In Nachbarschaft zum Sauerstoff hat 6-H in **2**, **7**, **8**, **10** und **12** eine große chemische Verschiebung: 3.9–4.2 ppm. Im Falle der Di-*endo*-Verbindungen **11** und **13** haben wir noch höhere Werte (4.40 und 4.45 ppm) gemessen.

Die Methylsignale der Verbindungen **2d**, **10** und **11** sind bei 2.28 bzw. 1.42, 1.50 und 1.46, 1.49 ppm zu identifizieren. Die C-2-Signale in $^{13}$C-NMR-Spektren sind charakteristisch für die unterschiedlichen funktionellen Gruppen (**2a–d**: 160.1, 158.8, 158.3 und 160.0 ppm; **7**: 157.3. **8**: 191.8 und **10–13**: 77.0, 84.3, 82.5 und 83.5 ppm). Die Carbonylsignale von **10–13** in Position 4 liegen bei 170.9, 171.5, 171.1 und 171.5 ppm.

Über $^1$H- und $^{13}$C-NMR-spektroskopische Untersuchungen wird später im Detail berichtet.

## Experimenteller Teil

$^1$H-NMR-Spektren: 250 MHz, $CDCl_3$-Lösung, Bruker WM-250-FT, TMS als innerer Standard. IR-Spektren: in KBr, Bruker IFS-113 V-FT Spektrometer. DC: Kieselgel, $CHCl_3$/MeOH (9 + 1).

*Säurehydrolyse des r-4a,c-5,6,7,c-8,c-8a-Hexahydro-2-phenyl-5,8-methano-4H-1,3-benzoxazins* (**2a**): 2.27 g (0.01 mol) **2a**, 50 ml konz. Salzsäure und 50 ml Ethanol werden 10 h unter Rückfluß erhitzt. Das Gemisch wird eingeengt und die Benzoesäure mit Ether entfernt. Der Rückstand wird in 15 ml Aceton gelöst und die Base durch 1.0 g Triethylamin freigesetzt. Nach Absaugen des Niederschlages wird die Mutterlauge eingedampft. Der ölige Rückstand wird fraktioniert (Sdp. 100–103 °C/530 Pa) und **3** als farbloses Öl gewonnen. Ausb. 0.42 g (30%).

*exo-3-(Aminomethyl)bicyclo[2.2.1]heptan-exo-2-ol* (**3**): 12.9 g (0.34 mol) $LiAlH_4$ werden in kleinen Teilen unter Kühlen und Rühren zu 700 ml trockenem Tetrahydrofuran gegeben und dann 21.0 g (0.135 mol) *exo*-3-Hydroxybicyclo[2.2.1]heptan-*exo*-2-carboxamid[24] (**5**) portionsweise hinzugefügt. Das Gemisch wird 20 h unter Rückfluß gehalten, wobei die Reaktion mittels DC verfolgt wird. Nach Abkühlen auf 0 °C werden 30 ml Wasser zugetropft und das Gemisch wird bis zur Ausbleichung gerührt. Der Niederschlag wird abgesaugt und mit heißem Tetrahydrofuran, dann mit Ethanol gewaschen. Nach Eindampfen der Mutterlauge und der Auszüge wird der ölige Rückstand fraktioniert und **3** als farbloses Öl gewonnen. Sdp. 100–103 °C/530 Pa. Ausb. 15.4 g (81%).

$C_8H_{15}NO$ (141.2) Ber. C 68.04 H 10.71 N 9.92 Gef. C 67.84 H 11.02 N 9.67

*r-4a,c-5,6,7,c-8,c-8a-Hexahydro-5,8-methano-4H-1,3-benzoxazin-2(3H)-on* (**7**): Zur Lösung von 0.70 g (5 mmol) **3** in 5 ml Wasser werden 0.42 g (5 mmol) $NaHCO_3$ gegeben und 0.54 g (5 mmol) Chlorameisensäure-ethylester hinzugetropft. Nach 30 min Erwärmen auf 70 °C wird das Gemisch mit Ether ausgeschüttelt. Der Rückstand des Etherextraktes wird mit 25 mg Natriummethylat 20 min auf 120 °C erwärmt und aus dem Gemisch **7** mit Essigester extrahiert. Das nach Eindampfen des Auszuges erhaltene Produkt wird aus Essigester/Petrolether kristallisiert. Schmp. 137–139 °C. Ausb. 0.5 g (60%).

$C_9H_{13}NO_2$ (167.2) Ber. C 64.55 H 7.84 N 8.38 Gef. C 64.32 H 7.75 N 8.52

*r-4a,c-5,6,7,c-8,c-8a-Hexahydro-5,8-methano-4H-1,3-benzoxazin-2(3H)-thion* (**8**): 2.4 g (0.017 mol) **3** und die Lösung von 1.1 g KOH in 10 ml Wasser werden auf 0°C abgekühlt und dann mit 8 ml Dioxan und 1.3 g (0.017 mol) $CS_2$ 5 min gerührt. Nach Zugabe von 10 ml 5.5proz. wäßr. KOH-Lösung werden 5.5 g $Pb(NO_3)_2$ in 30 ml Wasser zugegeben und das Gemisch 10 min bei 50°C gerührt. Das PbS wird warm abfiltriert und mit heißem Wasser gewaschen. Das Filtrat wird eingedampft und der Rückstand aus Ethanol kristallisiert. Schmp. 168–170°C. Ausb. 2.49 g (80%).

$C_9H_{13}NOS$ (183.3) Ber. C 58.98 H 7.15 N 7.64 Gef. C 58.75 H 7.29 N 7.55

*2-Aryl-r-4a,c-5,6,7,c-8,c-8a-hexahydro-5,8-methano-4H-1,3-benzoxazine* (**2a–d**) (*Allgemeine Vorschrift*): 1.4 g (0.01 mol) **3**, 0.01 mol Imidsäureester (**2a**: 1.5 g Ethyl-benzimidat; **2b**: 1.8 g Ethyl-4-chlorbenzimidat; **2c**: 1.8 g Ethyl-3-chlorbenzimidat; **2d**: 1.6 g Ethyl-4-methylbenzimidat) und 20 ml Ethanol werden in Gegenwart von katalytischen Mengen HCl unter Rückfluß erhitzt. Die Reaktion wird mit DC verfolgt. Das Gemisch wird eingedampft und der Rückstand aus Essigester/Petrolether kristallisiert. Farblose Kristalle (**2a–c**), bzw. Öl (**2d**). Ausb. 50–55%.

**2a**: Ausb. 1.16 g (51%); Schmp. 47–49°C (Lit.[21] 46–47°C).

$C_{15}H_{17}NO$ (227.3) Ber. C 79.26 H 7.54 N 6.16 Gef. C 78.96 H 7.68 N 5.98

**2b**: Ausb. 1.41 g (54%); Schmp. 86–88°C.

$C_{15}H_{16}ClNO$ (261.8) Ber. C 68.83 H 6.16 N 5.35 Gef. C 68.58 H 6.33 N 5.57

**2c**: Ausb. 1.31 g (50%); Schmp. 75–76°C.

$C_{15}H_{16}ClNO$ (261.8) Ber. C 68.83 H 6.16 N 5.35 Gef. C 68.65 H 6.40 N 5.22

**2d**: Ausb. 1.33 g (55%); Sdp. 140–142°C/530 Pa.

$C_{16}H_{19}NO$ (241.3) Ber. C 79.63 H 7.94 N 5.80 Gef. C 79.42 H 7.67 N 5.60

*r-4a,c-5,6,7,c-8,c-8a-Hexahydro-2,2-dimethyl-5,8-methano-2H-1,3-benzoxazin-4(3H)-on* (**10**) *und r-4a,t-5,6,7,t-8,c-8a-Hexahydro-2,2-dimethyl-5,8-methano-2H-1,3-benzoxazin-4(3H)-on* (**11**): 1.55 g (0.01 mol) **5**[24] oder **9**[24] werden in 10 ml 1% HCl enthaltendem Aceton 1 h bei Raumtemp. gehalten. Das Lösungsmittel wird durch Destillation entfernt, der Rückstand mit 5 ml Wasser und 10 ml $CHCl_3$ versetzt und die Lösung mit $NaHCO_3$ neutralisiert. Die $CHCl_3$-Phase wird mit Wasser gewaschen, mit $Na_2SO_4$ getrocknet und eingedampft. Nach Kristallisation aus Benzol/Hexan werden farblose Kristalle erhalten.

**10**: Ausb. 1.44 g (74%); Schmp. 202–203°C.

$C_{11}H_{17}NO_2$ (195.3) Ber. C 67.66 H 8.77 N 7.17 Gef. C 67.83 H 8.98 N 7.00

**11**: Ausb. 1.56 g (80%); Schmp. 173–174°C.

$C_{11}H_{17}NO_2$ (195.3) Ber. C 67.66 H 8.77 N 7.17 Gef. C 67.46 H 8.92 N 7.30

*2-(4-Chlorphenyl)-r-4a,c-5,6,7,c-8,c-8a-hexahydro-5,8-methano-2H-1,3-benzoxazin-4(3H)-on* (**12**) *und 2-(4-Chlorphenyl)-r-4a,t-5,6,7,t-8,c-8a-hexahydro-5,8-methano-2H-1,3-benzoxazin-4(3H)-on* (**13**): 1.55 g (0.01 mol) **5** oder **9**, 1.4 g (0.01 mol) 4-Chlorbenzaldehyd und 10 ml Ethanol werden in Gegenwart von katalytischen Mengen HCl unter Rückfluß erhitzt. Die Reaktion wird mit DC verfolgt. Das Gemisch wird eingedampft und nach Kristallisation des Rückstandes aus Benzol/Ethanol werden farblose Kristalle gewonnen.

**12**: Ausb. 2.06 g (74%); Schmp. 215–217°C.

$C_{15}H_{16}ClNO_2$ (277.8) Ber. C 64.87 H 5.81 N 5.04 Gef. C 64.82 H 5.72 N 4.95

**13**: Ausb. 1.94 g (70%); Schmp. 215–216°C.

$C_{15}H_{16}ClNO_2$ (277.8) Ber. C 64.87 H 5.81 N 5.04 Gef. C 64.94 H 5.70 N 5.13

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[380/83]

# Stereochemical Studies. Part 89. Saturated Heterocycles. Part 84.[1] Preparation and Nuclear Magnetic Resonance Study of Norbornane–Norbornene-fused 2-Phenylimino-1,3-oxazines and -thiazines

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*diexo*- and *diendo*-3-hydroxymethylbicyclo[2.2.1]hept-2-yl- and hept-5-en-2-yl-amines (1)—(4) and their *N*-methyl and *N*-benzyl derivatives with phenyl isothiocyanate furnished *via* thioureas (5)—(8) the condensed skeleton tricyclic 2-phenylimino-1,3-thiazines (9)—(12) and 1,3-oxazine-2-thiones (13) and (14) as by-products in acidic medium. By base-catalysed cyclization of the isothiuronium salts of (5)—(8), the 2-phenylimino-1,3-oxazines (15)—(18) were obtained. The complete series of structural and annelation isomers of the norbornanes–norbornenes and oxazines–thiazines permitted a systematic $^1H$ and $^{13}C$ n.m.r. spectroscopic study of the correlation between the spectral parameters and the structural features in this family of compounds.

In the course of our research on fused saturated 1,3-oxazine derivatives,[2-6] numerous 1,3-oxazine analogues containing a methylene-bridged cyclohexane ring have recently been synthesized by the ring closure of stereohomogeneous 1,3-aminoalcohols obtained in the reduction of the corresponding norbornane and norbornene 1,2-amino acids.[7,8] These compounds were converted into linearly and angularly fused azetidinones by cycloaddition.[9,10] A systematic spectroscopic study of these compounds provided confirmatory evidence of the stereochemistry of the annelation of the alicyclic and heterocyclic rings, and the *cis*- or *trans*-annelation of the oxazine and azetidinone rings, the steric position of the substituents (the configurations of the substituted skeletal carbon atoms), and the preferred conformations.[9-13]

In this paper we report the synthesis and a systematic spectroscopic study of the 2-arylimino-1,3-oxazines and -thiazines obtained from the stereoisomeric norbornene or norbornane 1,3-aminoalcohols.

## Results and Discussion

3-*endo*-Hydroxymethylbicyclo[2.2.1]hept-5-en-2-*endo*-ylamine (1a) was obtained by LAH reduction of the 3-*endo*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid.[7a] The amino acid obtained by catalytic hydrogenation and hydrolysis of the ethyl ester of the latter amino acid was reduced with LAH to 3-*endo*-hydroxymethylbicyclo[2.2.1]hept-2-*endo*-ylamine[7b] (3a).

The isomeric *diexo*-aminoalcohols (2a) and (4a) were prepared by reduction of the 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylic acid and its 5-unsaturated analogue, obtained by reduction[14,15] and hydrolysis of the chlorosulphonyl isocyanate adducts[16] of the norbornadiene or norbornene, respectively.

The *N*-methyl (1b)—(4b) and *N*-benzyl derivatives (1c)—(4c) of the aminoalcohols (1a)—(4a) were obtained from the corresponding amino acids by our earlier methods.[7b,17]

With phenyl isothiocyanate the aminoalcohols (1)—(4) were converted into thioureas (5)—(8) in nearly quantitative yields (Scheme).

On refluxing in ethanol containing 20% HCl,[18,19] the thioureas (5)—(8) were cyclized to the saturated and 6-unsaturated *diendo*- and *diexo*-2-phenylimino-5,8-methano-3,1-benzothiazines (9a—c)—(12a—c).

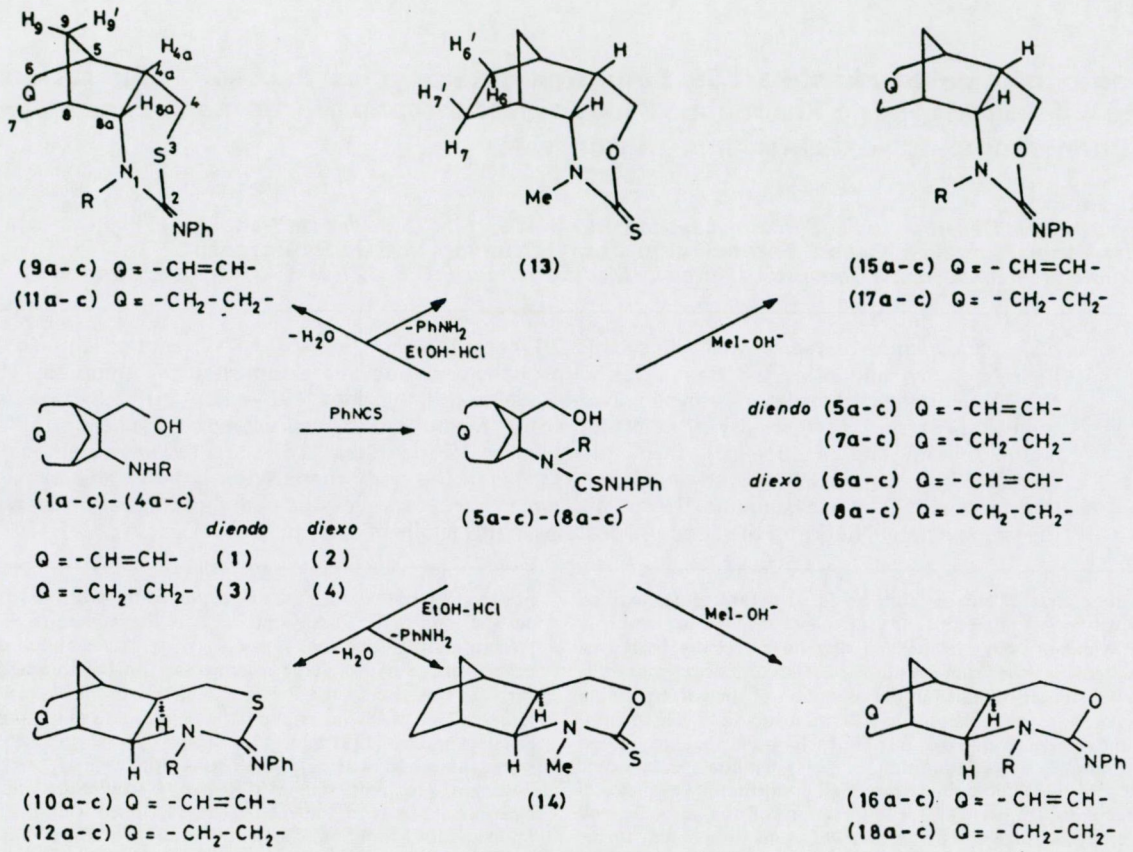
It was found that the acid-catalysed cyclization can follow two reaction paths, since the nucleophilic attack of the sulphur on the non-cyclic methylene carbon atom results in the formation of 1,3-thiazines (9)—(12), whereas the attack of the oxygen of the hydroxyurea intermediate on the thiocarbonyl carbon gives rise to the formation of tricyclic 1,3-oxazine-2-thiones. Two of the latter compounds, (13) and (14), could be isolated besides (11b) and (12b). These 1,3-oxazine-2-thiones were synthesized earlier.[7a,b] Analogous monocyclic 1,3-oxazine-2-thiones were prepared in 87% yield by refluxing aliphatic hydroxythioureas in toluene.[20] They assumed amine elimination and the formation of an isothiocyanate intermediate.

From the thioureas (5)—(8) with methyl iodide, we prepared isothiuronium salts, which were cyclized to the 1,3-oxazines (15a—c)—(18a—c) with base.[21] In the case of (15b), the isothiuronium salt intermediate was also isolated.

*I.r., $^1H$, and $^{13}C$ N.m.r. Spectroscopic Study.*—The characteristic i.r. data are collected in Table 1. The intense diffuse ν(NH) bands of the *N*-unsubstituted compounds (series a) appear in the range 3 250—2 750 $cm^{-1}$. In every spectrum the $\gamma(C_{Ar}H)$ and $\gamma(C_{Ar}C_{Ar})$ bands appear at *ca.* 770 and 700 $cm^{-1}$, respectively, frequencies characteristic of the monosubstituted benzene ring;[22] in series c, which contain a benzyl moiety too, they are split, or more intense. The γ(=CH) bands of the olefinic ring in the norbornenes appear at 705—741 $cm^{-1}$. The highest group frequency of the heteroring functional group [cyclic –NR–C(=NPh)X, where X = O or S] occurs between 1 616 and 1 684 $cm^{-1}$ in the oxazines, and between 1 600 and 1 622 $cm^{-1}$ in the thiazines. These groups display intense bands between 1 570 and 1 600 $cm^{-1}$, and between 1 200 and 1 260 $cm^{-1}$, and in the *N*-substituted series b and c in the region of 1 050—1 150 $cm^{-1}$.

The series a—c can also be distinguished through the $^1H$ and $^{13}C$ n.m.r. signals of the NR groups. In series a the NH signals between δ 5 and 8 could easily be recognized, partly on the basis of their broad contours, and partly because they disappear upon addition of $D_2O$. The *N*-methyl singlet of 3 H intensity appears between δ 2.9 and 3.1, and the corresponding $^{13}C$ line at δ 35.5—36.1 p.p.m. in the case of analogues b. The methylene proton and carbon signals of the benzyl group in derivatives c appear at δ 4.0—4.8 and 5.15—5.5 [the two protons are not equivalent, $J(A,B)$ 15—16 Hz] and δ 50.8—52.0 p.p.m., respectively, and the multiplets of the second benzene ring and the four carbon lines are also seen in the $^1H$ and $^{13}C$ n.m.r. spectra.

The norbornenes and norbornanes can easily be recognized




**Scheme.**

from the n.m.r. signals of H-6, -7 and C-6, -7 in the $^1H$ and $^{13}C$ n.m.r. spectra, respectively. The two double doublets of the olefinic protons in the unsaturated compounds, each of 1 H intensity, appear between δ 5.90 and 6.30 [merged into a singlet of 2 H intensity in the case of (**9a** and **b**)], whereas the signals of the methylene protons in the saturated analogues, overlapping those of the group in position 9, appear in the region δ 0.9—1.9 (6 H). In the norbornenes the C-6, -7 lines lie between δ 134.6 and 140.6 p.p.m., whereas the signals of the saturated carbon atoms of the norbornane compounds appear between δ 20 and 30 p.p.m. (Tables 2 and 3).

The thiazine and oxazine derivatives can be identified through the chemical shifts of H-4 and C-4. In the $^1H$ n.m.r. spectra of the former compounds the signals of the non-equivalent methylene protons appear between δ 2.4 and 2.95, whereas in the case of the latter compounds they appear in the region δ 3.65—4.30, as anticipated.[23a] The regions of the corresponding carbon chemical shifts for the two types of compounds, also as expected,[23b] are δ 26.7—31.1 and 65.5—69.8 p.p.m., respectively.

A considerable difference is found for the shift of C-2. In the thiazines compared with the oxazines, the adjacent sulphur atom causes a marked downfield shift of the C-2 signal. The C-2 signal in the thiazines appears between δ 156.7 and 160.0 p.p.m., whereas in the oxazines (**15**)—(**18**) it falls between δ 144.5 and 148.6 p.p.m. The chemical shift of C-1′ (2-phenyl group), however, though to a lesser extent, reveals an opposite effect: it is found in the interval δ 147.1—151.6 for the thiazines and 151.5—153.4 p.p.m. for the oxazines.

The *diendo*- or *diexo*-annelation of the hetero- and carbobicyclic rings is indicated by the multiplicity of the H-8a signal in the region δ 3.0—4.0.[9] For the *diexo*-compounds this signal is a doublet ($J$ 7—10 Hz), corresponding to 4a,8a coupling, whereas in the spectra of the *diendo* compounds it appears as a double doublet: besides the splitting originating from the 4a,8a spin–spin interaction (the magnitude of which varies in the range 6.5—12.5 Hz in this series), another significant splitting is observed due to the 8,8a coupling (3—4 Hz). The H-8–C-8-C-8a–H-8a dihedral angle is *ca.* 50°, whereas that in the *diexo*-compounds is *ca.* 90°, and therefore no splitting can be anticipated[24] [$J$(H-8,H-8a) < 1 Hz].[9]

The H-8a chemical shift depends mainly on the annelation: it is δ 3.01—3.36 for the *endo*-H-8a atom of the *diexo*-series and δ 3.30—3.95 for the *exo*-H-8a atoms of the *diendo*-compounds in accord with the literature data for norbornane and norbornene. Values of δ 1.18 and 1.46 have been measured for the protons of the former and δ 0.96 and 1.59 for those of the latter in the *endo*- and *exo*-configurations, respectively.[25–27]

This holds for the H-4a signal as well (Table 2): for (**10**) and (**16**) the shielding is stronger (δ 1.98—2.23) than for the isomers (**9**) and (**15**) (δ 2.5—2.8) and similarly is stronger for (**12**) and (**18**) (δ 1.98—2.2) than for (**11**) and (**17**) (δ 2.3—2.4).

Similarly, as expected, we have found that the position of the H-8a signal is also slightly dependent on the saturation of the

**Table 1.** Characteristic i.r. frequencies of compounds (9a—c)—(12a—d) and (15a—c)—(18a—c) in KBr ($cm^{-1}$)

| Compound | ν(NH) | Cyclic | -NR-C(=NPh)X (X = O or S)[a] | | γ(=CH) | γ($C_{Ar}$H) | γ($C_{Ar}C_{Ar}$) |
|---|---|---|---|---|---|---|---|
| (9a) | 3 250—2 750 | 1 622, 1 587 | 1 207 | | 727 | 773 | 700 |
| (9b) | | 1 585 | 1 217 | 1 065 | 731 | 770 | 698 |
| (9c) | | 1 601, 1 580 | 1 211 | 1 124 | 741[b] | 771[c] | 696[c] |
| (10a) | 3 250—2 750 | 1 614, 1 589 | 1 198 | | 714 | 766 | 696 |
| (10b) | | 1 582 | 1 215 | 1 061 | 717 | 773 | 700 |
| (10c) | | 1 574 | 1 211 | 1 109 | 719 | 773, 743[d] | 698[c] |
| (11a) | 3 250—2 750 | 1 614, 1 587 | 1 209 | | | 771 | 698 |
| (11b) | | 1 580 | 1 227 | 1 069 | | 771 | 698 |
| (11c) | | 1 603, 1 582 | 1 219 | 1 142 | | 771, 735[d] | 696[c] |
| (12a) | 3 250—2 750 | 1 618, 1 587 | 1 209 | | | 773 | 700 |
| (12b) | | 1 600, 1 582 | 1 221 | 1 067 | | 777 | 698 |
| (12c) | | 1 560 | 1 225 | 1 155 | | 765, 735[b] | 690[c] |
| (15a) | 3 250—2 750 | 1 684, 1 591 | 1 223 | | 735 | 764 | 698 |
| (15b) | | 1 643, 1 595 | 1 261 | 1 101 | 725 | 746 | 698 |
| (15c) | | 1 616, 1 578 | 1 252,[e] 1 246[e] | 1 134,[e] 1 124[e] | 729[b] | 760[c] | 694[c] |
| (16a) | 3 250—2 750 | 1 674, 1 595 | 1 220 | | 708 | 764 | 694 |
| (16b) | | 1 670, 1 595 | 1 258 | 1 084 | 714 | 773 | 694 |
| (16c) | | 1 624, 1 582 | 1 252 | 1 123 | 735[b] | 754[c] | 692[c] |
| (17a) | 3 250—2 750 | 1 678, 1 591 | 1 221 | | | 771,[e] 758[e] | 698 |
| (17b) | | 1 643, 1 593 | 1 265 | 1 053 | | 746 | 700 |
| (17c) | | 1 639, 1 585 | 1 256 | 1 124 | | 781, 774[d] | 704, 690[d] |
| (18a) | 3 250—2 750 | 1 666, 1 589 | 1 236 | | | 770,[e] 750[e] | 702,[e] 690[e] |
| (18b) | | 1 651, 1 593 | 1 259 | 1 097 | | 775,[e] 756[e] | 712,[e] 694[e] |
| (18c) | | 1 636, 1 591 | 1 252 | 1 125 | | 758[c] | 694[c] |

[a] The two higher frequencies are due to group frequencies of ν(C=N) and ν($C_{Ar}$=$C_{Ar}$) character, and the two lower ones to bands of ν(C–N) type vibrations of the ring and the N–C(R) group, respectively. [b] Overlapped by the γ($C_{Ar}$H) band of the *N*-benzyl (NR) group. [c] Coalesced bands of the two benzene rings. [d] *N*-benzyl (NR) group. [e] Split bands.

carbocycle. The H-8a atom of norbornenes is more shielded in the *diexo*-isomers with chemical shifts of δ 3.01—3.30, while for norbornanes the shifts between δ 3.10 and 3.36 were observed. For the *diendo*-compounds these intervals of chemical shifts are δ 3.3—3.6 for norbornanes, whereas for the norbornene analogues it is δ 3.61—3.95.

There are significant differences in the H-5, -8 chemical shifts of the saturated and unsaturated compounds. In the latter group of compounds the $-I$ effect of the olefinic group causes downfield shift: the H-5 signal is in the region δ 2.5—2.9, while that of H-8 lies at δ 2.54—3.25. In the norbornanes, however, the two shift intervals are δ 2.05—2.25, and 2.05—2.7, respectively.

In the $^{13}$C n.m.r. spectra of the norbornenes the C-5, -8, signals undergo a downfield shift due to the greater α-effect[23c] of the olefinic bond (δ 45.2—48.3 and 46.2—49.5, respectively, compared with the observed values of δ 39.5—42.1 and 39.6—44.1, respectively, for the norbornanes; Table 3).

In the spectra of the norbornanes, the C-4a and C-8a lines are shifted upfield due to the steric hindrance between H-6, -7 (*endo*) and the NR moiety or H-4 (steric-compression shift: carbons bearing sterically hindered groups are more shielded[28]).

In compounds (11) and (17) the mean shift of the C-4a signal is δ 42.2 and 38.3 p.p.m., respectively; this means a field effect of 5.2 p.p.m. compared with those in the analogues (12) and (18) (δ 47.4 and 43.5 p.p.m., respectively). For the C-8a signal the mean field effect is 4.1 and 3.9 p.p.m. In the norbornenes, due to the greater distance of the olefinic protons from H-4 and the NR group, the field effect disappears; furthermore, for the H-4a signal an opposite, albeit lower (average of 1.9 and 1.3 p.p.m.), shift can be observed.

Steric hindrance is also present in the *diexo*-compounds, but instead of H-6, -7 (*endo*), H-9′ (*endo*) is involved with 4-$CH_2$ or the NR group. This is indicated by the large field effect on the C-9 signals, which can be observed for both the norbornanes and the norbornenes. The average field effects for the pairs (10)—(9), (12)—(11), (16)—(15) and (18)—(17) are 5.1, 4.4, 4.5, and 4.2 p.p.m.

In the norbornene derivatives annelation also affects the chemical shift of the 9-methylene protons: in the *diexo*-compounds the heteroatoms in close proximity give rise to a downfield shift of *ca.* 0.4 p.p.m. in the H-9′ (*endo*) signal, and a similar, but smaller shift (*ca.* 0.1 p.p.m.) in the H-9 (*exo*) signal. This is in agreement with the assignment of the two signals, which is also proved by differential nuclear Overhauser effect experiments on the analogues.[9] The difference in the chemical shifts can be attributed to the anisotropic effect of the olefinic bond,[23d] which gives rise to an increased shielding at the H-9 (*exo*) atom over the plane of the double bond. In the norbornanes only one doublet of the AB spectrum is separated (the other overlaps the H-6, -6′, -7, -7′ signals) and this is hardly altered by annelation [in compounds (11), (12), (17), and (18) the average shifts are δ 1.80, 1.70, 1.84, and 1.80, respectively.]

All these data are in good agreement with our findings[9,29] from the systematic spectroscopic study of norbornane-condensed 2-aryldihydro-oxazines, and lend further support to the probable, but not unambiguous, assignments (especially concerning the C-4a, -5, -8 and C-4, -9 lines for certain compounds).

It is noteworthy that a potential *endo* ⇌ *exo* C=N bond tautomeric equilibrium is possible in the *N*-unsubstituted compounds (9a)—(12a) and (15a)—(18a). The synthesis route means that the corresponding *N*-substituted series b and c are exclusively isomers substituted on the ring nitrogen, containing an exocyclic C=N bond (Scheme). The fact that neither the chemical shifts of the aromatic protons of the 2-phenylimino group, nor those of the carbon atoms in this ring (with the exception of C-1′), are altered significantly compared with those in the *N*-substituted analogues is unambiguous evidence of the predominance of the tautomeric form containing an exocyclic C=N bond (*i.e.* an NH group in the ring) in $CDCl_3$ solution.

**Table 2.** $^1$H N.m.r. data of compounds (9a—c)—(12a—c) and (15a—c)—(18a—c)[a]

| | Chemical shifts (δ) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | H-4 2m (2 × 1 H)[b] | | H-4a m (1 H)[c] | H-5 ~s (1 H) | H-8 ~s (1 H) | H-8a d or dd (1 H)[d] | H-6 m (2 H or 4 H)[e] | H-7 | H-9 2d (2 H)[f] | | NH/NMe/NCH$_2$[g] | | ArH[h] dd (2 H) | ArH[m] dt (2 H) | ArH[p] ~t (1 H) | ArH (NCH$_2$Ph) m (5 H) |
| (9a) | 2.49 | 2.64 | 2.70 | 2.83 | 2.92 | 3.95 | 6.15[k] | | 1.42 | 1.55 | ~6.0 | | 6.95 | 7.28 | 7.05 | |
| (9b) | 2.45—2.55 | | 2.70 | 2.81 | 3.21 | 3.61 | 6.22[k] | | 1.40 | 1.62 | 2.98 | | 6.80 | 7.25 | 7.00 | |
| (9c) | 2.44 | ~2.8 | ~2.8[j] | ~2.8[j] | 3.15 | 3.78 | 6.15 | 6.25 | 1.32 | 1.42 | 4.34 | 5.31 | 6.68 | 7.25 | 6.95 | 7.3—7.5 |
| (10a) | 2.65—2.75 | | 2.12 | 2.50 | 2.54 | 3.26 | 6.21 | 5.90 | 1.42 | 1.94 | ~6.1 | | 6.95 | 7.30 | 7.05 | |
| (10b) | 2.65—2.70 | | 2.15 | 2.55 | 3.25 | 3.01[m] | 6.30 | 6.02 | 1.48 | 1.94 | 3.08 | | 6.85 | 7.25 | 7.00 | |
| (10c)[i] | 2.75—2.85 | | 2.23 | 2.61 | 3.24 | 3.30 | 6.30 | 6.24 | 1.45 | 2.00 | 4.78 | 5.28 | 6.84 | ~7.3[j] | 7.04 | ~7.25—7.55[j] |
| (11a) | 2.52 | 2.92 | ~2.4 | 2.25 | 2.32 | 3.60 | 1.3—1.6 m (5 H), ~1.8 m (1 H) | | | | ~5.35 | | 7.00 | 7.30 | 7.10 | |
| (11b) | ~2.4[j] | 2.89 | ~2.4[j] | 2.25 | 2.55 | 3.30 | 1.4—1.7 m (6 H) | | | | 2.93 | | 6.84 | 7.28 | 7.02 | |
| (11c) | ~2.4 | 2.93 | ~2.4 | 2.25 | ~2.4 | 3.50 | ~1.37 m (4 H), ~1.7 m (2 H) | | | | 4.19 | 5.47 | 6.80 | ~7.3[j] | 7.00 | 7.2—7.4[j] |
| (12a) | 2.6—2.8 | | 2.15 | ~2.05[j] | ~2.05[j] | 3.36 | 1.1—1.3 m (3 H), 1.5—1.6 m (2 H) 1.88 d (1 H) | | | | ~5.2 | | 6.90 | 7.30 | 7.05 | |
| (12b) | 2.65—2.8 m (3 H)[j] | | 2.15 | 2.05 | ~2.7[j] | 3.10 | 1.1—1.3 m (3 H), 1.4—1.6 m (1 H) 1.6—1.75 m (1 H), 1.87 d (1 H) | | | | 3.05 | | 6.82 | 7.25 | 7.00 | |
| (12c) | 2.7—2.85 | | 2.20 | 2.05 | 2.62 | 3.32 | 0.9—1.3 m (3 H), 1.4—1.6 m (2 H) 1.85 d (1 H) | | | | 4.61 | 5.25 | 6.80 | ~7.3[j] | 7.00 | 7.2—7.4[j] |
| (15a) | 3.76 | 4.25 | 2.65 | 2.87 | 2.96 | 3.90 | 6.18 | 6.21 | 1.38 | 1.55 | ~5.5 | | 7.04 | 7.26 | 6.96 | |
| (15b) | ~3.71[j] | 4.14 | 2.70 | 2.90 | 3.24 | ~3.71[j] | 6.18 | 6.21 | 1.40 | 1.62 | 2.93 | | ~6.95[k] | 7.25 | ~6.95[k] | |
| (15c) | 3.65 | ~4.05[j] | 2.50 | 2.72 | 3.01 | 3.65 | 6.14 | 6.04 | 1.13 | 1.42 | ~4.07[j] | 5.16 | 6.90 | | 7.15—7.45 m (8 H) | |
| (16a)[i] | 3.70 | 4.30 | 1.98 | 2.63 | 2.82 | 3.18 | 6.26 | 6.14 | 1.34 | 1.81 | ~7.7 | | 7.15—7.30 m (4 H) | | 6.90 | |
| (16b) | 3.94 | 4.19 | 2.10 | 2.68 | 3.18 | 3.12[m] | 6.30 | 6.09 | 1.48 | 1.90 | 3.04 | | ~6.95[j] | 7.22 | ~6.95[j] | |
| (16c) | 4.00 | 4.22 | 2.06 | 2.69 | 3.12 | 3.19 | 6.24 | 6.00 | 1.47 | 1.97 | 4.34 | 5.25 | 6.95 | | 7.2—7.45 m (8 H) | |
| (17a) | 4.03 | 4.19 | 2.30 | 2.25 | 2.25 | 3.60 | 1.35—1.50 m (4 H), 1.7—1.8 m (2 H) | | | | ~5.85 | | 7.10 | 7.28 | 7.00 | |
| (17b) | 3.98 | 4.07 | 2.37 | 2.27 | 2.59 | 3.38 | 1.4—1.8 m (6 H) | | | | 2.90 | | ~6.95[j] | 7.22 | ~6.95[j] | |
| (17c) | ~4.03[j] | 4.10 | 2.30 | 2.25 | 2.44 | 3.46 | 1.4—1.5 m (4 H), ~1.70 t (1 H) ~1.86 t (1 H) | | | | ~4.02[j] | 5.34 | ~7.0[k] | ~7.3[l] | ~7.0[k] | 7.2—7.4[l] |
| (18a) | 3.80 | 4.19 | 2.0—2.15 m (3 H) | | | 3.28 | 1.05—1.25 m (3 H), 1.45—1.55 m (2 H) 1.86 d (1 H) | | | | ~5.9 | | ~7.0[j] | ~7.3 | ~7.0[j] | |
| (18b) | 3.89 | 4.08 | 2.05 | 2.10 | 2.57 | 3.12 | 1.05—1.25 m (3 H), 1.4—1.7 m (2 H) 1.75 d (1 H) | | | | 2.97 | | ~6.95[j] | 7.20 | ~6.95[j] | |
| (18c) | 3.92 | 4.08 | 1.98 | 2.10 | 2.54 | 3.16 | 0.9—1.6 m (5 H), 1.80 d (1 H) | | | | 4.22 | 5.20 | ~6.95[j] | ~7.3[l] | ~6.95[j] | 7.2—7.4[l] |

[a] In $CDCl_3$ solution at 250 MHz (reference $Me_4Si$). [b] A and B parts (2dd) of an ABX multiplet. In the case of (9a—c) and (10a—c) in a rudimentary form as d + s. The upfield or downfield dd appears as a triplet, $J(A,B) \approx J(A,X) \approx 12.5$ Hz in the spectrum of (9a—c) and (11a—c), respectively. For compounds (12a—c) $\delta A \approx \delta B$ and the A and B lines partly overlap. $J(A,B)$ 10.8—11.2 Hz (15)—(18), $J(A,X)$ 7.3 (15a,b), 8.4 (16a), 5.8 (16b), 4.8 (16c), 6.3 (17a,b), 9.1 (18a) 5.4 (18b), and 4.4 Hz (18c), $J(B,X)$ 6.4 (15a), 5.9 (15b), 7.0 (16a) and (18a), 5.7 (16b), 5.4 (16c) and (18b), 6.0 (17a,b), 5.5 (17c), and 5.1 Hz (18c). [c] Symmetric complex multiplet, for the *diendo*-compounds dq. [d] d for *diexo*-compounds, $J(4a,8a)$ 7.3 (10a), 7.5 (10b,c) and (14b), 7.1 (12a), 7.8 (12c), (16a), and (18a), 8.8 (16b,c), 8.4 (18b) and 10.0 Hz (18c). For the *diendo*-compounds dd, $J(4a,8a)$ 8.4 (9a,c), 8.6 (9b), 10.2 (11a), and (17a), 10.0 (11b,c), 9.4 (15a), 6.6 (15b), 11.6 (17b), and 12.1 Hz (17c), $J(8,8a)$ 3—4 Hz. [e] Complex multiplets, overlapping with one d or both d of H-9,9′ with a total intensity of 5 H or 6 H, respectively, for the norbornanes. 2dd (2 × 1 H) for norbornenes, $J(6,7)$ 5.6—5.7 Hz, $J(5,6) \approx J(7,8)$ 2.6—3.2 Hz. [f] AB spectrum, $J(A,B)$ 8.8—10.0 Hz. The downfield d has a further triplet splitting of *ca.* 1 Hz for (9a,b), (15a,b), and (18b). [g] Broad signal of 1 H intensity for compounds a, s (3 H) in series b and AB spectrum for compounds c, $J(A,B)$ 15.0—15.8 Hz. [h] s (2 H). [i] In [$^2H_6$]DMSO solution. [j,l] Overlapping signals. [m] Further d splitting by *ca.* 1 Hz.

Table 3. $^{13}C$ N.m.r. data of compounds (9a—c)—(12a—c) and (15a—c)—(18a—c)[a,b]

| | Chemical shifts (δ) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | C-2 | C-4 | C-4a[c] | C-5[c] | C-6 | C-7 | C-8[c] | C-8a | C-9 | $NCH_3$ $NCH_2$ | C-1' | C-2',6' | C-3',5' | C-4' |
| (9a) | 159.9 | 29.9 | 44.7 | 46.3 | 135.9 | 135.3 | 47.4 | 56.7 | 46.9 | | 147.1 | 122.4 | 128.8 | 123.4 |
| (9b) | 159.1 | 28.7 | 45.8 | 47.2[d] | 136.6 | 134.0 | 47.2[d] | 63.2 | 47.8 | 36.0 | 150.5 | 122.2 | 128.6 | 122.8 |
| (9c) | 158.3 | 29.3 | 46.4 | 48.3 | 138.3 | 135.5 | 48.2 | 61.9 | 48.6 | 52.0 | 151.6<br>140.0[e] | 123.2<br>130.0[f] | 129.1[f]<br>129.6[f] | 123.7<br>128.0[e] |
| (10a) | 159.5 | 31.1 | 43.5 | 46.8 | 134.4 | 139.5 | 49.5 | 56.6 | 43.0 | | 148.4 | 122.2 | 128.9 | 123.3 |
| (10b) | 159.3 | 29.4 | 44.0 | 46.8 | 134.6 | 140.6 | 46.2 | 62.7 | 42.2 | 35.9 | 150.2 | 121.9 | 128.4 | 122.5 |
| (10c) | 158.2 | 29.7 | 43.7 | 47.0 | 135.2 | 140.6 | 47.2 | 61.3 | 43.0 | 51.4 | 150.2<br>139.1[e] | 122.1<br>127.8[f] | 128.7[f]<br>128.3[f] | 122.8<br>126.6[e] |
| (11a) | 160.0 | 27.8 | 42.2 | 40.6 | 23.0 | 20.8 | 41.8 | 56.6 | 37.7 | | 148.0 | 122.3 | 128.9 | 123.3 |
| (11b) | 160.0 | 26.7 | 42.6 | 41.7 | 23.8 | 20.0 | 41.3 | 63.0 | 37.6 | 36.1 | 150.8 | 122.2 | 128.7 | 122.7 |
| (11c) | 157.9 | 26.7 | 41.9 | 41.3 | 24.0 | 20.2 | 41.1 | 60.2 | 37.4 | 50.8 | 150.5<br>138.2[e] | 121.9<br>128.0[d,f] | 128.0[d,f]<br>128.6[f] | 122.5<br>126.5[e] |
| (12a) | 158.6 | 29.9 | 47.7 | 41.9 | 25.8 | 29.4 | 44.1 | 60.0 | 33.0 | | 148.6 | 122.3 | 128.7 | 123.0 |
| (12b) | 158.9 | 28.7 | 47.5 | 42.1 | 26.3 | 29.5 | 40.4 | 67.0 | 33.1 | 35.9 | 150.2 | 122.2 | 128.6 | 122.7 |
| (12c) | 156.7 | 28.4 | 46.9 | 42.1 | 26.2 | 29.4 | 41.9 | 65.0 | 33.6 | 51.0 | 149.9<br>139.0[e] | 121.9<br>127.5[f] | 127.9[f]<br>128.3[f] | 122.2<br>126.3[e] |
| (15a) | 144.5 | 67.9 | 39.6 | 45.6 | 135.9 | 134.8 | 48.0 | 54.0 | 48.5 | | 152.4 | 121.8 | 128.8 | 122.2 |
| (15b) | 148.6 | 66.8 | 40.7 | 45.4 | 136.8 | 132.7 | 46.8 | 60.4 | 47.9 | 35.5 | 152.4 | 123.5 | 128.2 | 121.5 |
| (15c) | 148.3 | 66.3 | 40.3 | 45.4 | 136.6 | 132.6 | 46.6 | 57.4 | 47.8 | 50.9 | 151.5<br>138.2[e] | 123.2<br>128.0[f] | 128.2[f]<br>128.1[f] | 121.1<br>126.8[e] |
| (16a) | 146.4 | 69.8 | 38.7 | 45.8 | 137.0 | 140.4 | 48.5 | 54.6 | 44.3 | | 153.1 | 122.3 | 129.7 | 122.3 |
| (16b) | 148.5 | 67.6 | 39.1 | 45.2 | 135.3 | 140.3 | 47.2 | 60.7 | 43.1 | 36.1 | 152.5 | 121.4 | 128.3 | 123.4 |
| (16c) | 148.3 | 67.6 | 39.0 | 45.4 | 135.4 | 140.3 | 47.8 | 58.1 | 43.3 | 51.3 | 152.0<br>138.5[e] | 121.4<br>128.0[f] | 128.3[f]<br>128.2[f] | 121.4<br>129.9[e] |
| (17a) | 145.5 | 66.8 | 38.7 | 40.3 | 24.1 | 21.0 | 43.0 | 53.8 | 37.3 | | 153.3 | 122.1 | 128.8 | 122.0 |
| (17b) | 148.3 | 65.5 | 37.9[d] | 40.7 | 23.9 | 20.2 | 39.6 | 60.1 | 37.9[d] | 35.5 | 152.7 | 123.2 | 127.8 | 120.9 |
| (17c) | 148.4 | 65.9 | 38.3 | 41.0 | 24.4 | 21.1 | 40.4 | 57.3 | 38.1 | 51.0 | 152.5<br>138.1[e] | 123.4<br>128.1[f] | 128.2[f]<br>128.3[f] | 121.2<br>126.9[e] |
| (18a) | 146.0 | 67.6 | 44.1 | 39.5 | 25.8 | 29.2 | 42.5 | 57.1 | 33.2 | | 153.4 | 122.6 | 128.7 | 122.1 |
| (18b) | 148.3 | 66.6 | 42.9 | 39.9 | 25.5 | 29.1 | 40.0 | 64.2 | 33.4 | 35.7 | 152.5 | 123.2 | 127.9 | 121.0 |
| (18c) | 148.4 | 67.1 | 43.4 | 40.6[d] | 25.8 | 29.4 | 40.6[d] | 61.7 | 34.1 | 51.0 | 152.4<br>138.6[e] | 123.4<br>128.3[f] | 128.1[f]<br>128.2[f] | 121.4<br>127.0[e] |

[a] In $CDCl_3$; in the cases of (9c) and (16a) in $[^2H_6]$DMSO solution. [b] At 20.14 MHz; in the cases of (9a—c), (10b), and (15c) at 62.89 MHz. [c,f] Assignments may be interchanged. [d] Overlapping lines. [e] Lines of the benzene carbons in the *N*-benzyl (NR) group.

Since this is also valid for compound (16a) a detectable change in the tautomeric equilibrium cannot be observed in $[^2H_6]$DMSO solution either.

By comparison of the spectra of *exo*- and *endo*-*N*-substituted 2-arylaminothiazolines of fixed structure, we have shown that the conjugation of the C=N double bond and the phenyl ring gives rise to a considerable upfield shift in the signals of the *ortho* and *para* protons and carbon atoms.[30,31] Accordingly, the $^1H$ and $^{13}C$ shifts observed [δ(H-2',6') 6.90—7.15, δ(H-4') 6.90—7.10, δ(C-2',6') 121.8—122.6 p.p.m., δ(C-4') 122.0—123.4 p.p.m.] indicate that the non-conjugated tautomeric form does not make a significant contribution to the tautomeric equilibrium. For comparison, for the thiazolines in question δ(C-4') was 122.0—123.6 and 127.8—129.6 p.p.m. for the conjugated *N*-methyl isomers and the non-conjugated isomers, respectively.

## Experimental

*General Methods.*—I.r. spectra were run in KBr discs on a Bruker IFS-113v Fourier transform spectrometer equipped with an ASPECT 2000 computer. $^1H$ and $^{13}C$ n.m.r. spectra were recorded in $CDCl_3$ or $[^2H_6]$DMSO solution in 5 and 10 mm tubes, at room temperature on Bruker WM-250 and WP-80-SY Fourier transform spectrometers, controlled by an ASPECT 2000 computer at 250.13 MHz ($^1H$) and 62.89 or 20.14 MHz ($^{13}C$), respectively, using the deuterium signal of the solvent as the lock and $SiMe_4$ as internal standard. The most important measurement parameters were: sweep width 5 and 5 or 15 kHz, pulse width 1 and 7 or 3.5 μs (*ca.* 20°) and *ca.* 30° flip angle), acquisition time 1.64 and 1.02 or 1.64 s, number of scans 32 and 1K—4K, computer memory 16K. Complete proton-noise decoupling (*ca.* 3 or *ca.* 1.5 W) for the $^{13}C$ spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 Hz).

*Preparation of Thioureas* (5a—c)—(8a—c).—To a solution of an aminoalcohol (1)—(4) (0.01 mol) in dry ether (25 ml), phenyl isothiocyanate (1.35 g, 0.01 mol) was added dropwise under stirring. After stirring for 1 h, the separated solid was filtered off and crystallized. Data for the thioureas (5)—(8) are in Table 4.

*Preparation of* 5,8-*Methano*-2-*phenylimino*-*tetrahydro*-(9a—c) *and* (10a—c) *and* -*hexahydro*-4H-3,1-*benzothiazines* (11a—c) *and* (12a—c).—A thiourea derivative (5)—(8) (0.01 mol) was boiled in ethanol (20 ml) containing 20% dry HCl. The reaction was monitored by t.l.c. [silica gel, benzene–ethanol–light petroleum (4:1:3), detection with iodine vapour]. After evaporation of the mixture, the residue was neutralized with 10% sodium carbonate solution and extracted with chloroform (3 × 15 ml). After washing with water and drying ($Na_2SO_4$), the solvent-free residue was recrystallized. Data on the thiazines (9a—c)—(12a—c) are in Table 4.

*Isolation of* 5,8-*Methano*-1-*methyl*-1,4,r-4a,t-5,6,7,t-8,c-8a-*octahydro*-3,1-*benzoxazine*-2-*thione* (13) *and* 5,8-*Methano*-1-

**Table 4.** Physical and analytical data of compounds (5a—c)—(12a—c) and (15a—c)—(18a—c)

| Compound | M.p. (°C) | Yield % | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (5a) | 143—145[a] | 94 | 65.8 | 6.5 | 10.2 | $C_{15}H_{18}N_2OS$ | 65.7 | 6.6 | 10.2 |
| (5b) | 153—154[c] | 92 | 66.75 | 7.3 | 9.65 | $C_{16}H_{20}N_2OS$ | 66.6 | 7.0 | 9.7 |
| (5c) | 119—120[d] | 84 | 72.35 | 6.7 | 7.5 | $C_{22}H_{24}N_2OS$ | 72.5 | 6.6 | 7.7 |
| (6a) | 156—157[b] | 95 | 65.75 | 6.6 | 10.0 | $C_{15}H_{18}N_2OS$ | 65.7 | 6.6 | 10.2 |
| (6b) | 154—156[a] | 96 | 66.5 | 7.1 | 9.9 | $C_{16}H_{20}N_2OS$ | 66.6 | 7.0 | 9.7 |
| (6c) | 121—123[d] | 94 | 72.4 | 6.85 | 7.8 | $C_{22}H_{24}N_2OS$ | 72.5 | 6.6 | 7.7 |
| (7a) | 112—114[b] | 90 | 65.3 | 7.2 | 10.1 | $C_{15}H_{20}N_2OS$ | 65.2 | 7.3 | 10.1 |
| (7b) | 120—122[a] | 95 | 65.9 | 7.7 | 9.7 | $C_{16}H_{22}N_2OS$ | 66.2 | 7.6 | 9.65 |
| (7c) | 71—72[b] | 85 | 72.1 | 7.05 | 7.6 | $C_{22}H_{26}N_2OS$ | 72.1 | 7.15 | 7.6 |
| (8a) | 156—158[b] | 96 | 65.1 | 7.4 | 10.2 | $C_{15}H_{20}N_2OS$ | 65.2 | 7.3 | 10.1 |
| (8b) | 158—160[b] | 97 | 66.3 | 7.9 | 9.4 | $C_{16}H_{22}N_2OS$ | 66.2 | 7.6 | 9.65 |
| (8c) | 130—132[b] | 97 | 71.9 | 7.2 | 7.7 | $C_{22}H_{26}N_2OS$ | 72.1 | 7.15 | 7.6 |
| (9a) | 235—236[d] | 61 | 70.6 | 6.4 | 11.2 | $C_{15}H_{16}N_2S$ | 70.3 | 6.3 | 10.9 |
| (9b) | 128—130[a] | 45 | 71.25 | 6.6 | 10.3 | $C_{16}H_{18}N_2S$ | 71.1 | 6.7 | 10.4 |
| (9c) | 92—94[a] | 71 | 76.4 | 6.3 | 7.9 | $C_{22}H_{22}N_2S$ | 76.3 | 6.4 | 8.1 |
| (10a) | 181—183[d] | 63 | 70.2 | 6.3 | 11.05 | $C_{15}H_{16}N_2S$ | 70.3 | 6.3 | 10.9 |
| (10b) | 95—97[a] | 77 | 71.05 | 6.9 | 10.4 | $C_{16}H_{18}N_2S$ | 71.1 | 6.7 | 10.4 |
| (10c) | 119—121[d] | 62 | 76.4 | 6.3 | 7.9 | $C_{22}H_{22}N_2S$ | 76.3 | 6.4 | 8.1 |
| (11a) | 237—238[c] | 67 | 69.8 | 7.0 | 10.9 | $C_{15}H_{18}N_2S$ | 69.75 | 7.0 | 10.8 |
| (11b) | 139—140[d] | 54 | 70.4 | 7.6 | 10.3 | $C_{16}H_{20}N_2S$ | 70.55 | 7.4 | 10.3 |
| (11c) | 89—91[a] | 85 | 76.0 | 6.9 | 7.9 | $C_{22}H_{24}N_2S$ | 75.8 | 6.9 | 8.0 |
| (12a) | 189—191[f] | 77 | 69.85 | 7.1 | 10.55 | $C_{15}H_{18}N_2S$ | 69.75 | 7.0 | 10.8 |
| (12b) | 70—72[a] | 59 | 70.6 | 7.3 | 10.0 | $C_{16}H_{20}N_2S$ | 70.55 | 7.4 | 10.3 |
| (12c) | 90—92[h] | 77 | 76.1 | 6.9 | 7.9 | $C_{22}H_{24}N_2S$ | 75.8 | 6.9 | 8.0 |
| (15a) | 194—195[b] | 98 | 75.1 | 6.8 | 12.1 | $C_{15}H_{16}N_2O$ | 75.0 | 6.7 | 11.7 |
| (15b) | 116—118[d] | 98 | 76.0 | 7.1 | 11.0 | $C_{16}H_{18}N_2O$ | 75.6 | 7.1 | 11.0 |
| (15c) | 65—67[a] | 60 | 79.85 | 6.85 | 8.4 | $C_{22}H_{22}N_2O$ | 80.0 | 6.7 | 8.5 |
| (16a) | 167—169[d] | 85 | 75.1 | 6.9 | 11.3 | $C_{15}H_{16}N_2O$ | 75.0 | 6.7 | 11.7 |
| (16b) | 88—90[d] | 81 | 75.8 | 7.3 | 11.2 | $C_{16}H_{18}N_2O$ | 75.6 | 7.1 | 11.0 |
| (16c) | 94—96[d] | 51 | 79.9 | 6.6 | 8.6 | $C_{22}H_{22}N_2O$ | 80.0 | 6.7 | 8.5 |
| (17a) | 176—177[c] | 82 | 74.2 | 7.2 | 11.6 | $C_{15}H_{18}N_2O$ | 74.35 | 7.5 | 11.6 |
| (17b) | 79—81[d] | 71 | 74.8 | 7.9 | 10.65 | $C_{16}H_{20}N_2O$ | 75.0 | 7.9 | 10.9 |
| (17c) | 143—145[a,i] | 61 | 59.7 | 4.8 | 12.3 | $C_{28}H_{27}N_3O_8$ | 59.9 | 4.85 | 12.5 |
| (18a) | 176—177[a] | 86 | 74.5 | 7.1 | 11.7 | $C_{15}H_{18}N_2O$ | 74.35 | 7.5 | 11.6 |
| (18b) | 84—86[d] | 85 | 74.8 | 7.9 | 11.0 | $C_{16}H_{20}N_2O$ | 75.0 | 7.9 | 10.9 |
| (18c) | 147—149[a,i] | 72 | 59.6 | 4.7 | 12.4 | $C_{28}H_{27}N_3O_8$ | 59.9 | 4.85 | 12.5 |

Crystallization solvents. [a] Ethanol. [b] Chloroform. [c] Nitromethane. [d] Benzene. [e] Ethyl acetate. [f] Benzene–chloroform (3:1) mixture. [g] Ether. [h] Chloroform–light petroleum (1:3) mixture. [i] Picrates. For i.r. and n.m.r. spectroscopy the bases liberated from the salt with KOH were applied.

*methyl*-1,4,r-4a,c-5,6,7,c-8,c-8a-*octahydro*-3,1-*benzoxazine*-2-*thione* (14).—A mixture of (11b) and (12b) was evaporated and transferred to an aluminium oxide column (Woelm neutral; activity grade I). The column was eluted with benzene, and then with ethyl acetate. The ethyl acetate eluate was evaporated and the residue (*ca.* 30%) was recrystallized from benzene and identified from the m.p. and i.r. spectrum.[7a,b]

*Preparation of* 5,8-*Methano*-2-*phenylimino*-*tetrahydro*-(15a—c) *and* (16a—c) *and* -*hexahydro*-4H-3,1-*benzoxazines* (17a—c) *and* (18a—c).—A thiourea derivative (5)—(8) (0.01 mol) and methyl iodide (7.10 g, 0.05 mol) were stirred together for 1—2 h. The mixture was evaporated and the residue was stirred with methanol (40 ml) containing 3N-KOH for 4 h. After evaporation and the addition of water (5 ml), the product was extracted with chloroform (3 × 15 ml). The extract was washed with water and dried ($Na_2SO_4$). Data on the compounds obtained after evaporation and recrystallization are in Table 4.

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# SYNTHESIS AND NMR STUDY OF NORBORNANE/NORBORNENE-FUSED TETRACYCLIC AZETIDINONES[1]

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ABSTRACT — Tetracyclic azetidinones 8, 9 and 12–17 were synthesized. In the cases of 8 and 9, the main component was isolated from the two-component product of the cycloaddition. The minor component was concentrated to give a mixture, from which a computer technique utilizing the known spectrum of the main component gave the proton resonance spectrum also of the minor component. Only one diastereomer could be isolated for the each of the analogues 12–17. Reaction of the 1,3-oxazine 3 with chloroacetyl chloride gave, besides the azetidinone 12, the 1,3-oxazine[2,3-b]-1,3-oxazin-4-one derivative 18. Configurations and conformations were determined by IR, $^{1}H$ and $^{13}C$ NMR spectroscopy.

## INTRODUCTION

In view of the great medicinal importance of the penicillins and cephalosporins containing an azetidinone ring, increasing interest is attached to β-lactams.[2] The methylene-bridged, partly saturated 1,3-[3] and 3,1-benzoxazines,[4-6] prepared earlier in our laboratory, readily undergo cycloaddition reactions with chloroacetyl chloride to give fused-skeleton azetidinones. This extension of skeleton rigid norborne- or norbornane fused isomeric 1,3-oxazines is of stereochemical interest. These tetracyclic β-lactams also seem promising from the point of view of biological activity, since the norbornane moiety is a component of many active compounds.[7] In the recent literature[8,9] the development of new pharmaceuticals from norbornane derivatives has been reported.

Accordingly, the object of the present work is the conversion into tetracyclic azetidinones of the tricyclic, fused-skeleton 1,3-oxazine derivatives we had prepared earlier from the diexo and diendo 2-(hydroxymethyl)-bicyclo[2.2.1]hex-5-enyl-3-amines[4-6] and by 1,4-cycloaddition from norbornene, norbornadiene and (hydroxymethyl)benzamides,[3] together with elucidation of the structures of the isomeric azetidinones obtained in the "acid chloride reaction".[10]

## SYNTHESIS

1,3-Aminoalcohols with norbornene skeleton, prepared by reduction from exo- and

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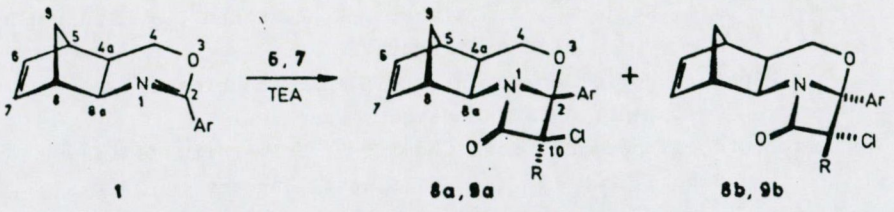
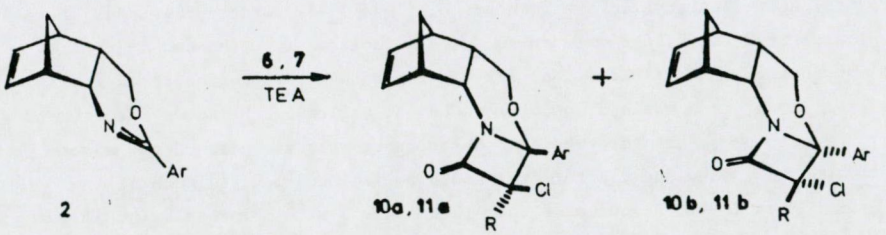
endo-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids,[4,11] were cyclized with imidates to 5,8-methano-2-(p-chlorophenyl)-r-4a,c-5,c-8,c-8a-tetrahydro-4H-3,1-benzoxazine (1) and 5,8-methano-2-(p-chlorophenyl)-r-4a,t-5,t-8,c-8a-tetrahydro--4H-3,1-benzoxazine (2).[4,6] The 2-substituted 5,8-methano-r-4a,c-5,6,7,c-8,c-8a-hexahydro-4H-1,3-benzoxazines (3 and 4) and 5,8-methano-2-(p-chlorophenyl)-r-4a,c-5,c-8,c-8a-tetrahydro-4H-1,3-benzoxazine (5) were synthesized from the appropriate (hydroxymethyl)benzamides by cycloaddition with norbornene and norbornadiene, respectively.[12]



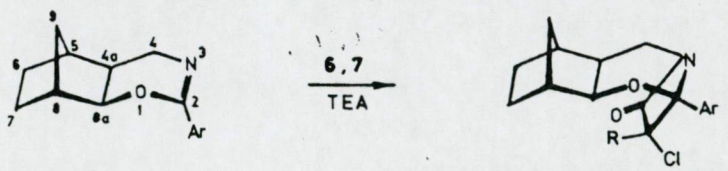

1 8a, 9a 8b, 9b

Ar : *p*Cl-Ph ; R: H (8a,b) or Cl (9a,b)



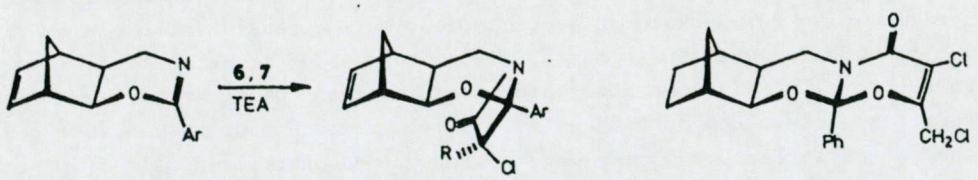

2 10a, 11a 10b, 11b

Ar: *p*Cl-Ph ; R: H (10a,b) or Cl (11a,b)




3 Ar: Ph
4 Ar: *p*Cl-Ph

12 Ar: Ph ; R: H 14 Ar: Ph ; R: Cl
13 Ar: *p*Cl-Ph ; R: H 15 Ar: *p*Cl-Ph ; R: Cl




5 16 R: H
17 R: Cl
18

Ar : *p*Cl-Ph

Compounds 1–5 were converted by means of chloroacetyl chloride (6) or dichloroacetyl chloride (7), in the presence of triethylamine, to the tetracyclic azetidinones 8–17. Two isomers each are possible for the tetracyclic dichloro derivatives (9, 11, 14, 15 and 17), which differ in the anellation of the oxazine and azetidinone rings, i.e. in the configuration of the carbon atom between the oxygen and nitrogen. In the case of the monochloro compounds (8, 10, 12, 13 and 16) two more isomers may exist, where the difference is in the mutual positions of the chlorine atom and the phenyl group. Two diastereomers each of 10 and 11 were isolated. Their

structure elucidation has previously been reported.[6] The new observation is now made that 11a (m.p. 137–139 °C) is converted, on heating to 180 °C, into the epimer 11b (m.p. 194–195 °C), i.e. the configuration of the 2R* carbon atom* changes to 2S*. Hence, 11b is the more stable isomer.

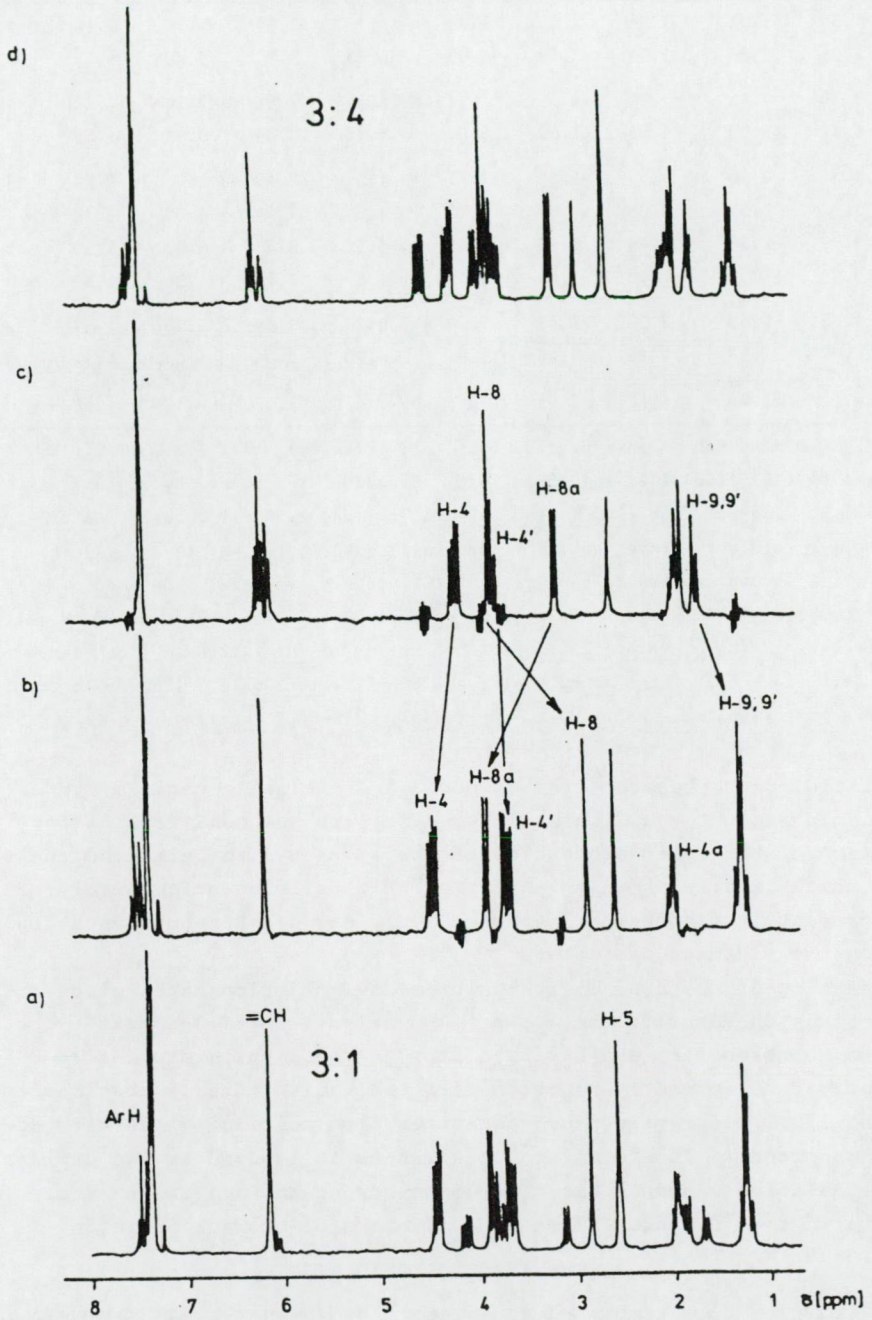



Fig.1. $^1$H NMR spectra of two diastereomeric mixtures of compounds 9a and 9b, with 9a-9b-compositions (a) 3:1 (m.p.: 123-125 °C) and (d) 3:4 (m.p.: 81-83 °C), and the computer-constructed spectra of the homogeneous diastereomers (b) 9a and (c) 9b in $CDCl_3$ solution at 250 MHz.

* In the Experimental (in the chemical names of the compounds) the numbering according to the IUPAC nomenclature is followed. However, in the text including the Figures and the Tables the numbering is different and uniform for all compounds investigated, in order to facilitate comparison of the spectrally analogous data.

Table 1. $^1$H NMR chemical shifts ($\delta_{TMS}$ = 0 ppm) of compounds 8a,b, 9a,b and 12-18 at 250 MHz in $CDCl_3$ solution.[a,b]

| Compound | H-4e' dd(1H) | H-4a' dd(1H) | H-4a m(1H) | H-5 s(1H) | H-6 dd(1H)[c] | H-7 dd(1H)[c] | H-8 s(1H) | H-8a d[d](1H) | H-9' endo[e] | H-9 exo[e] | H-10 s(1H) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 8a | 4.30 | 3.42 | 1.94 | 2.46 | 6.09 | 6.18 | 2.87 | 3.76 | 1.14 | 1.26[f] | 4.95 |
| 8b | 4.05 | 3.68 | 1.71 | 2.60 | 6.05 | 6.21 | 3.92 | 3.20 | 1.64[f] | 1.81 | 4.98 |
| 9a | 3.70 | 4.46 | 1.98 | 2.59 | 6.16 s (2H) | | 2.88 | 3.90 | 1.22 | 1.25 | - |
| 9b | 4.17 | 3.80 | 1.85 | 2.59 | 6.08 | 6.18 | 3.84 | 3.14 | 1.68 | 1.87 | - |
| 12 | 3.93 | 2.56 | ∿ 2.35[g] | 1.86 | ∿ 1.15[h], ∿ 1.5 | | 2.40[g] | 4.01 | 1.72 | 1.14[h] | 5.26 |
| 13 | 3.92 | 2.53 | ∿ 2.35[g] | 1.89 | ∿ 1.15[h], ∿ 1.5 | | 2.41[g] | 4.00 | 1.72 | ∿ 1.1[h] | 5.25 |
| 14 | 3.99 | 2.56 | ∿ 2.45[g] | 1.85 | ∿ 1.15[h], ∿ 1.5[i] | | 2.43[g] | 4.37 | ∿ 1.55[i] | ∿ 1.1[h] | - |
| 15 | 3.99 | 2.52 | ∿ 2.40[g] | 1.86 | ∿ 1.15[h], ∿ 1.5[i] | | 2.44[g] | 4.36 | ∿ 1.55[i] | ∿ 1.15[h] | - |
| 16 | 4.03 | 2.53 | ∿ 2.30 | 2.47 | 5.94 | 6.23 | 2.99 | 3.96 | 1.51 | 1.74 | 5.19 |
| 17 | 4.10 | 2.53 | 2.36 | 2.48 | 5.95 | 6.23 | 3.04 | 4.31 | 1.52 | 1.61 | - |
| 18 | 4.52 | 3.05 | 1.82 | 2.05 | 0.90[j], 1.05[k], 1.50[l] | | 2.42 | 3.19 | 1.96 | 1.24 | 4.07[e] 4.24[e] |

Notes: [a] IR νC=O band ($cm^{-1}$) in KBr: 1782 (8a, 13), 1774 (8b), 1792 (9a), 1770 (12), 1790 (14), 1803 (15), 1784 (16), 1801 (17) and 1672 (18); [b] Signal of the phenyl hydrogens: 7.40 (8a,b, 9b and 15), s, (4H), ∿ 7.38 and 7.46 (9a, 13 and 16) and 7.47 and 7.54 (17), resp., AA'BB'-type multiplet of 4H-intensity with very close central lines and 7.35-7.60, m, 5H (12, 14 and 18); [c] In case of 12-15 overlapping multiplets of 2-2H intensity (δH(exo) > δH(endo) [19]); [d] dd due to J(8,8a) coupling (c.f. Table 2) in case of 8a,b and 9a; [e] A or B part of an AB multiplet (2H), J(A,B): see Table 2 (8a,b, 9a,b, 12-18), for H-4 atoms of 18: 12.2 Hz; [f] Both lines of the A (8a) or B (8b) part (δA > δB) of the AB multiplet split by 1.7 (8a) or 1.5 (8b) Hz to triplets; [g,h,i] Overlapping signals; [j] H-7(endo); [k] H-6(endo); [l] H-6',7'(exo).

The azetidinones prepared from compound 1 are also isomeric mixtures, from which only the main product could be isolated as a pure compound. The different solubilities and chromatographic properties of the isomers also permitted the isolation of some epimeric mixtures in which an isomer originally occuring merely as a by-product was present in higher concentration. Only one diastereomer each could be isolated from the mixtures of isomers 12-17.

The reaction of compound 3 with chloroacetyl chloride takes place in two directions: besides the azetidinone 12, a 1,3-oxazino[2,3b]-1,3-oxazin-4-one derivative (18) fused to norbornane and having a nitrogen bridgehead could also be isolated; i.e. a derivative formed by reaction with two equivalents of chloroacetyl chloride. The synthesis of monocyclic dihydrooxazines from acyclic imines with acetyl chloride has been reported.[13] The formation of diketene is assumed as the explanation of the reaction. Relatively simple bicyclic compounds of the aza-ortho-ester type have been prepared from dihydro-1,3-oxazine by means of epoxide addition.[14]

## NMR SPECTROSCOPIC STUDY

### COMPUTER CONSTRUCTED $^1$H NMR SPECTRA AND STRUCTURE ELUCIDATION OF THE ANGULARLY FUSED DIASTEREOMERIC AZETIDINONES 8a,b AND 9a,b

The $^1$H NMR chemical shifts of compounds 8a,b, 9a,b and 12-17 are listed in Table 1, and the more important proton-proton coupling constants can be found in Table 2. The principles of determining the configurations and conformations have been described in a previous paper,[6] and hence only the essential features will be given below.

For all compounds examined, the expected diexo anellation of the oxazine ring to the norbornane or norbornene skeleton is unambiguosuly proved by the small value of

Table 2. Vicinal coupling constants of compounds 8a,b, 9a,b and 12 – 18 in Hz.

| Compound | J(4,4') | J(4,4a) | J(4',4a) | J(4a,8a) | J(5,6) | J(6,7) | J(7,8) | J(8,8a) | J(9,9') |
|---|---|---|---|---|---|---|---|---|---|
| 8a | 12.6 | 7.8 | 8.6 | 8.6 | 2.9 | 5.7 | 3.1 | 1.7 | 9.7 |
| 8b | 12.3 | 6.4 | 8.0 | 7.3 | 3.2 | 5.7 | 3.1 | 0.6 | 9.7 |
| 9a | 12.8 | 5.5 | 6.6 | 8.8 | | | | 1.2 | 8.2 |
| 9b | 12.1 | 6.6 | 12.2 | 7.2 | 3.2 | 5.7 | 3.0 | < 1 | 10.1 |
| 12 | 13.4 | 8.5 | 11.8 | 6.1 | | | | < 1 | 10.4 |
| 13 | 13.3 | 8.3 | 11.7 | 6.1 | | | | < 1 | 9.0 |
| 14 | 13.5 | 8.9 | 12.0 | 6.2 | | | | < 1 | 11.4 |
| 15 | 13.0 | 8.4 | 11.4 | 6.1 | | | | < 1 | ? |
| 16 | 13.5 | 8.2 | 11.7 | 6.2 | 3.2 | 5.7 | 3.0 | < 1 | ∿ 9 |
| 17 | 13.6 | 8.6 | 11.5 | 6.4 | 3.1 | 5.8 | 2.9 | < 1 | 9.3 |
| 18 | 13.2 | 8.1 | 11.5 | 6.7 | | | | < 1 | 10.5 |

the coupling constant J(8,8a) and the corresponding singlet and doublet structures of the H-8 and H-8a signal, respectively. Thus, the ring anellation remains unchanged during cyclization.

The structures of isomers 8a,b and 9a,b can be determined only in the knowledge of the spectral data on the homogeneous epimers. The computer of the Bruker WM-250 FT spectrometer was therefore utilized, and the spectra of the pure epimers, multiplied by an appropriate factor, were subtracted from the spectra of the isomeric mixtures, to obtain the spectra of the other epimers. The data derived in this way are given in Tables 1 and 2. The procedure is exemplified for two mixtures, with different compositions, of isomers 9a,b (Fig. 1).

A comparison of the spectral data reveals that in isomer 9a, isolated in the pure state and melting at 165 – 167 °C, the configuration of the C-2 atom is R*, i.e. the phenyl substituent is in the endo position; the other component of the mixture, 9b, is the 2S* exo-phenyl epimer. The main facts supporting this conclusion are as follows:

a) The H-9 and H-9' signals of compound 9a show a considerable upfield shift (0.62 and 0.46 ppm) as compared with epimer 9b. This is due to the anisotropic effect[15a] of the phenyl ring approaching H-9,9', causing shielding of the hydrogens situated "above" the plane of the ring.

b) The same effect can be observed for the H-8 signal; this signal is thus upfield shifted by 0.96 ppm as compared with that for 9b.

c) A downfield shift by 0.76 ppm, as compared with 9b, is found for the H-8a signal; this shift is due to the deshielding effect of the coplanar carbonyl group.[15b]

The directions of the above effects, unlike their magnitudes, are not influenced by the conformation of the flexible oxazine ring, and this must also be taken into account. As concerns the conformation, the deciding spectral data are the vicinal coupling constants of the C-4 methylene protons with H-4a. As shown by the molecular model, the oxazine ring may exist as two relatively stable conformers, which are interconvertible by ring inversion. Hence, when the configurations too are taken into account, there are four structures to be considered.

In the case of the configuration 9a with the twist-like conformation A (Fig. 2), O-3 is in the proximity of H-9'; the carbonyl oxygen is coplanar with H-8a, and H-4' (quasiaxial C-4 methylene hydrogen) is in the cis position to H-4a. The Newman projection viewed from the direction of the C-4,C-4a axis shows that the dihedral angles C-H(4a),C-H(4') and C-H(4a),C-H(4) are about 55° and 65°, respectively (Fig. 2). Couplings similar to each other in magnitude are therefore expected.

In the envelope-like conformation B, five atoms of the oxazine ring are nearly

coplanar; only O-3 lines out of the common plane. During inversion, the azetidinone ring moves "upwards" and the phenyl substituent "backwards": this does not cause considerable changes in the interactions described under (a)-(c), which are responsible for the mostly differing chemical shifts in the spectra of the isomers. There is, however, a decisive difference in the positions of the C-4 methylene hydrogens: the hydrogen in the cis position to H-4a (being parallel to the azetidinone ring) which in conformation A was axial is now in the equatorial position, while its equatorial trans counterpart in conformation A is now axial and situated above the plane of the phenyl ring. The dihedral angle made by C-H(4a),C-H(4a') is about 160°, whereas the C-H(4a),C-H(4e') angle is about 40°. Since the coupling constants J(4,4a) and J(4',4a) measured for 9a are 5.5 and 6.6 Hz, respectively, the preference of conformation A can be regarded as proved. Conformation A is favoured because of the smaller steric hindrance between the molecular skeleton and the phenyl ring in this case, and also because the phenyl group is here in the energetically more favourable quasiequatorial position relative to the oxazine ring, whereas in conformer B it should be quasiaxial.

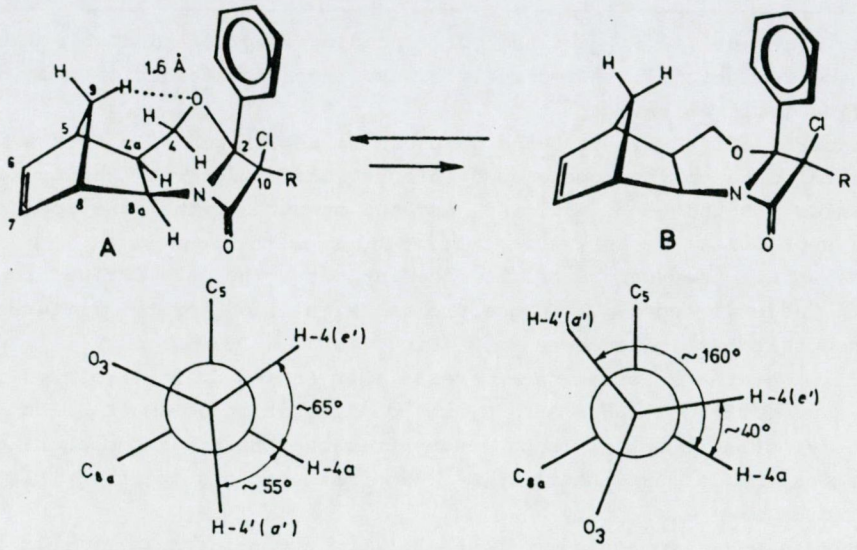



Fig. 2. Stable conformations of compounds 8a, 9a and the Newman projections from the direction of the C-4,C-4a axis.

The chlorine atom, which is trans to the phenyl ring in conformation A, is very close to H-4'(a'), with the notable consequence that the very general rule $\delta H_a < \delta H_e$, valid for cyclohexane and its hetero-analogues,[15c] is reversed in the case of 9a; the equatorial methylene hydrogen being the more shielded, while the chemical shift difference is also very marked (0.76 ppm).

This fact may be made the starting point in the determination of the C-10 configuration in the analogous monochloro-substituted analogue 8a. As compared with the epimer 8b, the 2R* configuration (endo phenyl group) can be inferred from the upfield shifts of H-8,9,9' signals and the downfield shift of H-8a signal, analogously to the case of 9a. On the other hand, conformation A, analogous to that of the dichloro compound 9a, follows from the similar coupling constants J(4,4a) and J(4',4a); 7.8 and 8.6 Hz. In the event of a similar stereostructure, a chlorine in trans position should give rise to a similar, anomalous shift relationship ($\delta H_a > \delta H_e$) for the C-4 methylene hydrogens. As this is not observed, the cis position of the phenyl and chlorine substituents relative to the azetidinone ring, and hence the R* configuration at C-10, are apparent. The assignments of the signals of the axial and equatorial methylene hydrogens are given on the basis of the relationship

J(4',4a) > J(4,4e), i.e. starting from the Karplus relation,[16] J(a,a)>J(a,e)>J(e,e). The steric position determined in this way for the chlorine atom is explained by the circumstance that, due to the coplanarity of the $C_2$–$O_3$ and $C_{10}$–$Cl_{trans}$ bonds, a strong electrostatic repulsion would appear between a trans chlorine atom and the O-3; the molecule can avoid this by assuming the R* configuration at C-10. This phenomenon may be regarded as a special case of the anomeric effect[17,18] well known in carbohydrate chemistry.

By an analogous train of thought, the conformation of 9b is obtained as follows. In the case of near situated endo H-9' and O-3, it is the oxygen which lies out of plane of the hetero ring in the envelope-like conformation; the methylene hydrogen in the cis position with the quasiaxial H-4a is "above" the plane of the phenyl ring; the dihedral angles made by C-H(4a),C-H(4') and C-H(4a),C-H(4) are ∿ 40° and 80°, respectively, and H-8 is coplanar with the carbonyl group (conformation C, Fig. 3). Steric hindrance appears between H-9' and the chlorine atom in the trans position to the quasiaxial phenyl ring.

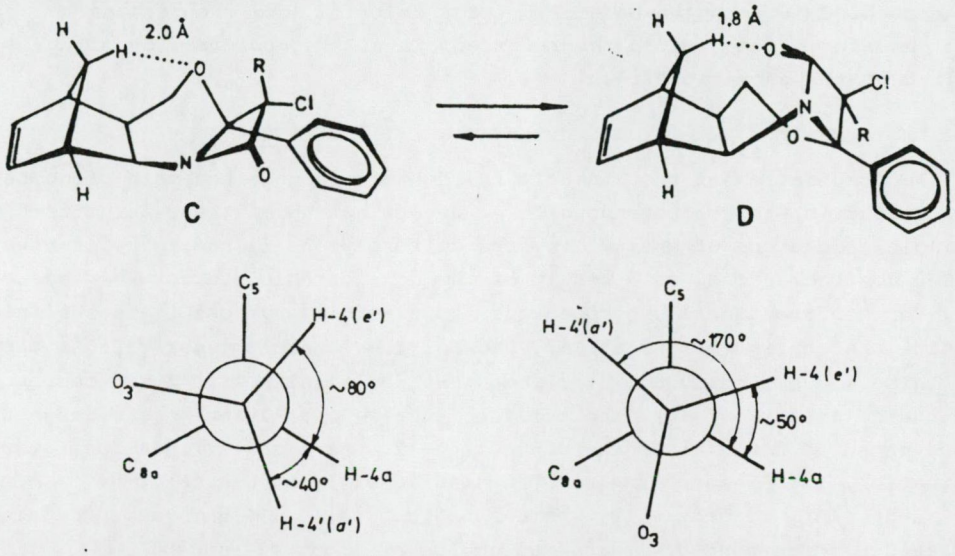



Fig. 3. Stable conformations of compounds 8b, 9b and the Newman projections from the direction of the C-4,C-4a axis.

In the inverse conformer D the six-membered hetero ring assumes the twisted boat form; the carbonyl oxygen remains in the proximity of H-8 and at the same time it also approaches close to the endo H-9'. In comparison to the situation in the stable conformer A of 9a, the methylene hydrogen, which is trans to H-4a and quasiaxial, is farther away from the chlorine, but nearer to the carbonyl oxygen. The dihedral angles C-H(4a),C-H(4) and C-H(4a),C-H(4') are now ∿ 50° and ∿ 170°, respectively. The phenyl ring is quasiequatorial and there is no steric hindrance between the trans chlorine and H-9'.

Thus, it is readily understandable that conformation D is the preferred one for compound 9b; unambiguous evidence in support of this is provided by the significantly different, but relatively high values of the coupling constants J(4,4a) = = 6.6 Hz and J(4',4a) = 12.2 Hz. The anomaly in the chemical shifts of the C-4 methylene hydrogens, observed in the case of 9a, is absent here; the signals of H-8 and H-9,9' are shifted downfield in comparison with those for 9a, due to the proximity of the carbonyl oxygen. On the other hand, the H-8a signal has suffered an upfield shift, since H-8a is farther removed from the carbonyl group and, as it is above the plane of the phenyl ring, it is more shielded.

Whereas the spectral data indicated the analogous conformation A for 8a and 9a, the spectral parameters of 8b suggest C as the preferred conformation. The most important evidence for this is given again by the similar and relatively smaller coupling constants J(4,4a) = 6.4 and J(4',4a) = 8 Hz, and also by the upfield shifts, which are slightly smaller for the signal of H-9, but higher for that of H-8 ( 0.55 and 1.05 ppm), than in the case of 8a (the corresponding differences in the pair 9a,b are 0.62 and 0.96 ppm). In the course of the inversion D → C the carbonyl oxygen is removed farther from H-9, and comes nearer to H-8. Conformation C is preferred in 8b, for in the absence of a trans chlorine atom the steric hindrance between the carbonyl oxygen and H-9' is suspended; though this hindrance does exist in the D form, the molecule can in this way eliminate the interaction between H-9' and $Cl_{trans}$, which would be even more unfavourable.

Conformation C is indicated by the upfield shift (3.68 ppm) of the H-4' signal as compared to 9b; in the C form H-4' is situated above the plane of the phenyl ring, and hence is more shielded. The preference of conformation C affords indirect evidence for the cis position of the chlorine atom and the phenyl ring (S* configuration of C-10); in the case of a trans chlorine (for the reasons described for 9b), conformation D would be preferred. Thus, the conformation of 8b is again explained by the anomeric effect.

ELUCIDATION OF THE STRUCTURES OF THE LINEARLY FUSED AZETIDINONES 12 – 17.

In the preparation of the linearly fused azetidinones, the main products 12-17 were isolated in stereohomogeneous form. Determination of their structures is fairly simple, since one of the two inverse conformations is unfavoured for both possible C-2 configurations, as a result of the considerable steric hindrance. Accordingly, for conformationally homogeneous "quasi-rigid" systems it is sufficient to elucidate the configurations at C-2, and for the monochloro derivatives those at C-10. This is substantiated by the fact that for all linearly fused compounds it holds that J(4,4a)<J(4',4a), the values of the J(4,4a) lying in the range 8.2-8.9 Hz, and those of J(4',4a) in the range 11.4-12.0 Hz (Table 2). In the favoured boat conformation, the dihedral angles of C-H(4a),C-H(4) and C-H(4a),C-H(4') bonds are ∿ 160° and ∿ 40°, respectively, whereas in the sterically unfavoured counterparts the same C-H bonds woud give dihedral angles of about 40° and 80°.

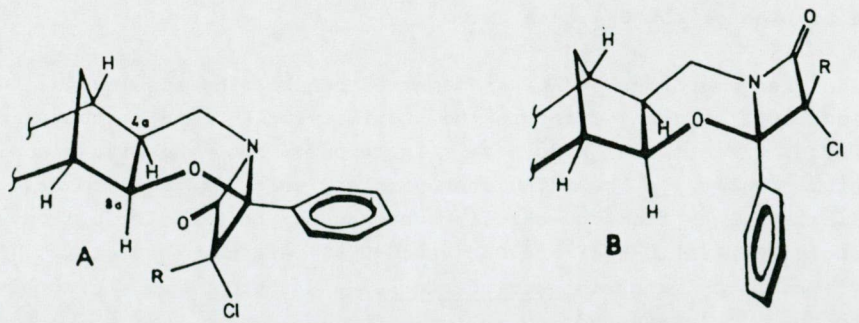



Fig. 4. Two diastereomeric structures of compounds 12-17, differing in configuration (2S* or 2R*) about the C-2 atom.

In view of the stable conformation, the S* configuration (A) at C-2 requires the quasiequatorial position of the phenyl substituent, and quasiaxial azetidinone ring (Fig. 4). The carbonyl oxygen is in the vicinity of H-4a, while the chlorine or hydrogen atom (which is trans to the phenyl ring, relative to the azetidinone ring) is in the proximity of H-8a.

The reverse situation is valid in the 2R* isomer (B) (Fig. 4). The β-lactam ring is quasiequatorial, the phenyl ring is quasiaxial, and H-4a,8a are situated

above the plane of the phenyl ring.

For structure A (2S*), therefore, a downfield shift of the H-4a signal would be expected, while the opposite shift of the H-4a and H-8a signals in conformation B (2R*).

In view of the data listed in Table 1, structure A, i.e. the S* configuration of C-2, can be assumed on the basis of the following arguments:

a) The H-4a atom is less shielded than in compounds 8a,b and 9a,b (the H-4a signal is shifted from 1.71-1.98 ppm into the region 2.30-2.45 ppm).

b) The H-8a shifts cannot be compared directly, as the neighbouring nitrogen is replaced by oxygen. However, it is known[15d] that the presence and vicinity of an amide nitrogen, e.g. in cyclohexanes, causes a geminal proton deshielding about 0.7 ppm greater than in the case of an ether oxygen substituent; accordingly, the observed downfield shift of the H-8a signal can be rationalized only by structure A.

c) A deciding argument in favour of configuration A is the very marked shift difference in the H-8a signals of the mono- and dichloro derivatives (0.36, 0.36 and 0.35 ppm for the pairs 12 – 14, 13 – 15 and 16 – 17, respectively.) The downfield shifts observed for the dichloro compounds are explained by the anisotropic effect of the chlorine atom.[15e] In the B isomers both chlorine atoms are far from H-8a, whereas in epimer A the chlorine trans to the phenyl ring is very close to H-8a. This is evidence of the cis position of the chlorine and phenyl substituents of the azetidinone ring, and of the S* configuration at C-10 in the monochloro compounds 12, 13 and 16.

The analogous structures of compounds 12-17 are obvious from the spectral data. Some proton resonance data on these compounds support the correctness of our conclusions concerning the stereostructures of the structural isomers 8a,b and 9a,b. Thus, the similar H-9,9′ shifts for 8b and 9b, and for 16 and 17, confirm the exo (2R*) configuration of the phenyl ring in the former compounds, and hence the endo-phenyl (2S*) configuration in 8a and 9a. The similar values of the coupling constants. J(4′,4a) for 12-17 and for 9b are evidence of conformation D for the latter compound. This differs from that of its counterpart 9a, and indirectly substantiates conformation A for 9a and 8a, and conformation C for 8b.

Finally, attention should be drawn to some other chemical shifts for compounds 12-15, which have a norbornane skeleton; these shifts are explained by the absence of the inductive and anisotropic effects of the $C_6$–$C_7$ double bond operating in the norbornene derivatives 8a,b, 9a,b, 16 and 17. The olefin hydrogen signals in the range 5.94–6.24 ppm are here substituted by the saturated methylene signals at about 1.5 and 1.15 ppm. The two signals correspond to the endo and exo hydrogens.[19] The exo H-9 in compounds 12-15 is considerably more shielded, due to the lack of the deshielding effect of the double bond.[20] On the other hand, the upfield shifts of the H-5,8 signals must be due to the absence of the -I effect of the olefinic bond.[15f]

## CARBON RESONANCE DATA ON THE AZETIDINONES

The carbon resonance shifts (Table 3) are in accordance with the structures of the compounds.

The data on pairs 8a,b and 9a,b could not be compared, as only isomers 8a and 9a were isolated as pure substances. However, the majority of the signals of isomer 8b could be identified from examination of a mixture containing this isomer as the main component. When these data are compared with those for 8a, the increased shielding of C-9 in 8a is marked. This is a consequence of the steric hindrance from the endo phenyl group (steric compression shift[21]). The same effect is responsible for the increased shielding of C-10 in compounds 12, 13 and 16 as compared with the posi-

Table 3. $^{13}C$ NMR chemical shifts ($\delta_{TMS}$ = 0 ppm) of compounds 8a,b,9a and 12–18 in $CDCl_3$ at 20 MHz.[a]

| Compound | C-2 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C-9 | C-10 | C = O |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 8a | 91.0 | 67.5 | 44.6[b] | 44.8[b] | 136.5[c] | 137.6[c] | 47.7 | 51.6 | 32.1 | 66.4 | 166.8 |
| 8b[f] | | 66.3 | 44.1[b] | 44.4[b] | 134.6 | 139.5 | 45.0 | 53.4 | 37.3 | 65.8 | |
| 9a | 93.4 | 66.8 | 44.7[b] | 45.0[b] | 136.0 | 139.1 | 46.5 | 51.6 | 34.1 | | 164.8 |
| 12 | 89.9 | 45.9 | 42.8[b] | 39.2[b] | 29.2 | 23.8 | 39.8[b] | 76.6 | 33.6 | 63.5 | 165.8 |
| 13[e] | 90.6 | 46.7 | 43.6[b] | 40.2[b] | 30.1 | 24.7 | 40.9[b] | 77.3 | 34.7 | 64.2 | 166.9 |
| 14 | 92.9 | 43.8 | 43.2[b] | 38.9[b] | 29.1 | 23.6 | 39.5[b] | 78.5 | 33.7 | 91.2 | 163.4 |
| 15 | 92.6 | 43.8 | 43.2[b] | 38.9[b] | 29.1 | 23.6 | 39.6[b] | 78.6 | 33.7 | 90.2 | 163.4 |
| 16 | 89.6 | 43.8[d] | | 41.5 | 134.4 | 140.8 | 48.4 | 72.6 | 40.5 | 63.2 | 165.8 |
| 17[g] | 93.6 | 45.0 | 45.1 | 39.7 | 133.5 | 142.3 | 49.9 | 76.2 | 42.0 | 91.3 | 163.8 |
| 18[h] | 110.4 | 42.0 | 40.7 | 38.8 | 27.8 | 25.2 | 40.7 | 79.0 | 33.5 | - | 157.8 |

Notes: [a] The lines of the benzene ring appear in the ranges as follows: C-1′: 133.9–136.8, C-2′–6′: 126.4–130.1 (In case of 9a the C-2′,6′ and C-3′,5′ signals are split due to restricted rotation of the benzene ring), C-4′: 135.0–136.6 (8a, 9a, 13, 15–17), 128.9 (12), 129.2 (14) and 130.5 (18); [b,c] Reversed assignment is also possible; [d] Two overlapping signals; [e] In DMSO-$d_6$; [f] In the spectrum of a mixture of 8a and 8b it was not possible to identify all lines of 8b; [g] Order of carbons determined by DEPT measurements; [h] $CH_2Cl$: 41.3; =CCl: 107.3; =C–O– : 153.2 ppm.

tional isomers 8. This supports the (2S*) configuration A, in which the trans H-10 atom is in steric hindrance with H-8a. The presumably even greater analogous effect of Cl-10 for the dichloro compounds could not be observed, as the data on 9a,b were not available.

STRUCTURE OF COMPOUND 18

The IR spectrum of compound 18 does not display the characteristic azetidinone carbonyl band.[22] Instead, the amide-I band at 1672 $cm^{-1}$, typical of simple amides, can be observed, precluding the possibility of a β-lactame structure. The amide-III band, characteristic of N-substituted δ-lactams,[23] is found at 1415 $cm^{-1}$. Besides the characteristic bands of the aromatic and aliphatic groups, the spectrum exhibits intense bands between 1300, and 945 $cm^{-1}$ due to polar bonds as C-O, C-Cl or C-N.

The $^1H$ NMR data (Table 1) afford evidence for the presence of the norbornane skeleton and the phenyl ring. The downfield shift of the H-4,4′ signals can be accounted for the anisotropy of the carbonyl group. The doublet split of the H-8a signal proves the unchanged diexo anellation of the norbornane and oxazine rings; the considerable upfield shift (∿ 0.8 ppm) of this doublet relative to that for the azetidinones 12–17, together with the somewhat smaller (∿ 0.6 ppm) H-4a shift in the same direction, reflects the parallel, "endo" position of the phenyl ring (R* configuration at C-2), since the anisotropic effect of the phenyl ring increases the shielding of H-4a,8a. In accord with this, H-9′(endo) is less shielded than in compounds 12–17. The conformation of the oxazine ring is the same as in the case of azetidinones 12–17; this follows unequivocally from the coupling constants J(4,4a) = = 8<J(4′,4a) = 11.5 Hz. In this conformation, if the configuration were C-2R* (exo phenyl), increased shielding of H-9′ would be observed, as a consequence of the proximity of the phenyl ring. The downfield shift of the H-5 signal by about 0.2 ppm is explained by the vicinity of the carbonyl group. Finally, the increased shielding of H-7(endo) is also attributable to the anisotropy of the phenyl group.

Further evidence for the proposed structure of 18 has been obtained by $^{13}C$ NMR. When the nine carbon signals of the norbornane-fused oxazine skeleton are compared with the signals of azetidinones, only the chemical shift of C-2 (110.4 ppm) is

appreciably altered: a downfield shift of about 20 ppm is observed. This is clear proof of the presence of a carbon in the vicinity of the three hetero atoms. (The analogous shifts for trimethyl and triethyl orthoformates are 115.0 and 112:5 ppm, resp.[24,25]) The signal of the chloro-substituted carbon is shifted to the range characteristic of olefins (107.3 ppm); the signals of the two carbons originating from the reaction of the second chloroacetyl chloride molecule are found at 41.3 (chloromethyl carbon) and 153.2 ppm (carbonyl group). The very large shift of the olefin signal is explained by the oxygen substitution and the electron distribution in the conjugated ene-one system; the preference for the limiting sturcture shown on the right-hand side of the mesomeric system $\geq C=C-C=\overset{\cdot\cdot}{O} \longleftrightarrow \geq C^{+}-C=C-\overline{O}|^{-}$ means that the electron density around the β-carbon is drastically reduced.[15g]

## EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-113v FT spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded at room temperature in $CDCl_3$ solution in 5 and 10 mm tubes, on Bruker WM-250 ($^{1}H$) and WP-80 SY ($^{13}C$) FT spectrometers at 250.13 ($^{1}H$) and 20.14 ($^{13}C$) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 5 kHz, pulse width 1 ($^{1}H$) and 3.5 ($^{13}C$) μs (∿ 20° and ∿ 30° flip angle), acquisition time 1.64 s, number of scans: 16 ($^{1}H$) and 1K-4K ($^{13}C$), computer memory 16K. Complete proton noise decoupling (∿ 3 W) for the $^{13}C$ spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement were used, line width 0.7 ($^{1}H$) and 1.0 Hz ($^{13}C$).

Preparation of compounds 8-17 (colourless crystalls, Table 4) rel-(1R,2R,5R,6R,9S,10S)- (8a) and rel-(1R,2R,5S,6S,9S,10S)-6-chloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (8b), rel-(1R,2R,5R,9S,10S)- (9a) and rel-(1R,2R,5S,9S,10S)-6,6-dichloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (9b), rel-(1R,2S,5R,6R,9R,10S)- (10a) and rel-(1R,2S,5S,6S,9R,10S)-6-chloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (10b), rel-(1R,2S,5R,9R,10S)- (11a) and rel-(1R,2S,5S,9R,10S)-6,6-dichloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (11b), rel-(1R,2S,4S,5R,9R,10S)-5-chloro-4-phenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (12), rel-(1R,2S,4S,5R,9R,10S)-5-chloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (13), rel-(1R,2S,4S,9R,10S)-5,5-dichloro-4-phenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (14), rel-(1R,2S,4S,9R,10S)-5,5-dichloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (15), rel-(1S,2S,4S,5R,9R,10R)-5-chloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridec-11-ene (16), and rel-(1S,2S,4S,9R,10R)-5,5-dichloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridec-11-ene (17). General procedure. The 1,3-oxazine 1, 2, 4, 5 (2.60 g; 0.01 mol) or 3 (2.25 g) was dissolved in dry benzene (5 ml) and a solution of 6 (1.10 g; 0.01 mol) or 7 (1.5 g; 0.01 mol) in benzene (5 ml) was added dropwise, with stiring, followed by the addition of TEA (1.0 g; 0.01 mol) dissolved in benzene (5 ml). The mixture was heated at 50 °C for 10 min and, after cooling, the solid was removed by filtration. The residue obtained on evaporation of the filtrate was applied to a silica gel column and eluted with benzene. The evaporation residue of the eluate was crystallized from a 1:1 mixture of benzene and petroleum ether to yield compound 8a, 9a, 10a, 11a or 12-17. Fractional crystallization of the material contained in the mother liquor gave the isomer 10b or 11b, or (in the cases of 8 and 9) an isomeric mixture, which was investigated as described above. The purity of the product was checked by DC (Kieselgel, benzene-ethanol-petroleum ether, 6:1:3).

rel-(1S,2S,4R,11R,12R)-7-Chloro-6-chloromethyl-8-oxo-4-phenyl-9-aza-3,5-dioxatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadec-6-ene (18). Compound 3 (2.25 g; 0.01 mol) was allowed to react with 6 (4.5 g; 0.04 mol) and TEA (4.0 g; 0.04 mol), as described above. Compound 12 crystallized first; fractional crystallization of the material in the mother liquor, using a mixture of benzene and petroleum ether, gave compound 18 (Table 4).

Epimerization of 11a. 11a (0.30 g, m.p. 137-139 °C) in a dry flask was heated in an oil bath at 180 °C for 5 min. After cooling, the residue was dissolved in benzene, applied to a silica gel column, and eluted with benzene. The crude product obtained on evaporation of the eluate and crystal-

Table 4. Physical and analytical data on compounds 8a,b – 11a,b and 12 – 18.

| Compound | M.p. °C | Yield % | Formula | Molecular weight | Analitical data (%), calculated – found C | H | N | C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| 8a | 154-156 | 37 | $C_{17}H_{15}NCl_2O_2$ | 336.22 | 60.73 | 4.50 | 4.17 | 60.50 | 4.27 | 4.12 |
| 8b[a] | 56-58 | | | | | | | 60.84 | 4.61 | 4.05 |
| 9a | 165-167 | 30 | $C_{17}H_{14}NCl_3O_2$ | 370.67 | 55.09 | 3.81 | 3.78 | 55.05 | 3.79 | 3.57 |
| 9b[b] | 81-83 | | | | | | | 55.02 | 3.80 | 3.59 |
| 10a | 180-182 | 18 | $C_{17}H_{15}NCl_2O_2$ | 336.22 | 60.73 | 4.50 | 4.17 | 60.54 | 4.32 | 4.11 |
| 10b | 146-148 | 21 | | | | | | 60.81 | 4.56 | 4.11 |
| 11a | 137-139 | 17 | $C_{17}H_{14}NCl_3O_2$ | 370.67 | 55.09 | 3.81 | 3.78 | 54.93 | 3.75 | 3.70 |
| 11b | 194-195 | 24 | | | | | | 54.85 | 3.72 | 3.65 |
| 12 | 140-141 | 34 | $C_{17}H_{18}NClO_2$ | 303.79 | 67.21 | 5.97 | 4.61 | 67.30 | 5.99 | 4.68 |
| 13 | 171-173 | 39 | $C_{17}H_{17}NCl_2O_2$ | 338.24 | 60.36 | 5.07 | 4.14 | 60.29 | 5.02 | 4.17 |
| 14 | 127-129 | 40 | $C_{17}H_{17}NCl_2O_2$ | 338.24 | 60.36 | 5.07 | 4.14 | 60.53 | 5.14 | 4.03 |
| 15 | 140-142 | 44 | $C_{17}H_{16}NCl_3O_2$ | 372.68 | 54.79 | 4.33 | 3.76 | 54.48 | 4.13 | 3.82 |
| 16 | 162-164 | 42 | $C_{17}H_{15}NCl_2O_2$ | 336.22 | 60.73 | 4.50 | 4.17 | 60.79 | 4.58 | 4.03 |
| 17 | 108-109 | 37 | $C_{17}H_{14}NCl_3O_2$ | 370.67 | 55.09 | 3.81 | 3.78 | 55.21 | 3.90 | 4.01 |
| 18 | 188-190 | 26 | $C_{19}H_{19}NCl_2O_3$ | 380.27 | 60.01 | 5.04 | 3.68 | 60.14 | 5.19 | 3.58 |

Notes: [a] Diastereomeric 1:3 mixture of 8a and 8b; [b] Diastereomeric 3:4 mixture of 9a and 9b.

lized from a 1:1 mixture of benzene and petroleum ether was the epimer 11b (colourless crystals, m.p. 194-195 °C), having identical IR, $^1H$ and $^{13}C$ NMR spectra with 11b.

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# Preparation and Steric Structure of 3(2*H*)-Pyridazinones and 1,2-Oxazin-6-ones Fused with Three- to Six-membered Saturated Carbocycles or Norbornane Skeleton [1]

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**Summary.** Reactions of *cis*-2-(4-methylbenzoyl)-cyclopropane- (**1**) and -cyclobutanecarboxylic acids (**2**), the stereoisomeric cyclohexyl homologues (**3** and **4**), and di-*endo*-3-(4-methylbenzoyl)-bi-cyclo-[2.2.1]heptane-2-carboxylic acid (**5**) with hydrazines yield the cycloalkane-condensed (3(2*H*)-pyridazinones **6–9** and the norbornane di-*endo*-fused derivatives **10**. With hydroxylamine, compounds **1** and **3–5** were transformed to the cycloalkane- and norbornane-condensed 1,2-oxazin-6-ones **11–14**. Transformation of **3–5** led to the *trans*-hexahydroanthrone **17a** and its methylene-bridged analogue **24**. From the stereoisomeric hexahydro-1(3*H*)-isobenzofuranones **20** and **21**, the partly saturated anthrones were also prepared; the products (**16b** and **17b**) contain the methyl substituent in position 6. On reduction, **16b** yield the 2-methyloctahydroanthracene **22**. The structures of the compounds were proved by $^1$H and $^{13}$C NMR spectroscopy, making use of NOE, DEPT, and CH-COSY techniques.

**Keywords.** Cycloalkanes; Heterocycles; *Friedel–Crafts* acylation; Isomerization; Methyloctahydroanthracen-9-ones; Reduction; *LAH*/$AlCl_3$.

**Synthese und räumliche Struktur von mit drei- bis sechsgliedrigen gesättigten Homocyclen oder Norbornan kondensierten 3(2*H*)-Pyridazinonen und 1,2-Oxazin-6-onen**

**Zusammenfassung.** Die Reaktion von *cis*-2-(4-methylbenzoyl)-cyclopropan- (**1**) und -cyclobutancarbonsäuren (**2**), der stereoisomeren cyclohexyl-Homologen (**3** und **4**) und von di-*endo*-3-(4-methylbenzoyl)-bicyclo[2.2.1]heptan-2-carbonsäure (**5**) mit Hydrazinen ergibt die cycloalkankondensierten 3(2*H*)-Pyridazinone **6–9** und das methylenüberbrückte di-*endo*-Derivat **10**. Die Verbindungen **1** und **3–5** wurden mit Hydroxylamin zu den cycloalkan- und norbornankondensierten 1,2-Oxazin-6-onen **11–14** umgesetzt. **3–6** reagierten zum *trans*-Hexahydroanthron **17a** und seinem methylenüberbrückten Analogen **24**. Die teilweise gesättigten Anthrone wurden auch aus den stereoisomeren Hexahydro-1(3*H*)-isobenzofuranonen **20** und **21** hergestellt (**16b** und **17b**), wobei der Methylsubstituent jedoch in Position 6 lokalisiert ist. Reduktion von **16b** ergab das 2-Methyloctahydroanthracen **22**. Die Strukturen der Verbindungen wurden durch NMR-Spektroskopie abgesichert ($^1$H, $^{13}$C, DEPT, CH-COSY, NOE).

## Introduction

In recent years, one of our main topics has been the synthesis and conformational analysis of fused-skeleton saturated and partially saturated six-membered 1,3-heterocycles [2–4]. One aim of these investigations was to prepare potential pharmacons [5]; the stereochemical aspects which have proved to be of considerable interest [6, 7], must also be emphasized.

Our earlier work was mainly related to six-membered 1,3-heterocycles which were *cis*- or *trans*-fused with normal-ring carbocycles (*e.g.* cyclopentane, cyclohexane, cyclohexene and cycloheptane), or with norbornane or norbornene.

The present work describes the synthesis of several small ring (cyclopropane- and cyclobutane-fused) analogues of some of the earlier heterocycles. An important feature of the compounds described here and in further papers to be published [8] is that the synthons used are 2-aroyl-1-cycloalkanecarboxylic acids [9, 10] which yield fused-skeleton heterocycles containing an aroyl group in the neighbourhood or on a bridgehead carbon atom in the fused heterocycle. In our previous work, the starting materials were stereohomogeneous *cis*- and *trans*-1,2-disubstituted 1,3-difunctional alicyclic compounds or stereohomogeneous 1,2-di-*endo*- or 1,2-di-*exo*-substituted 1,3-difunctional norbornane derivatives: β-hydroxy acids, β-amino acids or stereoisomeric 1,3-aminoalcohols either with a secondary hydroxy group and aminomethyl group or a hydroxymethyl group and an amino group on the carbocycles. In comparison with our earlier investigations, the recent modification in the structure results in essential changes from both structural and pharmacological aspects. Our aim was the preparation of pharmacologically active compounds. The 2-aroylcyclohexanecarboxylic acids and their cyclic derivatives have been reported to have anorectic and hypotensive effects [11, 12].

## Results and Discussion

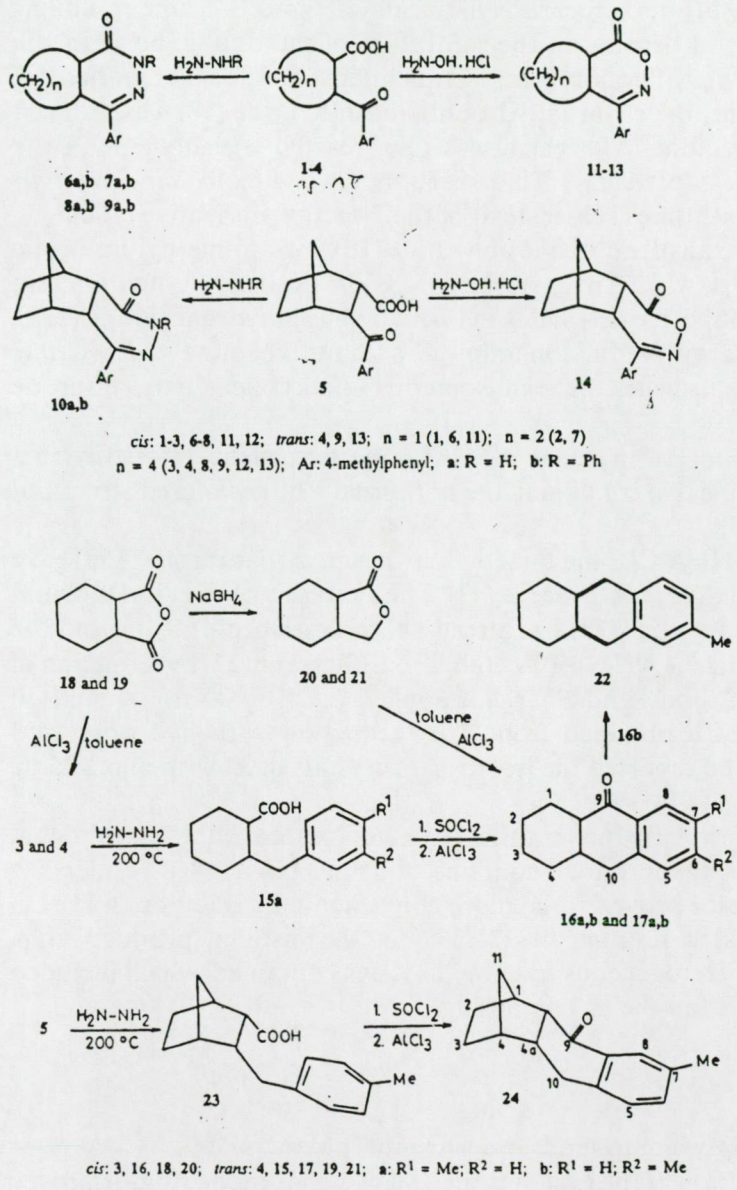
### *Syntheses*

*cis*-2-(4-Methylbenzoyl)-cyclopropane-(**1**) and -cyclobutanecarboxylic acids (**2**), *cis*-(**3**) and *trans*-2-(4-methylbenzoyl)-cyclohexanecarboxylic acids (**4**) and di-*endo*-3-(4-methylbenzoyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**5**), prepared according to the literature or analogously from di-*endo*-norborane-2,3-carboxylic anhydride by *Friedel-Crafts* acylation, were cyclized with hydrazine hydrate and phenylhydrazine to the cyclopropane-, cyclobutane- and cyclohexane-*cis*-fused 4,5-dihydro-3-(2*H*)-pyridazinones (**6a**, **7a**, **8a**), the corresponding *trans* derivative (**9a**) and their 2-phenyl derivatives (**6b**–**9b**) (Scheme 1).

For pharmacological aims, the analogous norbornane-di-*endo*-condensed pyridazin-3(2*H*)-ones (**10a**, **b**) were also prepared. As potential drugs, the non-condensed or differently substituted derivatives of the 4-5-dihydropyridazinones have already been synthesized [10, 12, 13].

With hydroxylamine hydrochloride, synthons **1** and **3**–**5** yielded the cyclopropane-*cis*- (**11**), cyclohexane-*cis*- (**12**) and *trans*- (**13**), and norbornane-di-*endo*-condensed (**14**) 4,5-dihydro-1,2-6*H*-oxazin-6-ones.

As the aroylcyclohexanecarboxylic acids looked to be also suitable for the synthesis of partially saturated anthracene derivatives, synthons **3**–**5** were reduced




**Scheme 2**

by the *Wolff–Kishner* method. The product obtained from both **3** and **4** was the *trans*-2-(4-methylbenzyl)-cyclohexanecarboxylic acid [14–16] **15a** while the reduction of **5** led to the corresponding norbornane derivative (**23**) (Scheme 2).

The isomerization of the *cis* compound **3** persumably took place during the vigorous hydrazine reduction (200 °C, KOH). For dihydrouracils, *cis-trans* inversion on the action of acids, bases or heating is already known [17]. In the present case, the isomerization **3**→**15a** was proved by further reactions. Reduction and cyclization of the *cis* (**3**) and the *trans* synthon (**4**) gave the same *trans* compound (**17a**). The configuration of the fixed methylene-bridged di-*endo* analogue **5** was not changed by the reduction.

From *cis*-4-cyclohexene-1,2- and di-*endo*-5-norbornene-2,3-dicarboxylic anhydride, the preparation of the ketocarboxylic acids of types **3–5** under similar conditions was unsuccessful because of the saturation of the double bond in the *Friedel–Crafts* reaction. We will report this reaction later. Thus, for the synthesis of the *cis*-hexahydroanthrone, the *cis*-hexahydrophthalic anhydride (**18**) was reduced with $NaBH_4$ to the *cis*-lactone (**20**), which was then reacted with toluene in the presence of a large excess of $AlCl_3$. This reaction gave directly *cis*-6-methyl-1,2,3,4,4a,9a-hexahydroanthrone (**16b**) instead of the 7-methyl derivative (**16a**).

Starting from *trans*-hexahydrophthalic anhydride (**19**), *trans*-6-methyl-anthrone (**17b**) was formed in this way. Thus, acylation, *Wolff–Kishner* reduction and cyclization of the *trans* anhydride (**19**) yields the 7-methyl hexahydroanthrone (**17a**), whereas the route starting with reduction followed by simultaneous *Friedel–Crafts* acylation and cyclization furnishes the regioisomeric 6-methyl-hexahydroanthrone (**17b**).

On cyclization of **23** in the presence of $AlCl_3$, the tetracyclic 1,4-methylene-bridged hexahydroanthrone (**24**) containing the norbornane di-*endo*-fused structural moiety was formed.

On reduction with *LAH*/$AlCl_3$, the 6-methyl-*cis*-hexahydroanthrone (**16b**) gave the corresponding *cis*-octahydroanthracene (**22**). The synthesis of the *cis*- (**16a**) and *trans*-octahydroanthracen-9-one (**17a**) has already been described [14–16] and the preparation of 6-methyl-1,2,3,4,4a,9,9a,10-octahydroanthracene (**22**) by reduction of **16a** is also known [14]. *Mathur* and *Bhargava* applied the *Wolff–Kishner* method to reduce the derivative **16** obtained from **3** by reduction with hydrazine and subsequent cyclization, and reported the isolation of crystals of **22** with m.p. 126 °C in very good yield (90.3%) [14].

We repeated their work with **16b**, but this gave a colourless liquid (yield 64%). $^1$H NMR indicated that the product contains starting **16b** (11%) besides **22**. Reduction of **16b** with *LAH* proved to be more convenient; for isolation, a HPLC method was applied, which resulted in **22** (35% of the distilled product), m.p. 77–80 °C. In addition, a heterogeneous fraction (53%) was obtained, which included derivatives partly saturated in the aromatic ring.

*Structure*

The spectral data of the new compounds are listed in Tables 1 and 2.

For **16b**, the *cis* anellation of the cyclohexane and cyclohexenone rings is proved by the broad $^1$H NMR signal (~15 Hz) of the anellated methine hydrogen vicinal to the carbonyl group. It also shows that the carbonyl group is *axial* and that the methylene group in the cyclohexenone ring is *equatorial*, which is in accordance with the higher spatial requirements of the methylene group compared to those of the carbonyl group [18]. In the second relatively stable conformation with the cyclohexane ring in the chair conformation, the two functional groups adopt the reverse positions. The 15 Hz signal width excludes an *axial* methine hydrogen relative to the cyclohexane ring, because large *diaxial* splittings would cause a broader signal [19]. In accordance, the corresponding signal width of the *trans* analogues **17a, b** is ~30 Hz (see Table 1). For **17a, b**, this signal appears 0.5 ppm upfield of that measured for **16b**, which is a consequence of the *equatorial* → *axial*

**Table 1.** IR and $^1$H NMR data

| Compd. | $\nu_{C=O}$ $cm^{-1}$ | $CH_3$ *s*(3H) | CH(anellated)[a] 2 × m (2 × 1H) | | $CH_2$ and CH[b] groups 1–5 m's (2/4/8/10/12H)[c] | ArH 1–4 m's (3/4/9H)[d] |
|---|---|---|---|---|---|---|
| **6a** | 1657 | 2.37 | 2.15 | 2.45 | 0.80[e] 1.78[f] | 7.20[g] 7.69[g] |
| **6b** | 1659 | 2.36[h] | 2.3[h] | 2.6 | 1.0[e] 1.80[f] | ~7.2[i] 7.40[j] 7.50[k] 7.73[g] |
| **7a** | 1659 | 2.35[h] | 3.38 | 3.88 | 2.35[h,l] ~2.6[i] | 7.17[g] 7.52[g] |
| **7b** | 1681 | 2.35[h] | 3.52 | 3.90 | 2.35[h,l] ~2.6[i] | 7.16[g] 7.25[l] 7.42[j] 7.55[m] |
| **8a** | 1667 | 2.37 | 2.75 | 3.12 | 1.25–1.74[n] 1.80[l] 2.55[o] | 7.20[g] 7.66[g] |
| **8b** | 1677 | 2.37 | ~2.9 | 3.20 | 1.3–1.9[p] 2.60[o] | ~7.2[i] 7.40[j] 7.60[k] 7.72[g] |
| **9a** | 1674 | 2.36 | ~2.1[h] | 2.60 | 1.0–1.4[m] ~1.85[q] ~2.1[h,l] 2.45[o] | 7.18[g] 7.22[g] |
| **9b** | 1688 | 2.35 | 2.25 | 2.72 | 1.0–1.5[m] 1.7–1.9[q] ~2.15[l] ~2.5[o] | ~7.2[i] ~7.3[m] 7.55[k] |
| **10a** | 1664 | 2.38 | 3.00 | 3.48[y] | 1.2–1.8[n] 2.64[b,r] 2.91[b,o,r] | 7.20[g] 7.60[g] |
| **10b** | 1644 | 2.36 | 3.10 | 3.60[y] | 1.2–1.8[n] 2.70[b,r] 3.01[b,o,r] | 7.2–7.8[h] 7.26[g,h] 7.66[g,h] |
| **11** | 1740 | 2.41[h] | ~2.35[h] | 2.55 | 1.30[e] 1.95[f] | 7.27[g] 7.68[g] |
| **12** | 1768 | 2.38 | 2.86 | 3.15 | 1.3–1.9[p] ~2.5[o] | 7.23[g] 7.65[g] |
| **13** | 1762 | 2.39 | 2.23 | 2.75 | 0.9–2.1[s] | 7.24[m,r] |
| **14** | 1751 | 2.39 | 3.10 | 3.50 | 1.2–1.7[n] 2.59[b,r] 2.94[b,o,r] | 7.24[g] 7.58[g] |
| **16b** | 1671 | 2.33[h] | ~2.33[h] | 2.62 | ~1.45[l] ~2.15[o] 2.85[t] 2.97[t] | 7.00[u] 7.05[v] 7.92[w] |
| **17a** | 1677 | 2.36[h] | ~2.1 | ~2.4[h] | ~1.3[m] 1.7–2.0[m] 2.70[t] 2.83[t] | 7.10[w] 7.25[v] 7.82[u] |
| **17b** | 1679 | 2.37[h] | ~2.1 | ~2.4[h] | ~1.3[m] 1.7–2.0[m] 2.70[t] 2.82[t] | 7.00[u] 7.10[v] 7.91[w] |
| **22** | – | 2.27 | ~2.0[h] | | 1.3–1.7[s] ~2.7[m] | 6.95–7.00 |
| **24** | 1669 | 2.36[x] | 2.6 | ~2.8[h,y] | ~1.0[l] ~1.25[i] 1.38[z] 1.53[z] ~2.8[b,y] 3.00[t] | 7.10[w] 7.25[v] 7.67[u] |

Chemical shifts in ppm, $\delta_{TMS} = 0$ ppm, coupling constants in Hz, in $CDCl_3$ solution at 250 MHz. Further IR data (in KBr discs): $\nu_{NH}$ band: 3200 (**6a**), 3225 (**7a**), 3212 (**8a**), 3236 (**9a**), 3192 (**10a**). $\delta_{NH}$ signal ($^1$H NMR): 9.70 (**6a**), 9.20 (**7a**), 9.42 (**8a**), 9.05 (**9a**), 8.60 (**10a**). [a] In cyclohexenone (**24**), in hetero ring (**10a, b** and **14**). [b] Anellated hydrogens of the cyclopentane rings in **10, 14** and **24**. [c] Total intensity: 10H (**16, 17, 24**), 12H (**22**), 8H (**8, 9, 10, 12–14**), 2H (**6, 11**), 4H (**7**). [d] Total intensity: 3H (**16b, 17, 22, 24**), 4H (**6a, 7a, 8a, 9a, 11–14**), 9H (**6b, 7b, 8b, 9b, 10b**). [e] Quartet-like multiplet of the cyclopropyl methylene-H *trans* to the anellated hydrogens, $J \sim 5$ Hz. [f] *dt* signal of the *cis* cyclopropyl methylene-H, $J \sim 9$ and 5 Hz. [g] A or B part of AA' BB' spin system; 2 × ~s (2 × 2H), $J \sim 8$ Hz. The upfield signal originates from H-3,5, the downfield one from H-2,6. [h] Overlapping signals. [i,l,m,n,p,q,s] Overlapping signals with total intensity: 3/1/4/6/7/2/8. [j] H-3,5 (phenyl), ~*t*(2H). [k] H-2,6 (phenyl), ~d(2H), $J \sim 8.8$ Hz. [o] Signal of the hydrogen coplanar to the $\beta$-carbonyl group. [r] Singlet-like signal. [t] A or B part of ABX spin system, dd (1H), *J*: 16.7, 6.0 and 5.1 (**16b**), 16.2, 11.2, 4.2 (**17a, b**), 17.0, 8.8, ? (**24**). [u] Coalesced *d* ($j < 2$ Hz). [v] dd. [w] d ($J \sim 8$ Hz). [x] Overlapping signals of one of the anellated H's (norbornane, H-4) and the methyl group (4H). [y] Overlapping signals of H-1, 9a, $10_{ax}$ (3H). [z] AB spectrum (2 × d, 2 × H) of the bridging methylene hydrogens; $J = 9.5$ Hz

**Table 2.** $^{13}C$ NMR chemical shifts[a,b]

| Compd. | $CH_3$ | Cycloalkane ring | | 4-Methylphenyl and phenyl groups | | | | | | $CH_2^c$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $CH_2$ | CH | C-1 | C-2 | C-6 | C-3 | C-5 | C-4 | C=N | C=O |
| **6a** | 21.3 | 8.8 | 18.5 19.0 | 132.8 | 126.2 | | 129.2 | | 139.9 | 148.2 | 166.6 |
| **6b** | 21.1 | 9.6 | 19.1 20.1 | 132.8 | 126.2[d] | | 129.0[e] | | 126.2[d] | 148.0 | 164.4 |
| | | | | 141.9 | 124.8 | | 128.2[e] | | 139.8 | | |
| **7a** | 22.5 | 27.8 28.8 | 35.1 35.5 | 133.8 | 127.1 | | 130.8 | | 140.5 | 149.7 | 168.7 |
| **7b** | 21.0 | 26.4 27.4 | 34.5 35.1 | 131.6 | 125.8[e] | | 129.0[f] | | 139.5 | 149.2 | 165.3 |
| | | | | 141.8 | 124.8[e] | | 128.1[f] | | 126.1 | | |
| **8a** | 21.2 | 22.0 23.3 24.3 25.5 | 35.8 36.1 | 131.8 | 125.7 | | 129.3 | | 139.7 | 153.8 | 169.9 |
| **8b**[g] | 21.1 | 21.8 23.9 24.9 25.6 | 36.2 37.2 | 131.9 | 125.9[d] | | 129.2[e] | | 141.7 | 154.3 | 167.2 |
| | | | | 139.8 | 124.6 | | 128.1[e] | | 125.9[d] | | |
| **9a** | 21.3 | 25.1 25.4 25.8 30.1 | 38.7 40.3 | 133.2 | 127.6 | | 128.8 | | 138.7 | 157.9 | 170.1 |
| **9b** | 21.3 | 25.1 25.3 26.3 30.3 | 38.7 41.4 | 133.3 | 127.8 | | 128.8[e] | | 138.8 | 158.7 | 167.9 |
| | | | | 141.3 | 124.7 | | 128.4[e] | | 126.2 | | |
| **10a**[g] | 21.3 | 25.1 23.5 39.1[h] | 41.2 41.3 43.1[d] | 133.3 | 126.1 | | 129.3 | | 139.7 | 149.5 | 167.6 |
| **10b** | 21.4 | 23.7 25.2 39.5[h] | 41.9 42.3 | 133.4 | 126.4[e] | | 129.3[f] | | 139.7 | 149.1 | 166.2 |
| | | | 43.4 44.3 | 141.9 | 125.3[e] | | 128.5[f] | | 126.6 | | |
| **11** | 21.4 | 13.4 | 17.0 18.9 | 128.8 | 126.8 | | 129.6 | | 141.8 | 158.3 | 167.6 |
| **12** | 21.1[e] | 21.2[e] 23.6 25.0 25.9 | 35.4 36.6 | 128.7 | 126.4 | | 129.5 | | 141.1 | 164.6 | 171.7 |
| **13** | 21.4 | 24.7 25.9 29.7 | 37.6 38.9 | | 127.7[d] | | 129.2 | | 140.1 | 168.0 | 172.1 |
| **14**[g] | 21.4 | 23.5 25.2 39.1[h] | 39.8 41.3 | 130.0 | 126.7 | | 129.6 | | 141.2 | 158.5 | 169.7 |
| | | | 42.4 43.7 | | | | | | | | |
| **16b**[g] | 21.1 | 23.1 23.6 25.1 28.5 | 35.6 47.8[i] | 129.3 | 129.2 | 142.3 | 126.8[e] | 127.0[e] | 143.4 | 33.0 | 198.6 |
| **17a**[g] | 20.7 | 25.3 25.7 25.9 33.9 | 39.9 51.6[i] | 131.8 | 127.0 | 135.7 | 140.3 | 128.2 | 133.8 | 36.6 | 199.2 |
| **17b** | 21.5 | 25.3 25.7 25.9 33.9 | 39.9 51.7[i] | 129.9 | 128.9 | 143.3[e] | 127.2[f] | 127.4[f] | 143.7[e] | 37.1 | 192.2 |
| **22** | 21.0 | 23.5[d] 29.1[d] | 33.8[d] | 135.5 | 129.1[e] | 134.7[f] | 132.6[f] | 129.7[e] | 125.7 | 32.7[j] | 32.2[j] |
| **24**[g] | 21.0 | 22.9 24.8 40.0[h] | 35.6 43.0[i] | 134.2 | 126.5 | 136.2 | 140.1 | 128.2 | 134.6 | 28.1 | 203.1 |
| | | | 43.8 49.2[i] | | | | | | | | |

[a] Solvent: $CDCl_3$; *DMSO*-$d_6$ for **7a**, [b] Measuring frequency: 62.89 MHz; for **6b**, **7a**, **b**, **8b**, **11**, **12** and **16b**: 20.14 MHz. [c] $CH_2$ (Pos. 10) for **16b**, **17a**, **b**, **22** and **24**. [d] Two overlapping lines. [e,f,j] Interchangeable assignments. [g] Assignments were proved by DEPT measurement. [h] Bridging methylene in the norbornane moiety. [i] Vicinal to the carbonyl group

change [19, 20a]. Similarly, the 15 Hz signal width and the downfield shift of the hydrogen vicinal to the carbonyl group as compared to the signals for the *trans* isomers **9a, b** suggest a conformer containing an *axial* carbonyl group for the *cis*-anellated compounds **8a, b**.

This also holds for the former of the *cis-trans* pair **12–13**: the signal of the methine hydrogen vicinal to the carbonyl group is sharper (signal width ~8 Hz; ~30 Hz for **12**) and downfield shifted (by 0.63 ppm). Thus the carbonyl group is *axial* to the cyclohexane chair ring in the preferred conformation.

Further proof of the *cis-trans* structures is that the sum of the cyclohexane carbon shifts is by 18.7 ppm smaller for *cis* **16b** with respect to *trans* **17b** [20b]. For **17a** and **17b**, the *trans*-anellated structure follows from the same magnitude of the carbon shifts (within measurement error, *cf.* Table 2).

For **6a, b** and **11**, the significantly different shielding and signal splitting of the two cyclopropane methylene hydrogens are noteworthy. The anisotropic effect of the hetero ring causes a strong upfield shift of the signal of the methylene hydrogen which is situated above the ring and *trans* to the vicinal hydrogens. The assignment based on the higher *cis* vicinal coupling [20c] is beyond any doubt.

For **10a, b** and **14**, the double doublet pattern of the signal of the heterocyclic anellated hydrogens [21] unambiguously proves the di-*endo* annelation of the hetero ring and the norbornane moiety.

The position of the methyl group in compounds **16b**, **17a, b** and **24** follows unambiguously from the $^1$H NMR signals of the aromatic hydrogens. From the AMX system characteristic for 1,2,4-trisubstituted benzene derivatives, the assignment of the aromatic protons is obvious [20d]. The substituent effect [20e] (strong deshielding) of the *ortho* carbonyl group is decisive with regard to the *meta* or *para* position of the methyl group relative to the carbonyl group. As the coupling of the downfield H-8 signal in the $^1$H NMR spectra of **16b** and **17b** is 8 Hz, the methyl group must be in position 6; this splitting is due to an *ortho* interaction with H-7. In **17a** and **24**, the coupling of the downfield H-8 doublet is <2 Hz, which indicates a methyl group in position 7; the coupling constant indicates a *meta* interaction of 6-H and 8-H.

For **16b**, the assignment of the H-9a signal was proved by combined DEPT and two-dimensional heteronuclear shift correlation (CH-COSY) methods. The signals of the two anellated carbons (C-4a,9a) at 35.6 and 47.8 ppm were identified by DEPT, and the $^1$H NMR signal (2.62 ppm) corresponding to the downfield resonance (47.8 ppm) was located in the CH-COSY-spectrum. For the preferred conformation, the 15 Hz half-signal-width of 9a-H was decisive.

For **17b**, the 6-position of the methyl group was also proved by nuclear *Overhauser* effect (NOE) measurements. Saturation of the methyl signal causes enhancement of the two upfield signals of the three aromatic signals (the doublet with the small coupling constant and the double doublet) thus indicating their vicinity to the methyl group. This is in accordance with the downfield position of the signal originating from H-8, owing to the anisotropic effect of the carbonyl group [20e]. Accordingly, the upfield doublet (H-5) and the 10-methylene signal at ~2.75 ppm give mutual NOE (irradiation of one of the signals increases the intensity of the other).

For **22**, the signal width (~15 Hz) of the anellation hydrogens and cyclohexene

methylene hydrogens indicates the unaltered *cis* anellation. The C and H signal pairs point to the quasi-symmetry of the molecule as a consequence of the rapid inversion of its two conformers.

For the norbornane derivative **24**, the unaltered di-*endo* anellation can be deduced only indirectly, because the splittings due to the couplings $J_{1,9a}$ and $J_{4,4a}$, which would serve as a direct proof [21], cannot be observed owing to signal overlap. From a comparison of the H-4 and C-2,3,11 shifts with the corresponding data on the methylene-bridged di-*exo*- and di-*endo*-2-aryl-3,1-benzoxazines [22] it is obvious that the di-*endo* structure of the starting compound **5** or the intermediate **23** is not altered during the reduction and cyclization.

## Experimental

IR spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer.

The NMR spectra were recorded in $CDCl_3$ or *DMSO*-$d_6$ solution in 5 or 10 mm tubes at room temperature on Bruker WM-250 ($^1H$, $^{13}C$) or WP-80-SY ($^{13}C$) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 ($^1H$) and 62.89 or 20.14 MHz ($^{13}C$), with the deuterium signal of the solvent as the lock and *TMS* as internal standard. The most important measuring parameters were as follows: spectral width, 5 and 15 or 5 kHz; pulse width, 1 and 5 or 3.5 μs (~20° and ~30° flip angle); acquisition time, 1.64 and 1.02 or 1.64 s; number of scans 16 or 32 ($^1H$) and 500–5000 (17000 in the case of **10a**) ($^{13}C$); computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening: 0.7 and 1.0 or 2.0 Hz) was applied.

NOE difference experiments were performed with the Bruker microprogram 12.5 in the Aspect 2000 Pulse Programmer. Gated decoupling to generate NOE was used.

The CH-COSY spectra were obtained using the standard BRUKER pulse program "XHCORRD.AU". The number of data points was 4 K in the $^{13}C$ domain, and 64-256 increments were used to give better than 5 Hz/point digital resolution in the $^1H$ domain. 256 transients were obtained with a relaxation delay of 3 s. All C-H correlations were found by using $J_{C,H} = 135$ Hz for calculating of the delays.

DEPT spectra [23] were run in a standard way [24], using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively.

HPLC: ISCO system with two pumps, suitable for gradient elution, Chem. Research control system and data processing program. For the semipreparative separation, a BST Si-100-S 10-RP-18 column (250 × 16 mm) was used; eluent: MeOH–$H_2O$–$CH_3CN$ (82 + 17 + 1 v/v%); flow rate: 9 ml/min. Injected sample: 500 μl of a 4% MeOH–THF (2 + 1) solution, detection at 270 nm.

*cis-2-(4-Methylbenzoyl)-cyclopropanecarboxylic acid* (**1**)

Prepared from 5.6 g (64 mmol) *cis*-cyclopropanedicarboxylic anhydride [25] according to Ref. [9]. Yield 9.7 g (89%), m.p. 105–107 °C. $C_{12}H_{12}O_3$ (204.2). Calcd.: C, 70.58; H, 5.92. Found: C, 70.71; H, 5.80.

*cis-2-(4-Methylbenzoyl)-cyclobutane-1-carboxylic acid* (**2**)

Prepared from 8.06 g (0.064 mol) *cis*-cyclobutane-1,2-dicarboxylic anhydride [26] according to Ref. [9]. Colourless crystals, m.p. 115–117 °C, yield 11.9 g (85%).

*di-endo-Bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride*

To a solution of 16.4 g (0.1 mol) di-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (Aldrich 24,763–4) in 250 ml dry *THF*, 16.3 g cyclohexene and 0.5 g 5% Pd on activated carbon were added. The mixture was refluxed for 15 h on a water bath. After cooling and filtration, the solution was evaporated and the residue was crystallized from benzene. Yield 15.0 g (90%), m.p. 170–172 °C. $C_9H_{10}O_3$ (166.2). Calcd.: C, 65.05; H, 6.07. Found: C, 65.14; H, 6.11.

*di-endo-3-(4-Methylbenzoyl)-bicyclo[2.2.1]heptane-2-carboxylic acid* (5)

Prepared from 8.31 g (0.05 mol) di-*endo*-bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride according to Ref. [10]. Colourless crystals, yield 11.49 g (89%), m.p. 162–164 °C. $C_{16}H_{18}O_3$ (258.3). Calcd.: C, 74.4; H, 7.02. Found: C, 74.28; H, 7.14.

*di-endo-3-(4-Methylbenzyl)-bicyclo[2.2.1]heptane-2-carboxylic acid* (23)

Prepared from 12.92 g (0.05 mol) **5** according to the method of *Mathur* and *Bhargava* [14]. Colourless crystals, yield 9.40 g (77%), m.p. 232–234 °C.

*(Bi)cycloalkane-condensed 4,5-dihydro-3(2H)-pyridazinones* (6a–10a) *(general method)*

A mixture of 0.01 mol 2-(4-methylbenzoyl)-(bi)-cycloalkanecarboxylic acid (1–5) and 0.5 g (0.01 mol) hydrazine hydrate in 25 ml toluene was refluxed for 1–2 h. After evaporation of the mixture, the residue was crystallized. Data of **6a–10a** are listed in Table 3.

*(Bi)cycloalkane-condensed 2-phenyl-4,5-dihydro-3(2H)-pyridazinones* (6b–10b) *(general method)*

A mixture of 0.01 mol 2-(4-methylbenzoyl)-cycloalkanecarboxylic acid (1–4) or its methylene-bridged homologue (5) and 1.08 g (0.01 mol) phenylhydrazine in 25 ml toluene was refluxed for 1–2 h. After evaporation, the residue was crystallized. Data of **6b–10b** are listed in Table 3.

*(Bi)cycloalkane-condensed 4,5-dihydro-6H-1,2-oxazin-6-ones* (11–14) *(general method)*

A mixture of 0.01 mol ketoacid (1–5), 0.69 g (0.01 mol) hydroxylamine·HCl and 1.64 g (0.02 mol) $CH_3COONa$ in 30 ml MeOH was refluxed for 2 h. After filtration, the solution was evaporated and the residue was crystallized. Data of **11–14** are listed in Table 3.

*trans-7-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one* (17a)

To a mixture of 4.18 g (18 mmol) *trans*-2-(4-methylphenyl)-methylcyclohexanecarboxylic acid **15a** und 50 ml dry benzene, 0.6 ml thionyl chloride was added dropwise under stirring and cooling. The mixture was refluxed for 3 h and evaporated. To the residue, 48 ml $CS_2$ and 2.4 g (18 mmol) anhydrous $AlCl_3$ were added and, after refluxing for 3 h on a water bath, the mixture was left to stand overnight. After removal of the solvent, cooled 10 ml 10% HCl was added and the mixture was extracted with 3 × 30 ml $CHCl_3$. The combined extract was washed with 5% $Na_2CO_3$ solution, dried ($Na_2SO_4$) and evaporated. Data of **17a** are listed in Table 3.

*cis- and trans-6-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one* (16b and 17b)

To a solution of 16.9 g (0.12 mol) **20** or **21** [27] in 100 ml dry toluene 60.0 g (0.45 mol) anhydrous $AlCl_3$ was added during 2 h under stirring. The brown mixture was kept for 16 h at 80–90 °C and then poured into a mixture of 300 g ice and 50 ml conc HCl under stirring, and the mixture was extracted with 3 × 70 ml ether. After washing of the combined extract with 2 × 50 ml water and drying ($Na_2SO_4$), the

**Table 3.** Physical and analytical data of the compounds obtained

| Compd. | M.p. °C | Yield % | Mol. formula | Mol. weight | Calcd. % | | | Found % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| **6a** | 169–171[a] | 51 | $C_{12}H_{12}N_2O$ | 200.2 | 71.97 | 6.04 | 13.99 | 71.25 | 6.10 | 14.05 |
| **6b** | 132–134[b] | 29 | $C_{18}H_{16}N_2O$ | 276.3 | 78.23 | 5.83 | 10.13 | 78.70 | 6.30 | 10.00 |
| **7a** | 166–168[a] | 72 | $C_{13}H_{14}N_2O$ | 214.3 | 72.87 | 6.58 | 13.07 | 73.01 | 7.02 | 13.60 |
| **7b** | 177–179[c] | 45 | $C_{19}H_{18}N_2O$ | 290.35 | 78.59 | 6.24 | 9.65 | 77.82 | 6.28 | 9.30 |
| **8a** | 176–178[a] | 62 | $C_{15}H_{18}N_2O$ | 242.6 | 74.34 | 7.48 | 11.56 | 74.60 | 7.20 | 11.30 |
| **8b** | 126–128[b] | 62 | $C_{21}H_{22}N_2O$ | 318.4 | 79.21 | 6.96 | 8.80 | 79.05 | 6.92 | 8.93 |
| **9a** | 201–203[a] | 84 | $C_{15}H_{18}N_2O$ | 242.6 | 74.34 | 7.48 | 11.56 | 74.40 | 7.66 | 11.30 |
| **9b** | 140–142[b] | 46 | $C_{21}H_{22}N_2O$ | 318.4 | 79.21 | 6.96 | 8.80 | 79.53 | 6.80 | 8.90 |
| **10a** | 254–256[c] | 59 | $C_{16}H_{18}N_2O$ | 254.3 | 75.56 | 7.13 | 11.01 | 75.26 | 7.11 | 10.70 |
| **10b** | 224–226[c] | 66 | $C_{22}H_{22}N_2O$ | 330.4 | 79.97 | 6.71 | 8.47 | 80.20 | 7.28 | 8.49 |
| **11** | 179–181[a] | 35 | $C_{12}H_{11}NO_2$ | 201.2 | 71.62 | 5.51 | 6.96 | 71.25 | 5.72 | 6.80 |
| **12** | 136–138[d] | 41 | $C_{15}H_{17}NO_2$ | 243.3 | 74.05 | 7.04 | 5.75 | 74.80 | 7.10 | 6.04 |
| **13** | 145–147[a] | 29 | $C_{15}H_{17}NO_2$ | 243.3 | 74.05 | 7.04 | 5.75 | 73.48 | 7.43 | 6.05 |
| **14** | 210–212[d] | 47 | $C_{16}H_{17}NO_2$ | 255.3 | 75.26 | 6.71 | 5.48 | 75.21 | 6.53 | 5.40 |
| **16b** | 84–86[e] | 29 | $C_{15}H_{18}O$ | 214.3 | 84.07 | 8.46 | – | 84.20 | 8.35 | – |
| **17a** | 97–99[d] | 65 | $C_{15}H_{18}O$ | 214.3 | 84.07 | 8.46 | – | 84.40 | 8.55 | – |
| **17b** | 101–103[d] | 26 | $C_{15}H_{18}O$ | 214.3 | 84.07 | 8.46 | – | 84.15 | 8.55 | – |
| **22** | 77–80[b] | 25 | $C_{15}H_{20}$ | 200.3 | 89.94 | 10.06 | – | 89.75 | 10.20 | – |
| **24** | 86–88[b] | 20 | $C_{16}H_{18}O$ | 226.3 | 84.91 | 8.01 | – | 85.20 | 8.10 | – |

Crystallized form: [a] EtOAC; [b] EtOH; [c] dioxane; [d] benzene; [e] $Et_2O$

solvent was removed by distillation and the residue was chromatographed on a silica gel column (Kieselgel 60, 0.060–0.20 mm, benzene). Data of **16b** and **17b** are listed in Table 3.

*di-endo-7-Methyl-1,4-methano-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one* (**24**)

**24** was prepared from di-*endo*-3-(4-methylbenzyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**23**) as **17a**. Data of **24** are listed in Table 3.

*cis-2-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracene* (**22**)

To a suspension of 0.64 g (17 mmol) *LAH* in 10 ml dry ether, a mixture of 4.66 g (35 mmol) anhydrous $AlCl_3$ and 10 ml dry ether was added under stirring and cooling, and 2.14 g (10 mmol) **16b** in 10 ml ether was then added dropwise in 10 min. After refluxing for 30 min on a water bath, the excess of *LAH* was decomposed by adding 1 ml ethyl acetate and the mixture was poured into dilute 10 ml 20% $H_2SO_4$. The organic layer was separated and dried ($Na_2SO_4$), and the solvent was removed. The oily residue was fractionated, b.p. 100–104 °C/800 Pa.

The oily product obtained was purified by HPLC. Fraction A (11%), crystallized from MeOH–$H_2O$, gave **16b** as colourless crystals, m.p. 88–90 °C; B (53%), a yellowish oily product, which crystallized from MeOH–$H_2O$, gave almost colourless crystals, m.p. 76–80 °C; C (35%), an almost colourless oil, crystallized from EtOH, gave **22**, m.p. 77–80 °C.

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# Synthesis and Structure of Methanobenzocyclooctene Derivatives†

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10-Oxo-5,9-methanobenzocyclooctene-8-carboxylic acid **4a** was prepared by the intramolecular cyclization of 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic acid **1a** in concentrated $H_2SO_4$ or in the reaction of 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic anhydride **2** in 80% $H_2SO_4$. To improve the yield, the esters **3a,b** were cyclized to the methanocyclooctene isomers **5a,b**, in a 1:5 ratio from **3a**, and in a 5:4 mixture (54%) from **3b** at elevated temperature. After separation, **5a** was hydrolysed, the keto group of **4a** was reduced by the Wolff–Kishner method and the resulting *cis* and *trans* methylene-bridged benzocyclooctenes **6a,b** (1:2) were separated. From **4a** with hydrazine, the tetracyclic pyridazinone derivative **7** was obtained. The structures were determined by $^1H$ and $^{13}C$ NMR methods and for **4a** also by X-ray crystallography.

In our earlier studies on fused-skeleton saturated and partially saturated 1,3-heterocycles, we studied the reactions of cyclic β-oxo carboxylic acids with alicyclic 1,3-amino alcohols in which one of the functional groups was attached directly, and the other through a methylene group to carbocycles such as cyclohexane, cyclohexene, norbornane or norbornene.[1–4] In these cyclizations, tetracyclic and pentacyclic hetero compounds were formed, and isomerization of the starting stereohomogeneous *cis* and *trans* amino alcohols also often occurred. Consequently, structure elucidation of the fairly complex tetracyclic or pentacyclic systems, and determination of the configuration and conformation, was always a challenging task; a comparative study of closely related ring systems and the *cis*- and *trans*-fused isomers added to the importance. The new compounds were synthesized with pharmacological aims.

For the synthesis of fused-skeleton isoindolones, *cis*- or *trans*-2-aroyl-1-cyclohexanecarboxylic acids were used as starting materials in our earlier studies. In the present paper, *cis*-4-cyclohexene-1,2-dicarboxylic anhydride was applied; through the addition of benzene to the double bond,[5] this furnished 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic acid **1a** with a phenyl equatorial[3] to the neighbouring carboxy group. The 4-phenyl substituent on cyclohexane-1,2-dicarboxylic acid was thought might provide a good opportunity to construct highly condensed systems by intramolecular acylation of the phenyl substituent with the 2-carboxy group. These systems containing two functional groups are suitable for the preparation of heterocycles and they provide good starting molecules for the production of new pharmacologically active derivatives as target compounds.

## Results

When heated in concentrated $H_2SO_4$, *trans*-4-phenylcyclohexane-*cis*-1,2-dicarboxylic acid (**1a**) or in 80% $H_2SO_4$, the anhydride **2** yielded 10-oxo-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**4a**; yield 13% and 15%, respectively) by intramolecular cyclization.

Similar cyclization via $AlCl_3$-catalysed intramolecular Friedel–Crafts acylation provides only a moderate yield (14–21%),[6] in spite of the absence of strain in the bicyclononanone ring system.[7] Other preparations,[8,9] e.g., from benzylcyclohexanone with MeLi,[10] from unsaturated enol silyl esters with ceric ammonium nitrates,[11,12] from alkenes by $MeSO_3H$ cyclization[13] and by carbo-

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cationic cyclization of unsaturated bromo imines[14] are also known.

To improve the yield of **4a**, we started from dimethyl 4-*trans*-phenylcyclohexane-*cis*-1,2-dicarboxylate (**3a**); cyclization with PPA at elevated temperature yielded a mixture of the isomeric esters **5a** and **5b** in a ratio of 1:5. In contrast, cyclization of dimethyl 4*t*-phenylcyclohexane-1*r*,2*t*-dicarboxylate (**3b**) gave the esters **5a** and **5b** in a 5:4 ratio (the yield of **5a,b** was 54%). Consequently, as a result of the transformation **3b** → **5a,b** with PPA, the 30% yield of **5a** (Table 3) isolated from the mixture **5a,b** by column chromatography proved to be enough to permit further reactions. We presume that in the cyclization the 2-carboxy groups which are axial in the ground state come close to the phenyl group by ring inversion and **3a** and **3b** partly isomerize to form the products **5a,b**. After separation of the isomers, the structures were established by NMR spectroscopy. The esters **5a,b** were hydrolysed and the acids **4a,b** were characterized by NMR and for **4a** also by X-ray analysis (Fig. 1). The oxo group was reduced by the Wolff–Kishner method to afford a mixture of *cis*- and *trans*-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acids (**6a,b**). With hydrazine, the oxo

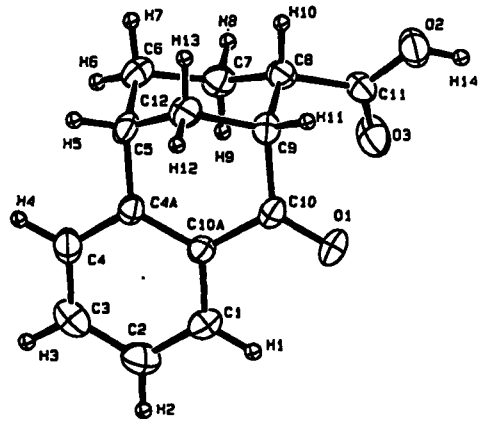



*Fig. 1.* X-Ray structure of compound **4a**.

*Table 1.* IR carbonyl frequencies in KBr[a] and $^1$H NMR data[b] on compounds **4–7** in $CDCl_3$ solution[c] at 250 MHz.[d]

| Compound | $\nu_{C=O}$ Posn. 8 | $\nu_{C=O}$ Posn. 10 | H-1 dd (1 H) | H-4 dd (1 H) | H-5,9[e] m (2 H) | H-ax Posn. 7 | H-8 m (1 H) | H-eq[f] Posn. 11 |
|---|---|---|---|---|---|---|---|---|
| **4a** | 1713 | 1678 | 8.03 | 7.24 | ≈3.2 | 1.50[g] | 2.79[h] | 2.50[i] |
| **4b** | 1696 | 1681 | 8.04 | 7.24 | 3.25 | 1.48[i] | 2.94[k] | 2.30[i] |
| **5a** | 1728 | 1681 | 8.06 | 7.23 | ≈3.2 | 1.52[g] | 2.73[h] | 2.45[i] |
| **5b** | 1729 | 1679 | 8.05 | 7.25 | 3.18 | 1.40[i] | 2.85[k] | 2.25[i] |
| **6a** | 1712 | — | ≈7.1[m] | 7.00 | 2.98[n] | 1.35[g] | ≈2.7[o] | 2.00[i] |
| **6b** | 1701 | — | ≈7.1[m] | 7.00 | 2.98 | 1.45[i] | 2.68[o] | ≈2.0[p] |
| **7** | 1671 | — | 7.80 | 7.20 | ≈3.1 | 1.35[g] | 2.55[h] | 2.00[i] |

[a]In $cm^{-1}$. [b]Chemical shifts in δ, $\delta_{TMS}=0$ ppm, coupling constants in Hz. [c]**4a** was also measured in DMSO-$d_6$ solution. [d]Assignments were proved by DR (**4a**) and DNOE (**6a,b**) measurements. Further signals, $^1$H NMR: $CH_3$ (s, 3 H): 3.72 (**5a**), 3.77 (**5b**); $CH_2$ (posn. 6, 7eq, 11ax), 4 × m (4 × 1 H) in the interval 1.7–2.2 ppm, partly overlapped. Separated signals: H-6ax: 1.90[j] (**4a**, **5a**), 2.18[j] (**4b**), H-6eq: 1.85[i] (**4a**), 1.65[i] (**4b**), 1.80[i] (**5a**), 1.60[i] (**5b**), 1.55[i] (**6b**), H-7eq: 1.75[i] (**4a**, **5a**), 2.05[i] (**4b**), 1.98[i] (**5b**), H-11ax: 2.05[h] (**4a**, **5a**), 2.22[h] (**4b**), 1.85[h] (**6a**); $CH_2$ (posn. 10): 2.78 d (split by 18.4) and 2.98[n] (**6a**), 2.68[o] and 3.27 dd (split by 18.0 and 7.5) for **6b**; H-2,3, 2 × dt (2 × 1 H): 7.30 and 7.50 (**4a**, **5a,b**), 7.38 and 7.55 (**4b**), coalesced at ≈7.1 (**6a,b**) and 7.3 (**7**); NH, (br s, 1 H): 8.65 (**7**); H-9 (≈s, 1 H): 3.00 (for **4a** in DMSO-$d_6$); IR, $\nu_{OH}$: 3300–2200 (**4a,b**, **6a,b**); $\nu_{NH}$: 3185 (**7**). [e]Overlapping signals, except for **6a,b**, where the H-9 signal at about 2.7 ppm is coalesced with the H-8 m (**6a**) and the upfield m of $CH_2$ (posn. 10) group (**6b**). [f]To ring *C* (*S-cis* to the condensed aromatic ring). [g]Quartet split by ca. 13.5 with further doublet split by ca. 4.5. [h]Doublet (split by 13.2 ± 0.2) with further triplet split by ca. 4 (for H-8) or 2.5 (H-11ax). [i]Quartet (split by ca. 13) with further quartet split by 2.5. [j]Triple triplet split by ca. 13.5 (H-6ax) or 14.5 (H-7ax) and 4. [k]Singlet-like signal with coalesced fine structure. [l]Doublet-like signal with coalesced further fine structure, split by 14 ± 0.5. [m]In overlap with the H-2,3 signal. [n,o]Overlapping signals. [p]In overlap with the H-6ax signal.

*Table 2.* $^{13}$C NMR chemical shifts[a] of compounds **4–7** in $CDCl_3$ solution at 63 MHz.[b]

| Compound | C-1 | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8[c] | C=O | C-10[c] | C-9[c] | C-11 | C-10a[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | 125.4 | 126.8 | 134.2 | 128.5 | 147.1 | 33.6 | 29.8 | 19.6 | 44.4 | 174.1 | 198.1 | 45.0 | 33.2 | 133.7 |
| **4b** | 126.7[d] | 127.0[d] | 134.4 | 128.2[d] | 147.2 | 34.5 | 27.6 | 19.1 | 41.9 | 179.6 | 200.3 | 43.8 | 29.9 | 133.3 |
| **5a**[e] | 126.9 | 126.5 | 134.1 | 128.0 | 146.8 | 34.3 | 30.3 | 19.7 | 45.3 | 173.4 | 198.5 | 45.4 | 33.8 | 134.0 |
| **5b**[e] | 126.0 | 126.4 | 133.7 | 127.7 | 146.7 | 34.0 | 27.1 | 18.7 | 41.3 | 173.1 | 199.4 | 43.6 | 29.3 | 132.8 |
| **6a** | 128.0[f] | 125.7 | 125.4 | 128.0[f] | 140.5 | 33.6 | 33.2 | 19.2 | 47.8 | 181.2 | 30.7 | 29.5 | 31.7 | 137.0 |
| **6b** | 127.9 | 125.7 | 125.5 | 128.2 | 140.6 | 33.7 | 30.2 | 18.8 | 46.5 | 181.3 | 35.3 | 28.8 | 27.8 | 136.8 |
| **7** | 123.5 | 127.4[d] | 129.5 | 127.9[d] | 143.4 | 32.2 | 28.9[f] | 18.3 | 35.0 | 174.9 | 157.6 | 39.0 | 28.9[f] | 133.3 |

[a]$\delta_{TMS}=0$ ppm. [b]Assignments were confirmed by 2D-HSC (except for **4b** and **7**) and DEPT measurements. [c]For easier comparison of spectroscopically analogous data, the numbering of **4** and **5** is used also for **6** and **7** here and in the text. The IUPAC numbering is given in the Experimental part. [d]Interchangeable assignments. [e]$OCH_3$: 51.8 (**5a**), 51.5 (**5b**). [f]Two overlapping lines.

carboxylic acid **4a** was cyclized to the tetracyclic methanobenzocycloocta[9,8-*c*,*d*]pyridazinone **7**.

*Structure.* The characteristic IR, $^1H$ and $^{13}C$ NMR data are listed in Tables 1 and 2. For the isomeric pairs **4a,b** and **5a,b**, establishment of the stereo structure is complicated by the flexibility of ring *C* resulting in two relatively stable (chair and boat) conformations. Hence, both the C-8 configuration and the conformation have to be determined.

Owing to the strong steric hindrance between the α-axial COOR group and the skeleton (no sign of which appears in the spectra), the presumption of a *cis* H-8,H-9 configuration (5*R**,8*S**,9*R**) allows no boat conformation of ring *C* (Scheme 1, **4a***i*). For a chair conformation and a *cis* configuration (Scheme 1, **4a***ii*), the axial H-8 is in a *trans*-diaxial position with one of the neighbouring H-7 atoms, and the correspondingly large coupling[15] appears in the $^1H$ NMR spectra of one each of the acid and ester isomers; for **4a** and **5a**, the H-8 signal is a triplet of doublets split by 13.3, 4.1 and 4.1 Hz. (For a boat conformation of ring *C*, the equatorial H-8 would not display as large coupling as 13.3 Hz.)

As the H-8 multiplet of **4b** and **5b** does not exhibit a large splitting, the chair conformation of ring *C* is also preferred for the *trans* isomers (5*R**,8*R**,9*R** configuration); hence, the COOR group is axial and the equatorial H-8 has no diaxial (i.e., large vicinal) coupling (Scheme 1). Accordingly, for *trans* **4b** and **5b**, the $^{13}C$ NMR spectra indicate a sterically more unfavourable structure: the sum of the chemical shifts of the carbons in ring *C* is less[16a] (by 8.8 and 14.8 ppm) than that for the isomers **4a** and **5a**. If the simultaneous alteration of the C-8 configuration and *C*-ring conformation for the *trans* isomers is assumed, no essential difference in steric hindrance would be observable in comparison with the *cis* compounds, because the COOR group is equatorial in both isomers.

Further proof of the tentative structures is the field effect[16b] (i.e., the upfield shift of the $^{13}C$ lines[17]), which indicates sterically unfavourable structures and which is higher for the C-6 and C-11 (and of course C-8) lines than for the other three carbons (C-5,7,9), because the first two carbons are positioned 1,3-diaxially to the 8-COOR group. For the *cis–trans* pairs of acids and esters, the sum of the shift differences for the C-6,8,11 lines amounts to 8.0 and 11.7 ppm, while the corresponding values for C-5,7,9 are only 0.8 and 3.1 ppm.

For **4a**, the X-ray determination (Fig. 1) revealed that the compound forms hydrogen-bonded monomers in the solid state. In the H-bond [O(2) ··· H(14) ··· O($3_I$), $I=-x, 2-y, -z$], the O ··· O distance is 2.661(2) Å and the OH ··· O angle is linear 177(2)°. These are typical values for carboxylic acid dimers.

The spectral data on the reduced products **6a,b** confirm the above structures. For C-7 and C-11, the chemical shifts hardly differ from those measured for **4a,b** and **5a,b**. In the event of a boat conformation, the hindrance between the axial H-7 and H-11 would cause a strong steric effect, i.e., significant upfield shifts of the C-7 and C-11 lines. On the basis of the summed carbon shifts for ring *C* (the difference is 9.2 ppm), the assignments of the *cis* (5*R**,8*S**,9*S**) and *trans* (5*R**,8*R**,9*S**) H-8,H-9 configurations to the two isomers are unambiguous.

As stated above, for the isomeric pairs **4a,b** and **5a,b**, the shifts of C-6, C-8 and C-11 differ significantly due to the strong steric hindrance between the axial 8-COOR group and H-$6_{ax}$ and H-$11_{ax}$ in the *trans* isomers. For **6a,b**, only the shift difference for C-6 and C-11 is significant; that for C-8 is significantly smaller ($\Delta\delta$C-8 = 1.3 ppm). The explanation lies in the strong steric hindrance between the *endo* 10-methylene hydrogen and the equatorial 8-COOH group of the *cis* isomer, and therefore the C-8 line is also shifted upfield for the *cis* isomer.

For steric reasons, the *cis* H-8,H-9 (5*R**,8*S**,9*R**) configuration is retained in the tetracyclic **7**, while for the starting **4a**, a change in the configuration on ring closure is not expected. The splittings of H-8 (13, 4 and 4 Hz) suggest the chair form of ring *C*, i.e., the conformation remains; the ≈13 Hz split confirms diaxial coupling (Scheme 1), and such an interaction is impossible in the boat form (H-8 would not be equatorial).

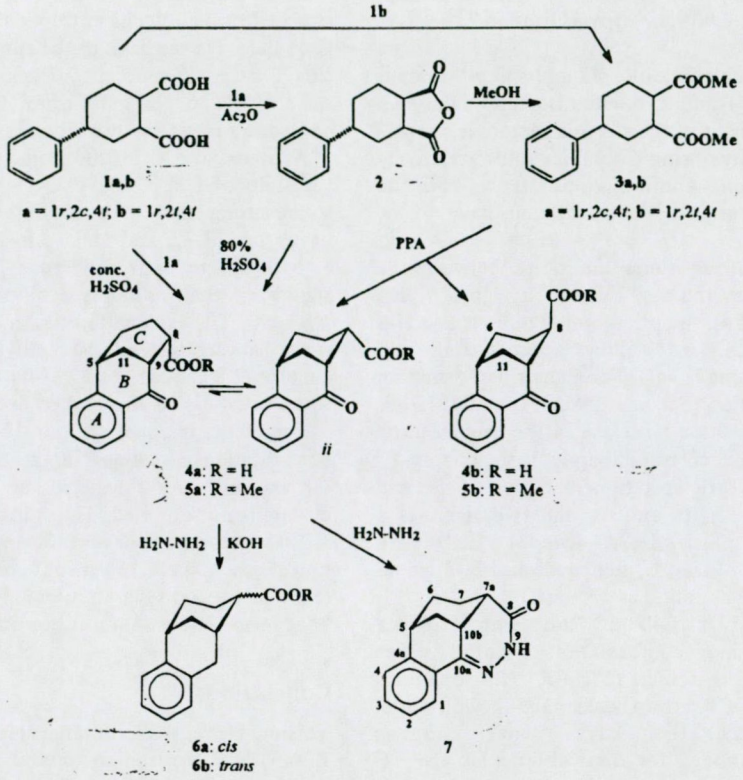
## Conclusions

To summarize, the intramolecular cyclization of **3a** with PPA yielded the isomers **5a** and **5b**, which differ in the configuration of C-8; for **5a**, H-5, H-8 and H-9 lie on the same side of ring *C*, while in **5b**, H-5 and H-9 are on the same side and opposite to the hydrogen geminal to the carboxy group. On reduction of the acid **4a**, the isomers **6a** (all-*cis*) and **6b** (5*r*H,8*t*H,9*c*H) are formed in a 1:2 ratio; the epimerization probably takes place via enolization of the 8-CO (carboxy) group.

**5a** can be prepared from the *trans* ester **3b** more advantageously than from the *cis* ester **3a**, and its 30% yield allows its use as a starting molecule for the synthesis of highly condensed systems. Hence, intermolecular acylation with PPA at an elevated temperature is an appropriate method of obtaining the methanobenzocyclooctene system.

## Experimental

IR spectra were run for samples in KBr discs on a vacuum optic Bruker IFS-113v FT spectrometer equipped with an Aspect 2000 computer. $^1H$ and $^{13}C$ NMR spectra were recorded for $CDCl_3$ solutions in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 ($^1H$) and 63 ($^{13}C$) MHz, respectively, using the deuterium signal of the solvent as the lock and $Me_4Si$ as an internal standard. For DNOE measurements,[16c,18] the standard Bruker microprogram DNOEMULT.AU to generate NOE was used. 2D-HSC spectra[19] were obtained by using the standard Bruker pulse program




*Scheme 1.*

XHCORRD.AU. DEPT spectra[20] were run in a standard way,[21] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively.

*Crystal data for* **4a**. Triclinic, space group $P\bar{1}$ (No. 2), $a = 8.526(2)$, $b = 10.784(2)$, $c = 7.368(2)$ Å, $\alpha = 93.97(2)$, $\beta = 112.68(2)$, $\gamma = 67.53(1)$, $V = 575.2(3)$ Å$^3$, $Z = 2$, $D_c = 1.329$ g cm$^3$, $\mu$(Mo K$\alpha$) = 0.87 cm$^{-1}$, $F(000) = 244$, $T = 294(1)$ K, colourless prisms, crystal dimensions $0.26 \times 0.34 \times 0.40$ mm.

*Data collection and refinement.* A Rigaku AFC5S diffractometer was used with graphite monochromated Mo K$\alpha$ radiation ($\lambda = 0.710\,69$) in the $\omega$–$2\theta$ scan mode with a $\omega$ scan rate of 8.0° min$^{-1}$ and a scan width of $1.63 + 0.30 \tan\theta$. The weak reflections [$F < 10\sigma(F)$] were rescanned up to two times. The data obtained were corrected for Lorentz and polarization effects. A total of 2165 unique reflections were measured ($2\theta_{max} = 50°$ and $R_{int} = 0.011$). The structure was solved by direct methods[22] and difference Fourier syntheses.[23] Structural parameters were refined by a full-matrix least-squares refinement, non-hydrogen atoms with anisotropic, and non-aromatic hydrogen atoms with fixed isotropic temperature parameters (1.2 times $B_{eq}$ of carrying atom). The aromatic hydrogens were kept in the calculated positions. In the final cycles, the 1531 data with $I > 2\sigma(I)$ yielded an $R$ value of 0.043 ($R_w = 0.037$, sigma weights) for 184 parameters. The residual electron density was from 0.15 to 0.17 e Å$^3$.

All calculations were performed with TEXSAN-89 software,[24] using a VAXSTATION 3520 computer. The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.[25] The final atomic positional coordinates, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

HPLC: ISCO system with two pumps, suitable for gradient elution. The Chem. Research control system and data processing program were used. For the semi-preparative separation, a 5 µm BST Si-100-S 10-RP-18 column (250 × 16 mm) was used; eluent: *n*-hexane–isopropyl alcohol (98:2 v/v%); flow rate: 8 ml min$^{-1}$; injected sample: 250 µl; 0.5 g dichloromethane–eluent (1:3) detection at 220 nm.

*10-Oxo-5r,6,7,8c,9c,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid* (**4a**): *method A.* 4*t*-Phenylcyclohexane-1*r*,2*c*-dicarboxylic acid[5] (**1a**) (5.0 g, 0.02 mol) in concentrated $H_2SO_4$ (20 ml) was heated to 150 °C and kept at this temperature for 1 h. After being cooled, the mixture was poured onto ice and extracted

with $CH_2Cl_2$ (3 × 20 ml). The extract was washed with water and dried ($Na_2SO_4$). On evaporation, the residue crystallized from EtOAc, m.p. 210–215 °C, yield 0.60 g (13%). Analytical data: found C 73.2; H 6.1. Calc. for $C_{14}H_{14}O_3$: C 73.0; H 6.1%.

*Method B.* To $H_2SO_4$ (80%, 30 ml), 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic anhydride (**2**) (5.0 g, 0.02 mol) was added in portions, with stirring. The mixture was kept at 80 °C for 16 h and, after being cooled, poured onto ice and then extracted with $CHCl_3$ (3 × 300 ml). The extract was washed with water (2 × 50 ml), dried ($Na_2SO_4$) and evaporated to dryness. The product (**4a**) was purified on a silica gel column (Acros 0.035–0.07 mm) eluting with *n*-hexane–EtOAc (2:1). On evaporation, the residue crystallized from EtOAc, yield 0.70 g (15%).

*Dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate* (**3a**) *and 4t-phenyl-1r,2t-dicarboxylate* (**3b**). A mixture of anhydride **2**[26] (4.6 g, 0.02 mol) or dimethyl 4*t*-phenylcyclohexane-1*r*,2*t*-dicarboxylate **1b** (5.0 g, 0.02 mol) and benzene (25 ml) in MeOH (45 ml) was refluxed with concentrated $H_2SO_4$ (0.23 ml) for 4 h, a Dean–Stark water separator being applied. After evaporation of the solvent, the residue was neutralized with $Na_2CO_3$ solution (5%) and extracted with $Et_2O$ (3 × 25 ml). The $Et_2O$ extract was washed with water (2 × 20 ml), dried ($Na_2SO_4$) and evaporated to dryness. The residue was loaded onto a silica gel column (Acros 0.035–0.07 mm) and eluted with *n*-hexane–EtOH (5:1). On evaporation, the yield was 4.30 g (78%) **3a**, $n_D^{23}$: 1.5176, or 4.73 g (86%) **3b**, $n_D^{23}$: 1.5162. The products were used for the further preparations without purification.

*Cyclization of dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate* (**3a**) *to the isomeric methyl esters* (**5a** and **5b**). To PPA (28.0 g), **3a**[3] (2.76 g, 0.01 mol) was added dropwise at 110 °C with stirring. The mixture was heated at this temperature for 3 h, then cooled and poured onto crushed ice. The mixture was extracted with $Et_2O$ (3 × 150 ml), and the combined extract was washed with water (2 × 200 ml), dried ($Na_2SO_4$) and evaporated to dryness. The residue was transferred onto a silica gel column (Acros 0.035–0.07 mm) and eluted initially with an *n*-hexane–EtOAc mixture (5:1). First **5b** was eluted [higher $R_f$, monitoring by TLC, Alufolien Kieselgel 60 $F_{254}$ Merck, 0.2 mm, solvent: benzene–EtOH–petroleum ether (b.p. 40–60 °C) 4:1:3, development in iodine vapour] and **5a** (lower $R_f$) was then eluted with an *n*-hexane–EtOAc mixture 4:1 mixture. On evaporation of the solvents and crystallization, from EtOAc–$Et_2O$, m.p. 122–123 °C, yield 0.77 g (31.5%) (**5b**) and from EtOAc, m.p. 105–107 °C, yield 0.15 g (6%) (**5a**) were obtained. Analytical data: found C 73.6; H 6.55 (**5b**) and C 73.85; H 6.8 (**5a**). Calc. for $C_{15}H_{16}O_3$: C 73.75; H 6.6%.

*Cyclization of dimethyl 4t-phenylcyclohexane-1r,2t-dicarboxylate* (**3b**) *to the isomeric 5,6,7,8,9,10-hexahydro-5,9-methanocyclooctene derivatives* (**5a,b**). The reaction was performed with **3b** (2.76 g, 0.01 mol) according to the cyclization of **3a** to **5a,b** in PPA, but at 120 °C. After chromatographic purification (silica gel column, Acros 0.035–0.07 mm; *n*-hexane–EtOAc 5:1), yields of 0.59 g (24%) for **5b** and 0.73 g (30%) for **5a** were obtained.

*10-Oxo-5r,6,7,8t,9c,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid* (**4b**). **5b** (2.44 g, 0.01 mol) in NaOH solution (10%, 20 ml) was stirred for 3 h at 50 °C. After being cooled, the solution was acidified with concentrated HCl to pH 3, then extracted with $CHCl_3$ (3 × 30 ml); the extract was washed with water (2 × 50 ml) and dried ($Na_2SO_4$). On evaporation, the residue was crystallized from $Et_2O$–*n*-hexane, m.p. 135–137 °C, yield 2.02 g (88%). Analytical data: found C 72.9; H 5.9. Calc. for $C_{14}H_{14}O_3$: C 73.0; H 6.1%.

*5r,6,7,8c,9c,10-* (**6a**) *and 5r,6,7,8t,9c,10-hexahydro-5,9-methanobenzocyclooctene-8t-carboxylic acid* (**6b**). The oxo acid **4a** (2.30 g, 0.01 mol) and hydrazine hydrate (98%, 1.53 g, 0.03 mol) were added to a solution of KOH (1.68 g, 0.03 mol) in diethylene glycol (15 ml) at such a rate as to keep the temperature below 100 °C. The mixture was then heated for 1 h at 110 °C. The temperature was then raised slowly to 200 °C and maintained there for 4 h, during which time some hydrazine–water mixture distilled off. After being cooled, the mixture was added to water and the pH was adjusted to 2. Following extraction with $CHCl_3$ (3 × 50 ml), the extract was washed with water (2 × 50 ml) and dried ($Na_2SO_4$), and the $CHCl_3$ was evaporated off. Crystallization from *n*-hexane yielded a mixture of isomers **6a** and **6b** (1:2). Separation of a 60 mg sample by HPLC and crystallization from $CH_2Cl_2$–*n*-hexane, yielded **6a**: m.p. 110–112 °C, yield 34 mg (56%) and, from *n*-hexane **6b**: m.p. 145–148 °C, yield 20 mg (33%). Analytical data: found C 77.6; H 7.4 (**6a**) and C 77.6; H 7.4 (**6b**). Calc. for $C_{14}H_{16}O_2$: C 77.75; H 7.5%.

*5r,6,7,7ac,10a,10bc-Hexahydro-5,10b-methanobenzocycloocta[9,8-cd]pyridazin-8-one* (**7**). A mixture of **4a** (0.46 g, 2 mmol) and hydrazine hydrate (98%, 0.1 g, 2 mmol) in EtOH (20 ml) was refluxed for 2 h and then evaporated. The residue was dissolved in 1,2-dichlorobenzene (10 ml) and refluxed for an additional 2 h. The crystals that separated out on cooling were filtered off by suction and recrystallized from EtOH, m.p. 238–239 °C, yield 0.29 g (65%). Analytical data: found C 74.15; H 6.15; N 12.95. Calc. for $C_{14}H_{14}N_2O$: C 74.3; H 6.2; N 13.2%.

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# SATURATED HETEROCYCLES, PART 257*. PREPARATION AND STRUCTURE OF PARTIALLY SATURATED ISOINDOLO[1,2-*b*]- AND -[2,1-*a*]QUINAZOLINONES

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*Abstract* – Through the reactions of 2-carboxybenzaldehyde (1) with *cis*- or *trans*-2-amino-1-cyclohexylmethylamine (2a,b) or *cis*- or *trans*-2-amino-4-cyclohexenyl-1-methylamine (2c,d), the partially saturated isomeric isoindolo[1,2-*b*]- (3, 4, 6-8) and -[2,1-*a*]quinazolinones (5) were obtained. After separation, the structures of products (3-8) were established by NMR methods, including 2D-HSC DNOE and DEPT measurements. From the *cis* 2a, two linearly *C/D cis*-fused and one angularly *C/D trans*-fused tetracycles were formed.

Our earlier studies on the syntheses of saturated or partially saturated heterocycles from aroyl(bi)-cycloalkanecarboxylic acids[1,2] prompted us to prepare new condensed tetracyclic systems. In the present experiments, 2-carboxybenzaldehyde (1) as starting synthon reacted with cyclic diamines in which one of the functional groups was bound directly to a cyclohexane/ene ring, and the other indirectly through a methylene group. Platinum derivatives of diamines (2a-d) have antitumour effects.[3] 2a-d used in the present experiments differ from the cyclic 1,3-amino alcohols applied previously in that the ring closures involve two amino groups of similar nucleophilicities. Hence, the formation of structurally isomeric heterocycles with linearly or angularly fused ring systems can be expected. Additionally, isomers can be formed that differ in the mutual positions of the annelational hydrogen in the *C/D* ring fusion and the hydrogen on the carbon between the two nitrogens. Furthermore, establishment of the stereostructure in the *C/D* ring fusion is essential, because *cis–trans* isomerization of the starting compounds often occurs during similar ring closures.[1]

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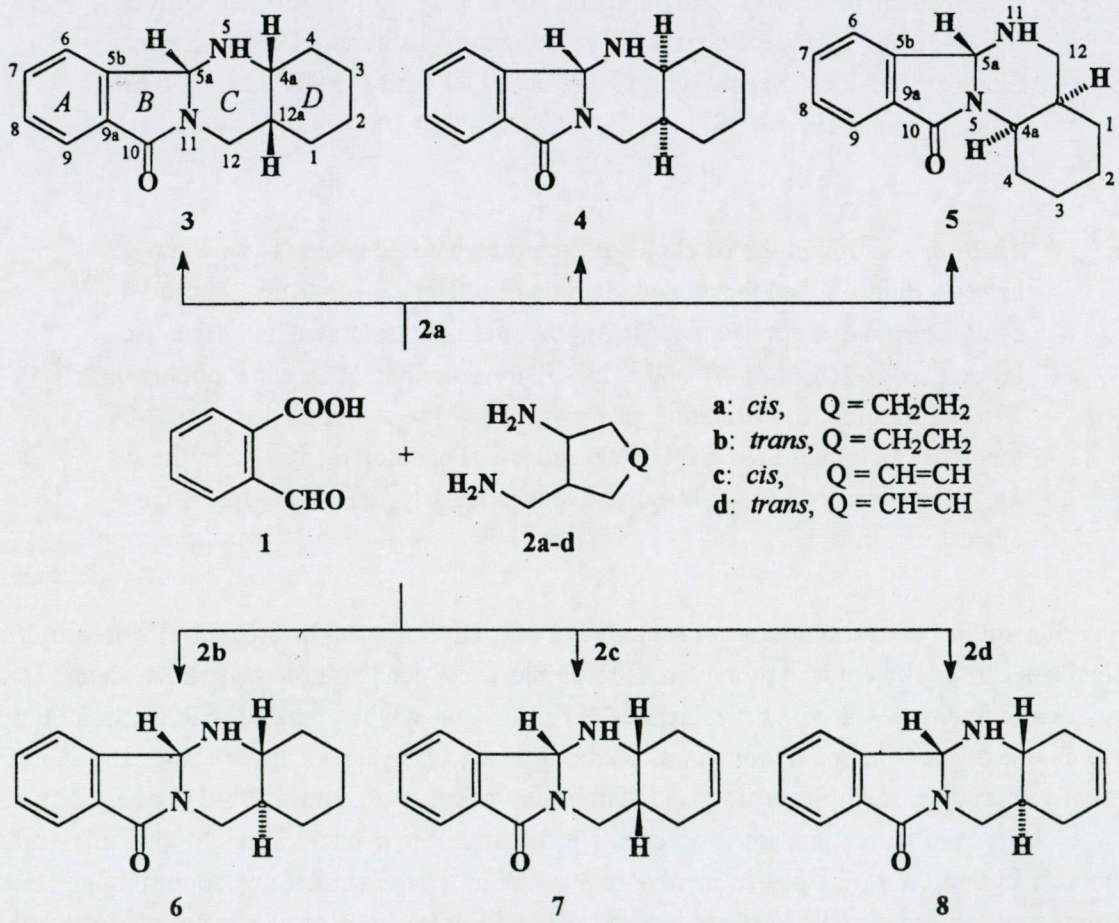
## RESULTS

When boiled together in toluene, 2-carboxybenzaldehyde (**1**) and *cis*-2-amino-1-cyclohexylmethylamine (**2a**) yielded three products: the linearly condensed **3** and **4** and the angularly-fused **5** (Scheme), which were separated by HPLC. After isolation and crystallization, the structures of tetracycles (**3-5**) were established by NMR spectroscopy. The linearly-fused products (**3**) and (**4**) proved to be isoindoloquinazolinones containing an aromatic ring *A*, two condensed hetero rings and one terminal cyclohexane unit. Similar structural isomers have been prepared in the reaction of γ-aroylpropionic acid with **2a**.[2]




Scheme

In the reaction of **1** with *trans*-2-amino-1-cyclohexylmethylamine (**2b**), only one product (**6**) was isolated. Likewise, in the reactions of **1** with *cis*- or *trans*-2-aminocyclohex-4-enyl-1-methylamine (**2c** and **2d**), **7** and **8** were obtained. Similarly to **3** and **4**, these compounds are linearly condensed isoindoloquinazolinones. The spectral data given in Tables 1 and 2 indicate that the formation of these tetracyclic ring systems is straightforward.

The theoretically equally possible linearly or anguarly condensed ring systems can be differentiated on the basis of the chemical shifts of the NC*H* and NC$H_2$ hydrogens. Due to the

anisotropic effect of the amide carbonyl,[4a] the former and one of the latter give significantly downfield shifted signals: 4.5 ppm (**5**) instead of 2.6-3.4 ppm (**3**, **4**, **6-8**), and 3.37 (**5**) instead of 4.15-4.43 ppm (**3**, **4**, **6-8**). Consequently, **3**, **4** and **6-8** contain the methylene group vicinal to the amide nitrogen, while in **5** the CH group is bound to this nitrogen atom. Hence, all these new compounds have linearly condensed skeletons, with the exception of **5**, which alone has an angular structure.

Table 1. Characteristic IR frequencies ($cm^{-1}$)[a] and $^1$H-NMR data (chemical shifts in ppm[b] and coupling constants in Hz) for compounds (**3-8**)*

| | νNH band (broad) | νC=O band[c] | γCH band | $CH_2$ (Pos. 1-4) + CH (12a) 1-6 *m*'s (9H) | $NCH_2$[d] (2x1H) | | NCH[e] *m* (1H) | NCHN *s* (1H) | ArH (benzene ring) *dd* (1H)[f] | (Pos. 6-8)[g] |
|---|---|---|---|---|---|---|---|---|---|---|
| **3** | 3293 | 1677 | 735 | ~1.10 ~1.30[h,i] 1.50[h,i] ~1.65[j] 1.90 | ~3.35[h] | 4.15 | ~3.35[h] | 5.17 | 7.83 | 7.40–7.55 |
| **4** | 3600-2800[k] | 1681 | 745 | 1.25–2.20 | 3.42 | 4.20 | 3.09 | 5.31 | 7.80 | 7.45–7.65 |
| **5** | 3455 3233 | 1659 | 753 | 1.50–2.00 | 2.90 | 3.37 | 4.50 | 5.26 | 7.85 | ~7.55 |
| **6** | 3280 | 1693 | 738 | ~1.05[h,l] 1.26[m] 1.41[m] 1.75[h,i] 1.82[n] ~2.60[h] | 2.83 | 4.39 | ~2.6[h] | 5.20 | 7.82 | 7.49 7.53 7.61 |
| **7** | 3428 | 1679 | 726 | 1.60-2.20[j] 2.50[n] 5.53[o] | ~3.40[h] | 4.22 | ~3.40[h] | 5.23 | 7.83 | 7.45–7.65 |
| **8**[p] | 3262 | 1700 | | 1.35 ~1.70[h,i] 2.11 2.39 5.60[o] | 2.79 | 4.43 | 2.89 | 5.12 | 7.72 | 7.40 7.45 7.53 |

*For easier comparison of analogous spectral data, the numbering of **3** was used for all compounds in the text, the Scheme and the Tables. The correct numbering is given in the Experimental. Assignments were supported by DNOE measurements (except for **4**). [a]In KBr pellets; [b]In $CDCl_3$ solution at 500 MHz; $\delta_{TMS} = 0$ ppm; [c]Split, with the second maximum at 1665 (**4**) or 1681 (**6**); [d]*dd*, *J*: 13.4 and 0.7 (downfield signal of **3**, **5** and **7**, for **7** the *dd* is coalesced to a *t*), *J*: 13.3 and 5.5 (downfield signal of **4**, **6** and **8**), *J*: 13.8 and 4.0 (upfield signal of **5**), *J*: 13.0 and 11.2 (upfield signal of **6** and **8**), *t*, *J*: 13.0 (upfield signal of **4**); [e]Multiplicity: *td*, *J*: 12.6, 4.4 and 4.4 (**4**), ~9, ~5, ~5 (**5**), *dt*, *J*: 10.5, 10.5 and 5.5 (**8**); [f]Pos. 9 (*ortho* to CO substituent), $J_{ortho} \approx 7.4$; [g]Overlapping signals, separated to *t*, *t* and *d* for **6** and **8**, $J_{ortho} \approx 7.5$; [h]Overlapping signals; [i,l]Intensity 2H/3H; [j]In overlap with the NH signal, intensity 4H (**3**), 5H (**7**); [k]Diffuse band with a superimposed maximum at about 3270; [m]Quartet-like signal (1H) of the *axial* H in Pos. 2 or 3; [n]Doublet-like signal (1H) of the *equatorial* H in Pos. 2 or 3; [o]Singlet-like signal (2H) of the olefinic hydrogens in Pos. 2 and 3; [p]NH: 1.05 br *s* (1H).

The *cis*- or *trans*-condensed cyclohexane rings differ in the carbon shifts: due to the field effect[4b] (steric compression shift[5]), the sum of the carbon shifts ($\Sigma\delta C$) is significantly smaller for the *cis* compounds. $\Sigma\delta C$ is 184.5 (**3** and **5**) or 188.8 ppm (**4**) for the *cis*-annelated cyclohexanes, and 217.9 ppm for their *trans* counterpart **6** ($\Delta\Sigma\delta C \approx 32.0$ ppm). Similarly, $\Delta\Sigma\delta C$ is 22.6 ppm for the cyclohexene *cis–trans* pair **7** and **8**: $\Sigma\delta C$: 381.7 ppm (**7**) and 404.3 ppm (**8**). Hence, the *trans* annelation of the cyclohexane/ene ring in **6** and **8** and the *cis* annelation for **3-5** and **7** is unquestionable.

A further problem is to determine the relative positions of the isoindolone NC*H*N hydrogen and the annelational hydrogens of the partially or wholly saturated quinazoline ring. This was established by means of DNOE measurements.[4c,6]

On saturation of the isoindolone H-5a, responses from H-4a, H-12*ax* and H-6 were observed for **3** and **6-8**, which proves the steric proximity of the latter atoms to H-5a. The close location (1,3-*diaxial*) of H-4a and H-5a means the 4a*R**,5a*R**,12a*S** configuration for the *trans* compounds (**6**)

and (8), *i.e.* the *cis* position for H-4a and H-5a, and *trans* orientation for H-5a and H-12a (Scheme). In the *cis*-annelated 3 and 7, the same NOE between H-4a and H-5a confirms the all-*cis* arrangement for H-4a,5a,12a, *i.e.* the configuration 4a*R**,5a*R**,12a*R**. In accordance, a significant field effect (upfield shift by 7.9 or 8.3 ppm) was observed for C-1 relative to C-4 in 3 and 7, due to the steric interaction of the lone electron pair of N-5 and H-1*ax*. In consequence of the β-effect of N-5,[4d,7] the shift difference ΔδC-1,4 (which causes the downfield shift on C-4) is much smaller (3.9 and 3.3 ppm) in the *trans* isomers (6) and (8).

For 5, irradiation of the H-5a signal in the DNOE experiment yielded no response of the H-5a multiplet. This proves the stereostructure containing the annelation hydrogens 4a,12a in the *trans* position with H-5a, *i.e.* the configuration 4a*R**,5a*R**,12a*R**.

Table 2. $^{13}$C-NMR chemical shifts (δ, ppm[a]) for compounds (3-8)[b]

| | $CH_2$ (1) | $CH_2$ (2) | $CH_2$ (3) | $CH_2$ (4) | CH (4a) | NCH (5a) | C-5b | CH (6) | CH (7) | CH (8) | CH (9) | C-9a | C=O (10) | $CH_2$ (12) | CH (12a) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 23.1 | 24.9 | 19.3 | 31.0 | 52.1 | 71.1 | 142.4 | 122.5 | 131.0 | 128.9 | 123.1 | 132.5 | 165.4 | 43.9 | 34.1 |
| 4 | 28.3 | 20.5 | 24.6 | 26.0 | 53.9 | 65.9 | 143.2 | 122.8 | 131.3 | 129.2 | 123.5 | 133.0 | 165.4 | 38.1 | 35.5 |
| 5 | 28.2 | 20.5 | 25.0 | 26.5 | 48.8 | 68.0 | 142.4 | 122.9 | 131.3 | 129.3 | 123.4 | 133.0 | 165.0 | 45.0 | 35.9 |
| 6 | 29.6 | 25.8[c] | 26.1[c] | 33.5 | 59.7 | 72.1 | 143.0 | 123.3 | 131.8 | 129.7 | 123.9 | 133.5 | 165.4 | 44.6 | 43.2 |
| 7 | 22.9 | 122.9[c] | 124.9[c] | 31.2 | 50.9 | 71.3 | 142.2 | 122.6 | 131.2 | 129.0 | 123.2 | 132.3 | 166.0 | 43.4 | 29.9 |
| 8 | 29.0 | 125.5[c] | 125.0[c] | 32.3 | 55.0 | 71.2 | 142.5 | 122.8 | 131.4 | 129.2 | 123.4 | 132.9 | 164.7 | 43.7 | 37.5 |

[a]In $CDCl_3$ solution, at 125.72 MHz; $\delta_{TMS}$ = 0 ppm; [b]Assignments were proved by DEPT, and for 3 and 6-8 also by 2D-HSC measurements; [c]Interchangeable assignments.

For 4, the *cis* annelation of the cyclohexane and the vicinity of the methylene group with the amide-N was proved above. In the knowledge of the stereostructure of the diastereomer (3), which also contains a *cis*-annelated cyclohexane ring, for 4, the only possible structure that remains is that in which the annelation hydrogens and H-5a are in the *trans* position. In comparison with 3, the significant field effects on C-5a (5.2 ppm) and C-12 (5.8 ppm), due to the steric interaction with the 4-methylene group in the 1,3-*diaxial* position, are proof of this structure. The corresponding field effects on 2-$CH_2$ and 4-$CH_2$ are 4.4 and 5.0 ppm. Consequently, 4 has the configuration 4a*R**,5a*S**,12a*R**.

The above results support our previous finding:[1,2,8] in similar cyclizations, the *cis* or *trans* cyclic 1,3-amino alcohols or 1,3-diamines always react with retention of the configuration.

## EXPERIMENTAL

The $^1$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker DRX 500 spectrometer at 500.13 ($^1$H) and 125.76 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock, and TMS as internal standard. The standard Bruker microprogram DNOEMULT.AU to generate NOE was used with a selective pre-irradiation time. DEPT spectra[9] were run in a standard manner,[10] using only the θ = 135° pulse to separate the $CH/CH_3$ and $CH_2$ lines phased "up" and "down", respectively. The 2D-HSC spectra[11] were ob-

tained by using the standard Bruker pulse program HXCO.AU. IR spectra were run for KBr discs on a Bruker IFS-55v FT-spectrophotometer controlled by Opus 2.0 software. HPLC: ISCO system with two pumps, suitable for gradient elution; Chem. Research control system and data processing program. For the semipreparative separation, a 250 × 4 mm Nucleosil 5 Si column (250 × 16 mm) was used. Injected sample: 500 µl, of a 4% MeOH–THF (2 + 1) solution, detection at 270 nm.

**10*H*,12*H*-1,2,3,4,4a,5,5a,12a-Octahydroisoindolo[1,2-*b*]quinazolin-12-ones (3, 4, 6), 6*H*,12*H*-1,2,3,4,4a,10b,11,12a-octahydroisoindolo[2,1-*a*]quinazolinone (5) and 10*H*,12*H*-1,4,4a,10b,-11,12a-hexahydroisoindolo[1,2-*b*]quinazolin-6-ones (7 and 8). General procedure**

A mixture of 2-carboxybenzaldehyde (1) (1.5 g, 0.01 mol), *cis*- or *trans*-2-amino-1-cyclohexylmethylamine (2a) or (2b) (1.3 g, 0.01 mol) or -4-cyclohexenyl-1-methylamine (2c) or (2d) (1.3 g, 0.01 mol) and *p*-toluenesulphonic acid (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 6 h with use of a water separator. After cooling, the mixture was evaporated to dryness at reduced pressure. For the preparation of 3-5, the residue was separated by HPLC; eluent: *n*-hexane–MeOH–*i*-PrOH–$CH_2Cl_2$ (90 + 4 + 1 + 5 v/v%); flow rate: 1 ml/min. For 6-8, it was transferred to an $Al_2O_3$ column (basic $Al_2O_3$, activated, 50-200 µm, Janssen) and eluted with EtOAc. After the solvent was evaporated off, the residues were crystallized. Data on 3-8 are listed in Table 3.

Table 3. Physical and analytical data for compounds (3-8)*

| Compd | mp °C | Yield % | Formula | Analysis Calcd % C | H | N | Found % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 172-174[a] | 24 | $C_{15}H_{18}N_2O$ | 74.35 | 7.49 | 11.64 | 74.27 | 7.36 | 11.50 |
| 4 | 177-179[a] | 20 | $C_{15}H_{18}N_2O$ | 74.35 | 7.49 | 11.64 | 74.39 | 7.38 | 11.71 |
| 5 | 148-150[b] | 33 | $C_{15}H_{18}N_2O$ | 74.35 | 7.49 | 11.64 | 74.50 | 7.61 | 11.65 |
| 6 | 127-129[b] | 62 | $C_{15}H_{18}N_2O$ | 74.35 | 7.49 | 11.64 | 74.81 | 7.61 | 11.73 |
| 7 | 167-168[c] | 68 | $C_{15}H_{16}N_2O$ | 74.97 | 6.71 | 11.66 | 75.11 | 6.82 | 11.79 |
| 8 | 115-117[b] | 64 | $C_{15}H_{16}N_2O$ | 74.97 | 6.71 | 11.66 | 75.08 | 6.67 | 11.81 |

*Crystallization solvent: [a]EtOH, [b]EtOAc, [c]dioxan

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# The First Preparation of a Heterotricycle, [1,3]Oxazino[2,3-*a*]isoindole-2,6-dione, by a Retro Diels–Alder Method†‡

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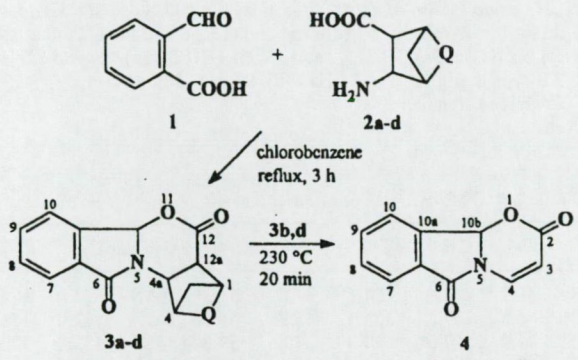
**Abstract:** Hexahydro- **3a,c** and tetrahydroisoindolo[2,1-*a*][3,1]-benzoxazine-6,12-diones **3b,d** were prepared by the reaction of 2-carboxybenzaldehyde (**1**) with *diendo*- and *diexo*-3-aminobicyclo-[2.2.1]hexane/ene-2-carboxylic acids **2a–d**. When heated, **3b** and **3d** (containing a norbornene structural moiety) undergo retrodiene decomposition by splitting off cyclopentadiene to give the 1,3-oxazino[2,3-*a*]isoindole-2,6-dione (**4**). This is the first example of the preparation of a condensed heterotricyclic compound in a retro Diels–Alder reaction. The results reveal that this reaction can be extended to the formation of new condensed-skeleton polycyclic hetero compounds which have an electron-rich moiety in the terminal ring of the fused heterocycle formed by the splitting off of cyclopentadiene. The structures of the pentacyclic hetero compounds **3a–d** were determined by NMR spectroscopy.

**Key words:** [1,3]oxazino[2,3-*a*]isoindole-2,6-dione, retro Diels–Alder, 1,4-methanohexahydro- and tetrahydroisoindolo[2,1-*a*]-[3,1]-benzoxazine-6,12-diones




**a**: *diendo*, Q = $CH_2CH_2$; **b**: *diendo*, Q = CH=CH
**c**: *diexo*, Q = $CH_2CH_2$; **d**: *diexo*, Q = CH=CH

*diendo*- and *diexo*-3-Aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids **2b,d**[1, 2] were recently used to prepare known and previously unknown heteromonocycles[3] and bicyclic derivatives in retro Diels–Alder (RDA) reactions.[4, 5] The principle of these procedures is the synthesis of the partially saturated parent heterocycles on cyclopentadiene, which is removed from the condensed-skeleton molecules in the final reaction step, resulting in the target compound by introduction of a new double bond. The importance of the RDA reaction was recently highlighted by its application for the preparation of an enantiomerically pure compound[6] and its study in aqueous solution.[7, 8] The present paper describes an extension of the scope of this new retrodiene reaction, i.e. the application of 2-carboxybenzaldehyde (**1**) for the preparation of fused-skeleton heterotricycles from norbornene amino acids **2b,d**.

The reaction of 2-carboxybenzaldehyde (**1**) with *diendo*- or *diexo*-3-aminobicyclo[2.2.1]hexane-2-carboxylic acids **2a,c** or *diendo*- or *diexo*-3-aminobicyclo[2.2.1]hex-5-ene-2-carboxylic acids **2b,d** gave 1,4-methanohexahydro-**3a,c** and tetrahydroisoindolo[2,1-*a*][3,1]benzoxazine-6,12-diones **3b,d** in moderate yields (45–54%). In all these compounds, the *diexo*- or *diendo*-norbornene annulational hydrogens and the 1,3-oxazinoisoindoledione NC*H*O hydrogen are in the *cis* position. Similarly, as observed earlier for related norbornene-fused 1,3-heterocycles, **3b,d** undergo retrodiene decomposition when heated to their melting points. In these reactions, cyclopentadiene is split off and 2*H*,6*H*-1,3-oxazino[2,3-*a*]isoindole-2,6-dione (**4**) is formed, which can be isolated in 38–42% yield after a simple purification by column chromatography.

The structures of the new compounds **3a–d** and **4** follow straightforwardly from the spectral data given in Tables 1 and 2. For **3a–d**, the *diexo* or *diendo* annulation of the norbornane/ene unit to the oxazinone ring can be determined via the multiplicity of the annulated hydrogens in positions 4a and 12a.[9, 10] In the *diexo* compounds **3c,d**, as a consequence of the dihedral angles which are ~90°, the H-1/H-12a and H-4/H-4a interactions are not significant (according to the Karplus relation[11]), and hence the H-4a and H-12a signals are doublets corresponding to the mutual interactions of these hydrogens, while for the *diendo* **3a,b** these signals are double doublets (here the above dihedral angles are ~30°). The relative configuration of C-10b (between the N and O) must also be determined. This is possible by means of NOE measurements.[12, 13] The results of these experiments (Table 3) show the all-*cis* arrangements for H-4a, H-10b and H-12a in all pentacyclic compounds.

Cycloreversion proceeds readily in the retrodiene decomposition, i.e. a new double bond is formed between the two carbons of the target molecule, if an oxo- or thioxo-substituted heteroaromatic or quasi-heteroaromatic system is formed, e.g. pyrimidinone, pyrimidinedione, thioxopyrimidinone or 1,3-oxazin-6-one.[3] The present case is the first example of the formation of a fused tricyclic hetero compound containing two fused partially saturated hetero rings and one aromatic ring in a RDA reaction. The overall structure, but especially the fused 1,3-oxazin-6-one terminal ring in **4**, is very similar to the heteromonocycle 2-aryl-1,3-oxazin-6-ones which were prepared in an analogous way,[14] with the difference that **4** contains no C=N bond between the aryl-substituted carbon and the ni-

Table 1. IR Carbonyl Frequencies ($\nu_{co}$, $cm^{-1}$)[a] and $^1H$ NMR Data ($\delta$)[b] of 3a–d and 4[c]

| | H-1 ~s (1H) | H-2[d] 2 × m (2 × 1H) | H-3[d] 2 × m (2 × 1H) | H-4 ~s (14) | H-4a[e] d/dd (1H) | H-7 dd (1H) | H-8,9,10 m(3H) | H-10b s (1H) | H-12a[e] d/dd (1H) | $CH_2$(13)[f] 2 × d (2 × 1H) |
|---|---|---|---|---|---|---|---|---|---|---|
| 3a | 2.85 | ~1.50[g] | ~1.50[g] | 3.45 | 4.12 | 7.84 | ~7.6 | 6.18 | 3.08 | ~1.50[g] 1.60 |
| 3b | 3.52 | 6.23 | 6.15 | 4.20 | 4.42 | 7.80 | ~7.55 | 6.13 | 3.22 | 1.48[h] 1.73[i] |
| 3c | 3.02 | ~1.35[g,h] ~1.7[g,i] | ~1.35[g,h] ~1.7[g,i] | 4.02 | 3.98 | 7.80 | ~7.6 | 6.11 | 2.74 | ~1.35[g] 1.45 |
| 3d | 3.54 | 6.31 | 6.25 | 4.60 | 3.86 | 7.80 | ~7.6 | 6.17 | 2.66 | 1.45[h] 1.60[i] |
| 4 | – | – | – | – | 7.85 | 7.92 | ~7.7 | 6.59 | 5.60 | – – |

[a] KBr disc.
[b] $CDCl_3$ solution at 500 MHz, $\delta_{TMS} = 0$
[c] Assignments were supported by 2D-HSC and DNOE measurements (except for 4).
[d] $CH_2$ group for 3a, c $C(sp^2)H$ group for 3b, d, 2 × dd, (2 × 1H), $J$ = 5.5 and 3.0 Hz.
[e] dd for the diendo 3a, b, d for the diexo 3c, d and for 4. Further split to ddd (3a) due to long-range coupling with H-13$_{exo}$, $J$ = 10.8, 3.9 and 1.1 Hz (H-4a, 3a), 10.8, 5.0 and 1.7 Hz (H-12a, 3a), 8.7 and 3.5 Hz (H-4a, 3b), 8.7 and 4.1 Hz (H-12a, 3b), 8.0 Hz (3c), 7.5 Hz (3d and 4).
[f] AB-type multiplet, $J$ = 9.4 Hz (3b), 9.7 Hz (3d).
[g] Coalesced signals.
[h] endo.
[i] exo.

Table 2. $^{13}C$ NMR Data ($\delta$) of 3a–d and 4[a]

| | C-1 | C-2 | C-3 | C-4 | C-4a | C-6 | C-6a | C-7 | C-8 | C-9 | C-10 | C-10a | C-10b | C-12 | C-12a | C-13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3a | 40.9 | 24.6 | 21.6 | 39.8 | 54.3 | 165.9 | 133.0 | 124.6 | 123.9 | 133.5 | 131.5 | 140.2 | 84.8 | 171.6 | 43.8 | 36.7 |
| 3b | 46.3 | 137.3 | 135.1 | 45.7 | 54.2 | 165.4 | 132.0 | 123.6 | 123.5 | 132.4 | 130.6 | 138.7 | 84.2 | 170.2 | 43.3 | 45.6 |
| 3c | 41.9 | 27.0[b] | 27.4 | 37.8 | 59.3 | 166.1 | 132.8 | 123.7 | 123.4 | 132.6 | 130.7 | 138.2 | 83.9 | 170.2 | 48.4 | 34.7 |
| 3d | 47.4 | 137.6 | 137.0 | 43.5 | 55.6 | 166.3 | 132.7 | 123.9 | 123.8 | 132.9 | 131.0 | 138.9 | 84.7 | 170.9 | 43.5 | 44.9 |
| 4 | – | – | – | – | 137.2 | 162.5[b] | 130.8 | 124.2 | 125.1[c] | 134.5 | 131.3 | 139.3 | 83.8 | 163.2[b] | 101.2 | – |

[a] In $CDCl_3$ solution at 125.72 MHz. $\delta_{TMS} = 0$. Assignments were supported by DEPT (except for 3b) and 2D-HSC measurements (except for 4).
[b] Interchangeable assignments.

Table 3. DNOE Results for 3a–d[a]

| Saturated signal | H-4a | H-10b | H-12a |
|---|---|---|---|
| H-4a | | 3a, c, d | 3a–d |
| H-10b | 3a–d | | 3a–d |
| H-12a | 3a–d | 3a–d | |
| H-13 (*endo*) | 3a, b | | 3a,b |
| H-2,3 (*endo*) | 3c | | 3c |
| H-2 | | | 3d |

[a] Nontrivial responses[b] proving the *cis* arrangements of H-4a, H-10b and H-12a and the *diexo* or *diendo* annulation to the oxazinone ring
[b] The trivial responses of the a) H-1, b) H-4 and c) H-10 signals were observed when the a) H-12a, b) H-4a and c) H-10b signals were saturated for all compounds 3a–d.

trogen of the six-membered hetero ring. However, in the structure of 4, a fused aromatic ring is attached to the $sp^3$ carbon situated between the two hetero atoms, and a benzoyl carbonyl is attached to the bridgehead nitrogen. This structural pattern lends a quasi-aromatic character to the 1,3-oxazin-6-one system produced by the splitting-off of cyclopentadiene, although it is obvious that the formation of this ring system is less favorable than that of the related heteroaromatic monocycles, for in these tricycles the second double bond in the six-membered hetero ring is missing. The energy difference between the heteroaromatic monocyclic and quasi-heteroaromatic tricyclic systems is reflected by the much higher temperature necessary for the formation of 4.

The present results encourage us to extend the scope of the RDA method in the direction of more complicated hetero compounds in which the electrons required for terminal hetero ring formation are supplied by heteroatoms, i.e. the preparation of new polycyclic hetero compounds can be anticipated. Analogous condensed-skeleton heterocyclic compounds similar to the earlier synthesized heteromonocycles may be obtained in RDA reactions from molecules containing electron-rich structural moieties which promote the formation of the new double bond in the product and substitute the second double bond formally required for the aromaticity of the (terminal) hetero ring of the product.

The above method affords an easy synthesis of the previously unknown tricyclic system 4 and illustrates the general scope and importance of formation of a partially unsaturated or aromatic hetero compound via the RDA technique, by building up a heterocyclic molecule on the norbornene derivative prepared from cyclopentadiene and splitting off the cyclopentadiene by heating in the final reaction step. This method does not require the flash vacuum pyrolysis applied in traditional RDA reactions.[15]

IR spectra were as KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ in 5 mm tubes at r.t., on a Bruker DRX-500 spectrometer at 500.13 ($^1H$) and 125.76 ($^{13}C$) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. For

DNOE measurements,[12, 13] the standard Bruker microprogram DNOEMULT.AU to generate NOE[12] was used, with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of ~3–40 mW; number of scans 4–8, pulse width 5.0 μs (90°) and 16 K data points for ~2 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

The standard Bruker microprogram NOEMULT.AU to generate NOE[16] was used with a selective pre-irradiation time. DEPT spectra[17] were run in a standard manner,[18] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased "up" and "down", respectively.

The 2D-HSC spectra[19] were obtained by using the standard Bruker pulse program HXCO.AU.

All elemental analysis results agreed with the calculated values within ±0.2%.

***diendo*- and *diexo*-1,4-Methano-1,2,3,4,4a,12a-hexahydro- (3a,c) and -1,4,4a, 12a-Tetrahydro-6*H*,12*H*-isoindolo[2,1-*a*][3,1]benzoxazine-6,12-diones (3b,d):**

A mixture of 2-carboxybenzaldehyde (1) (1.50 g, 10 mmol) and 3-*endo*-aminobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid[1] (2a) or -2-*exo*-carboxylic acid[2] (2c) (1.55 g, 10 mmol) or the -hept-5-ene derivatives (*diendo*: 2b and *diexo*: 2d) (1.53 g, 10 mmol) and TsOH (0.05 g) in anhyd chlorobenzene (70 mL) was refluxed for 3 h, a water separator being applied. After evaporation to dryness at reduced pressure in the cases of 3a and 3c, the residue was transferred to a chromatography column (alumina, Acros, 50–200 μ, activated basic) and eluted with benzene and then with EtOAc. Evaporation of the latter and crystallization of the residue from EtOH led to 3a [yield: 1.45 g (54%); mp 202–204 °C, $C_{16}H_{15}NO_3$] or 3c [yield: 1.51 g (56%); mp 202–224 °C]. For 3d, the EtOAc eluate was evaporated off and the residue was crystallized from EtOAc [yield: 1.20 g (45%); mp 185–188 °C]. For 3b, the residue was purified by a HPLC method using an ISCO system with two pumps suitable for gradient elution. The Chem. Research control system and data processing program were applied. For the semipreparative separation, a Nucleosil 5 Si column was used [hexane/MeOH/i-PrOH/$CH_2Cl_2$ 90:4:1:5 v/v; r.t.; flow rate 1.0 mL/min] [yield: 1.28 g (48%); mp 225–227 °C ($CH_2Cl_2$/i-$Pr_2O$), $C_{16}H_{13}NO_3$].

**2*H*,6*H*-1,3-Oxazino[2,3-*a*]isoindole-2,6-dione (4):**

3b or 3d (1.0 g, 3.7 mmol) was melted and kept at 230 °C for 20 min. The cooled mixture was dissolved in EtOAc, transferred onto a chromatography column (alumina, Acros, 50–200 μ, activated basic) and eluted with EtOAc. After evaporation of the solvent, the residue was crystallized from EtOH; yield: 0.28 g (38% from 3b) or 0.31 g (42% from 3d); mp 196–198 °C, $C_{11}H_7NO_3$.

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# Comparative Bioanalytical Study of $^{3}$H-Deramciclane in Dog Plasma, Using a Gas Chromatography-Nitrogen-Selective Detection (GC-NPD), a New GC-Radiochemical Detection (GC-RD) and a Liquid Scintillation Method

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## Key Words

$^{3}$H-Deramciclane
$^{3}$H-N-desmetil deramciclane metabolite
Gas chromatography-nitrogen-selectiv detection (GC-NPD)
Gas chromatography-radiochemical detection (GC-RD)
Liquid scintillation counting (LSC)

## Summary

A new, highly sensitive and selective gas chromatography method, using radiochemical detection (GC-RD) was developed for the selective determination of $^{3}$H-labelled deramciclane and its N-desmethyl metabolite in dog plasma. Inter-day accuracy and precision, as well as system suitability of the GC-RD method was investigated during the method validation. The calibration curve was proved to be linear ($r = 0.9986$) in a wide concentration range (13–1000 ngeqv $mL^{-1}$).

The lower limit of quantitation (LLOQ) was 13.7 ngeqv $mL^{-1}$, and the limit of the detection (LOD) was 1 ngeqv $mL^{-1}$.

Using this new GC-RD method, plasma levels of $^{3}$H-labelled deramciclane and its metabolite were determined in dogs, after the administration of a single 10 mg $kg^{-1}$ oral dose. Pharmacokinetic curves and the calculated pharmacokinetic parameters were compared to those obtained using a previously elaborated gas chromatography-nitrogen selective detection method (GC-NPD) and to those obtained by measuring the plasma level of total radioactivity (liquid scintillation counting, LSC). Pharmacokinetic curves and the calculated pharmacokinetic parameters obtained with the two different gas chromatography detection methods (NPD and RD) showed good correlation. Comparison of these results to those acquired by total radioactivity measurement demonstrated that deramciclane was intensively metabolised. Moreover, the biological half-life ($t_{1/2}^{\beta}$) of the unknown metabolites proved to be more than a magnitude longer than the half-life of the parent compound or that of N-desmethyl metabolite.

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## Introduction

Deramciclane fumarate (*1R,2S,4R*)-(-)-N,N-dimethyl-2-[(1,7,7-trimethyl-2-phenyl-bicyclo-[2,2,1]hept-2-yl)oxy] ethanamine-2-(E)-butenedioate (1:1) (EGIS-3886, Figure 1) is a new non-benzodiazepine type anxyolitic compound [1–4] developed by EGIS Pharmaceuticals Ltd. (Budapest, Hungary).

For the determination of deramciclane levels in plasma samples collected in pharmacokinetic studies performed in different species, several different gas chromatography methods were elaborated. In the case of pharmacokinetic studies performed in rats, dogs and rabbits, different high sensitivity nitrogen selective (NPD) and mass spectrometry detection methods had to be applied due to the low doses and to the "first-pass" metabolism that varied in intensity depending on the species [5–8]. Using these methods, parent compound and its N-desmethyl metabolite (EGIS-7056) were selectively determined in plasma samples. For the in vitro and in vivo metabolism studies of deramciclane, thin layer chromatography with digital autoradiography detection (TLC-DAR) [9] and TLC-DAR-FAB-MS-MS [10] coupling as well as high performance liquid chromatography separation, followed by radiochemical detection (HPLC-RD) were applied [11].

In pharmacokinetic studies, liquid scintillation counting (LSC) is a frequently used method for the determination drug molecules labelled with different radioiso-



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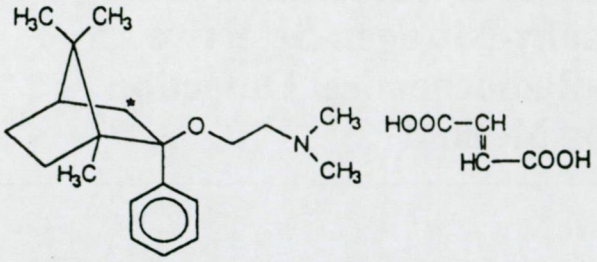

**Figure 1**
Structural formula of $^3$H-deramciclane fumarate (EGIS-3886). * denotes the position of $^3$H-labelling.

topes in biological matrices. The method allows the determination of total radioactivity of the sample without separating the parent compound and its metabolite(s) [12–14].

From among the techniques used in pharmacokinetic and metabolite kinetic studies – unlike HPLC-radiochemical detection (HPLC-RD) – radio-gas chromatography (GC-RD) developed in the 80-s is used relatively infrequently [15, 16]. As an advantage, the HPLC-RD technique offers the possibility of metabolite isolation for structure identification at the micropreparative level. On the other hand, the advantages of GC-RD method are high selectivity for the radiolabelled components and extreme sensitivity.

In the present study, comparative bioanalytical investigations were made by the analysis of plasma samples of Beagle dogs treated with $^3$H-deramciclane. Total radioactivity was determined using liquid scintillation counting (LSC), while the plasma level of $^3$H-deramciclane and its N-desmethyl metabolite was determined by capillary gas chromatography, applying two different detection techniques. The previously elaborated GC-NPD bioanalytical method was compared to the recently elaborated and optimised coupled technique of GC-radiochemical detection (GC-RD) that allowed the selective determination of the radioactive components of the sample. Various pharmacokinetic parameters calculated from the plasma concentration-time curves of the parent compound and its metabolite measured by different analytical methods were compared to those obtained by the determination of total radioactivity levels. On the basis of the above results, the usefulness of the analytical method for the analysis of biological samples could also be evaluated.

## Experimental

### Chemicals and Other Materials

Deramciclane fumarate and bencyclane fumarate (3-[1-bencycloheptyl)oxy]-N,N,-dimethylpropylamine-fumarate, the internal standard for the GC-NPD method) were manufactured by EGIS Pharmaceuticals Ltd.

Radiolabelled deramciclane-camphor-3-$^3$H-fumarate (specific activity 65.38 MBq mg$^{-1}$; radiochemical purity > 98.5 %) was prepared in the Isotope Institute and in the Central Chemical research Institute of the Hungarian Academy of Sciences, Budapest [17].

For liquid scintillation counting, Soluene®-100 tissue solubiliser (Canberra Packard, Groningen, The Netherlands), and Aquasol® liquid scintillation solution (NEN®, Boston, USA) were used.

For the extraction of dog plasma and for the different gas chromatographic examinations, the following chemicals were used: *water*, chromatography grade; *acetic acid, acetonitrile*, analytical grade; *2-propanol, methanol*, residue analysis grade (E. Merck, Darmstadt, Germany), and *Selecton B$_2$* ($Na_2$-EDTA), analytical grade (Reanal, Budapest, Hungary). For the extraction of plasma samples, a *LiChrolut* solid phase extraction column (SPE) with 200 mg of RP-18 packing (E. Merck) was used.

High purity helium (4.6), hydrogen (3.8) and methane (4.5) were used for the different gas chromatography measurements (Linde Gas Hungary Ltd, Répcelak, Hungary).

### Instrumentation

Total radioactivity was determined with a Packard® Tri-Carb 2000 CA liquid scintillation counter (LSC) (Canberra Packard, Groningen, The Netherlands).

Analysis of plasma extracts was performed with a Hewlett-Packard 5890 Series II. gas chromatograph equipped with nitrogen-phosphorous selective detector, HP 7673A autosampler, a Vectra VL Series 3 5/75 computer with a GC ChemStation software (G2071AA Version A.03.02) and a HP DeskJet 500 printer (Palo Alto, CA, USA). The gas chromatograph was connected online to a RAYTEST RAGA-93 Radioactivity Gas Analyser (radio-gas chromatography detector; GC-RD), (Raytest Isotopenmessgeräte GmbH, Straubenhardt, Germany). The Raytest detector was operated with the Gina Chromato-Graphic-System ver. 3.2. software.

Depending on the labelling ($^{14}$C or $^3$H), the RAYTEST RAGA-93 GC radioactivity detector pyrolyses the sample catalytically to $CO_2$ or $CH_4$ in a silica reactor tube at approximately 700 °C and measures the radioactivity by proportional counting. Reduction of $^3$H-deramciclane was carried out in the presence of a platinum catalyst at 750 °C in a hydrogen atmosphere.

### Liquid Scintillation Counting (LSC)

The total radioactivity content (deramciclane and its metabolites) of plasma samples was determined with the commonly used liquid scintillation procedure [12, 14]. One mL of dog plasma sample was added to 1 mL of Soluene® and 10 mL of Aquasol®. Automatic quench correction was made using the external standard ratio method. The detection limit of radioactivity was stated to be twice the background level activity.

## Standard Solutions

For the purpose of the development of the GC-RD bioanalytical method, a series of calibrators were prepared using 1 mg $mL^{-1}$ concentration methanolic stock solution of the reference standard ($^3$H-deramciclane) substance.

The stock solution was diluted with distilled water to obtain a 1000 ng $(50\ \mu L)^{-1}$ solution. This solution was diluted 20-fold to obtain a 1000 ng $mL^{-1}$ concentration solution. Serial dilution of the above solutions yielded the following plasma concentrations: 1000, 500, 250, 100, 41 and 13.7 ng $mL^{-1}$.

## Processing of Plasma Samples

Dog plasma samples stored at -20 °C were allowed to thaw at room temperature and extracted with previously washed and activated LiChrolut 200 mg RP-18 solid-phase extraction (SPE) column, using a previously developed method [5, 7]. Substances to be determined were eluted with 1 mL of 1 % (v/v) acetic acid in methanol into an Eppendorf-tube. The eluate was then evaporated to dryness in a stream of nitrogen on a lukewarm water-bath. The residue was then dissolved in 50 µL of 2-propanol and transferred into disposable microvial. Two microlitres were injected into the gas chromatograph with an autosampler (GC-NPD) or manually (GC-RD).

## GC-NPD Gas Chromatography Conditions

Unchanged deramciclane and N-desmethyl-deramciclane levels of dog plasma samples were determined by a previously elaborated [5] gas chromatography nitrogen selective detection (GC-NPD) method validated according to internationally accepted criteria [18]. Using optimised column temperature and carrier gas pressure programming, good resolution and sensitive determination was achieved in the biological matrix. Linearity of the calibration curve of the parent compound was good in the 0.5–1000 ng $mL^{-1}$ concentration range. The lower limit of quantitation was 0.5 ng $mL^{-1}$ for deramciclane and 1 ng $mL^{-1}$ for the N-desmethyl metabolite. The difference was due to different relative detector responses.

## GC-RD Gas Chromatography Conditions

For the selective, highly sensitive determination of $^3$H-deramciclane and its $^3$H-N-desmethyl metabolite, a new radio-bioanalytical method was elaborated and validated.

Gas chromatography parameters were optimised according to the demands of the on-line connected radiodetector (RD). The stationary phase was a Supelco SPB-5 30 m × 0.25 mm ID, 0.25 µm film thickness fused silica capillary column (Supelco, Bellefonte, PA., USA). The oven temperature and the carrier gas pressure were programmed (EPC) according to the tolerance of the flexible PEEK reactor supporting tube, that was located in the oven:

- Temperature: 100 °C (0.4 min), 13 °C $min^{-1}$: 185 °C (20 min), 50 °C $min^{-1}$: 250 °C (4 min), 70 °C $min^{-1}$: 100 °C.
- Pressure: 340 kPa (0.05 min), 500 kPa $min^{-1}$: 190 kPa (7 min), 400 kPa $min^{-1}$: 100 kPa: (21 min), 100 kPa $min^{-1}$: 340 kPa.

The injector was operated in the split mode (10 mL $min^{-1}$, 240 °C). The injection volume was 2 µL.

The reactor of the RAYTEST RAGA-93 radioactive gas analyser (detector) was connected to the capillary column in the oven of the gas chromatograph. The packing of the reactor consisted of approximately 6 g of platinum wire shavings. The packing was placed into the 2 mm ID, 165 mm long fused silica reactor tube so that it was located in the middle third of the catalyst. Platinum shavings were fixed with asbestos wool. Reduction was carried out at 750 °C in a mL $min^{-1}$ hydrogen stream. High purity (4.5) methane at a 15 mL $min^{-1}$ flow rate was used as counter gas. The proportional counter was operated at 3400 V, the splitter was set to 100 %.

## Linearity, Precision and Accuracy of the GC-RD Method

The new GC-RD bioanalytical method was validated according to the consensus reported in [18]. *Linearity* of the calibration curve was investigated in the 13.7–1000 ng $mL^{-1}$ concentration range, using spiked plasma samples. The calibration equation was calculated from the peak area values (reported by GINA Chromato-Graphic-System ver. 3.2.) of $^3$H-deramciclane with 1 $y^{-2}$ weighting, that is common in bioanalytical practice. The 8.9-fold difference between the specific activity of the $^3$H-deramciclane reference standard and that of the tritiated deramciclane used for the animal treatment was taken into consideration when calculating the calibration equation. Accordingly, the equation of the curve fitted to the calibration points was: $Y = 5.705456 + 2.04158 \times X$ ($r = 0.9987$).

Three calibrators were measured at each concentration level of the wide calibration range to determine the linearity, accuracy and precision of the determination of $^3$H-deramciclane. Linearity, precision and accuracy were characterised by the coefficient of variation, the RSD% and the deviation from the nominal concentration, respectively.

System suitability of the radio-gas chromatograph was tested at the 200 ng $mL^{-1}$ concentration, after five parallel injections ($n = 5$) from a spiked and extracted plasma sample.

## Animal Experiment

$^3$H-deramciclane and unlabelled deramciclane were weighted separately, and then mixed in the ratio of 1 : 14 to obtain an appropriate radioactive concentration according to the desired limit of detection (approximately 500 pg $mL^{-1}$ plasma). Homogeneity and specific activity of the mixture was checked using liquid scintillation

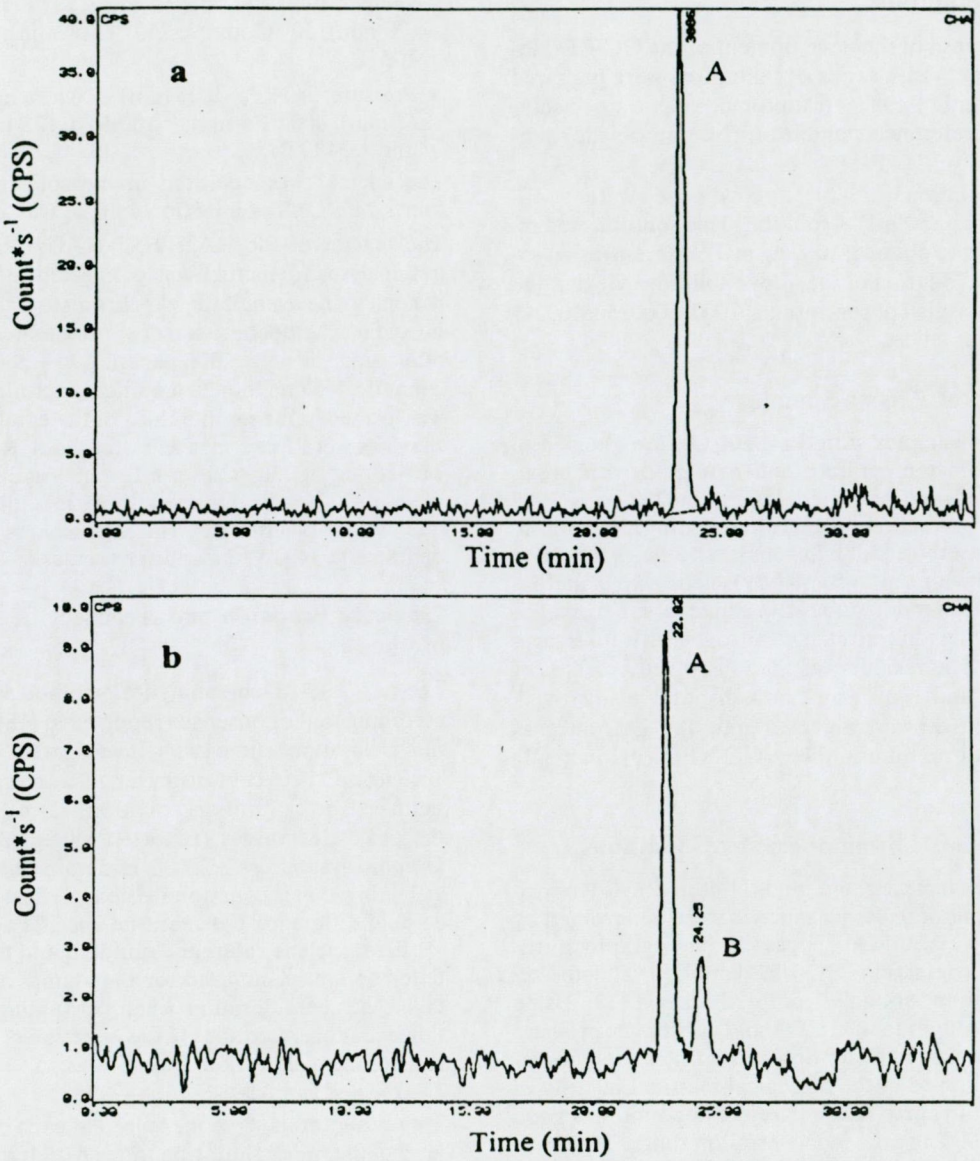


**Figure 2**

**a** Radio-gas chromatogram of $^{3}$H-deramciclane reference standard from testing radiochemical purity. Injected amount: 2 µL of 200 ng mL$^{-1}$ methanolic solution.

**b** Radio-gas chromatogram of a dog plasma extract, resolution test. Sampling: 4 hours after the administration of 10 mg kg$^{-1}$ $^{3}$H-deramciclane. Radio-chromatorgaphic parameters are described in the text. (A: $^{3}$H-deramciclane; B: $^{3}$H -N-desmethyl-deramciclane)

counting (LSC). The specific activity of the homogenate was 4.80 MBq mg$^{-1}$ (287831 dpm µg$^{-1}$). The radioactive test material was formulated in a hard gelatine capsule.

After 7 days of acclimatisation and 12 hours of fasting period, a one year old male Beagle dog weighing 9.9 kg, (WOBE Beagle Kennel Ltd. Budapest, Hungary) was treated with a single 10 mg kg$^{-1}$ oral dose of the above $^{3}$H-deramciclane formulation [19, 20].

## Blood Sampling for Pharmacokinetic Investigations

Blood samples for the pharmacokinetic experiments were taken from the brachial vein with a VASOCAN cannula (B. Braun, Melsungen AG., Melsungen, Germany) containing 1 % heparin in physiological saline solution, or with occasional venipuncture. Nine mL of blood was drawn into glass tube containing 1 mL of anticoagulant (EDTA) solution. Blood sampling times are presented in Figure 2.

Blood samples were centrifuged at 2000 g for 20 min. Plasma was then separated and stored in a deep-freezer at -20 °C until processing.

### Determination of $^3$H-Deramciclane and $^3$H-N-Desmethyl Deramciclane Concentration of Plasma Samples

Quantitative determination of $^3$H-deramciclane and its metabolite was performed on the basis of the peak area values reported by the GC-RD instrument. The equation of the external standard calibration was the following:

$$Q = 1.111\ (y - b)\ a^{-1}$$

where Q stands for the ngeqv/mL value of $^3$H-deramciclane, a and b are the parameters of the calibration line, y represents the peak area and 1.111 is a correction factor for the dilution caused by the anticoagulant. The $^3$H-desmethyl deramciclane concentration of plasma samples was also calculated with the above equation.

In each run, the stability of the radioactivity detector response was checked using a 200 ng mL$^{-1}$ methanolic solution of $^3$H-deramciclane. The selectivity of the GC-RD system was checked with an extracted plasma sample taken 4 hours after treatment.

### Pharmacokinetic and Statistical Analysis

The pharmacokinetic parameters were determined from the plasma concentration-time data using Siphar/Win validated pharmacokinetic software (SIMED SA. Biostatistics and Data Processing, Creteil, Cedex, France) [21, 22]. Statistical evaluation was performed with Statistica For Windows ver. 4.5 software (StatSoft Inc., Tulsa, OK, USA).

## Results and Discussion

### The New Radio-Gas Chromatography Method

A new, highly sensitive, simple and validated radiochromatography (GC-RD) method was developed and validated for the selective determination of $^3$H-deramciclane and $^3$H-desmethyl deramciclane. The two solutes were separated in a fused silica capillary column under optimised programmed temperature and pressure conditions. Tritium-labelled molecules were subjected to reduction at 750 °C in the presence of a platinum catalyst in a hydrogen stream to yield a radioactive gas that could be measured with high sensitivity.

Figure 2a shows the radio-gas chromatogram of $^3$H-deramciclane reference standard (external standard) obtained while checking radiochemical purity.

After checking the selectivity of the separation of $^3$H-deramciclane and $^3$H-desmethyl deramciclane peaks, the optimised GC-RD system was used to determine the $^3$H-deramciclane concentration in biological samples.

The radio-chromatogram (Figure 2b) of the extract of a dog plasma sample taken 4 hours after treatment with a single 10 mg kg$^{-1}$ oral dose of $^3$H-deramciclane shows the well-separated, symmetrical peaks of the parent compound and its metabolite.

The calibration curve showed very good linearity for $^3$H-deramciclane in the 13.7-1000 ngeqv mL$^{-1}$ concentration range ($r = 0.9986$). According to the validation results, the lower limit of the quantitation (LLOQ) of the gas chromatography – radiochemical detection method was 13.7 ngeqv mL$^{-1}$. The detection limit (LOD) was 1 ngeqv mL$^{-1}$ that, in spite of the low specific activity, was comparable to the sensitivity of the GC-NPD method [5].

The performance of the coupled analytical technique was examined by validating the method. Inter-day precision and accuracy values for $^3$H-deramciclane fulfilled the acceptance criteria specified for non-radioactive methods [18]. In spite of the absence of appropriate, $^3$H-labelled internal standard, the linearity and reproducibility (Tables I and II) were acceptable with external standard calibration. Accuracy and precision values amounted to 2.35 and 7.19 %, respectively, on the average (Table I). The RSD% value obtained during the system suitability test of the GC-RD system was 1.78 % (Table II).

### Comparative Pharmacokinetic Investigations

Using the above gas chromatography radioactivity detection (GC-RD) method, plasma levels of $^3$H-labelled deramciclane and its N-desmethyl metabolite were measured in dog (Figure 3) after the administration of a single oral dose of 10 mg kg$^{-1}$. $^3$H-deramciclane showed a relatively fast absorption and plasma levels could be detected up to the 36th hour. Pharmacokinetic parameters of $^3$H-N-desmethyl deramciclane were in good agreement with the pharmacokinetic parameters of the same metabolite obtained with GC-NPD method [7, 20]. The pharmacokinetic curve and the most important pharmacokinetic parameters of $^3$H-deramciclane were compared to those obtained after previous GC-NPD measurements, and to the non-selective total radioactivity (LSC) data (Table III, Figure 4).

The pharmacokinetic curves (Figure 4) and the calculated pharmacokinetic parameters obtained with the two different, independent gas chromatography methods (NPD, RD) showed close similarity (Table III).

The comparison of these results and those obtained with the measurement of total radioactivity in plasma (LSC) showed that the low plasma concentration ($AUC_{0-\infty}$) of the parent compound was indicative of a very fast and intensive first-pass metabolism. Moreover, the elimination of radioactivity (additional metabolites) ($t_{\frac{1}{2}}^{\beta}$ = 97.3 h) was very slow as compared to those of the parent compound and the N-desmethyl metabolite (7.6 h) (Table III, Figure 4).

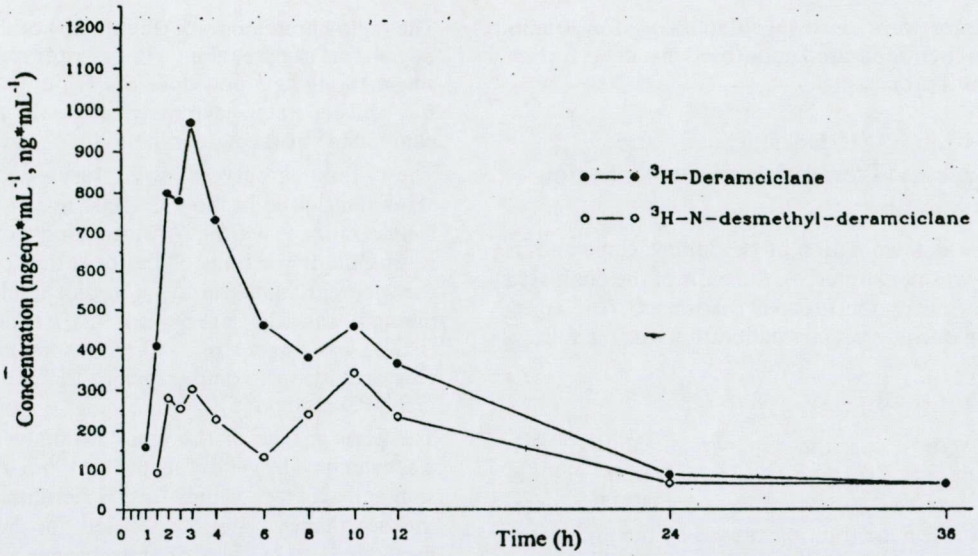


**Figure 3**
Pharmacokinetic curves of $^{3}$H-deramciclane and $^{3}$H-N-desmethyl-deramciclane in dogs determined with GC-RD after the administration of 10 mg kg$^{-1}$ oral dose of $^{3}$H-deramciclane.

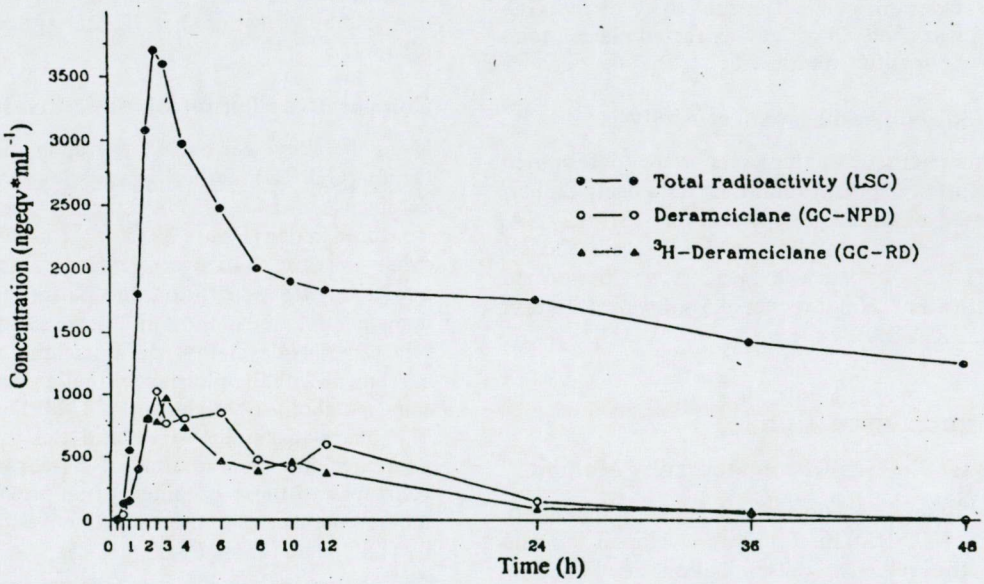


**Figure 4**
Comparison of the pharmacokinetic curves obtained in dogs with various bioanalytical methods.

## Conclusion

A new, high sensitivity (LLOQ = 13 ngeqv mL$^{-1}$) gas chromatography method with radioactivity detection was elaborated and validated for the selective determination of $^{3}$H-deramciclane and its N-desmethyl metabolite. This GC-RD method proved to be appropriate for the pharmacokinetic investigations of the $^{3}$H-labelled compound and also for the testing of radiochemical synthesis and for the monitoring of radiochemical decomposition and purity.

## Acknowledgment

Thanks are due to Mss. Edina Deli, Mrs. Zsuzsa Juhász and Mrs. Ilona Minarik-Deák for their excellent technical assistence.

**Table I.** Inter-day accuracy and precision of the determination of $^3$H-deramciclane in dog plasma, using the GC-RD method.

| Concentration of $^3$H-deramciclane (n = 3), ngeqv mL$^{-1}$ | | Precision RSD% | Accuracy % |
|---|---|---|---|
| Nominal | Measured | | |
| 13.7 | 15.32 ± 2.48 | 16.20 | 11.89 |
| 41 | 33.45 ± 3.95 | 11.80 | - 18.41 |
| 100 | 107.17 ± 7.27 | 6.79 | 7.17 |
| 250 | 256.64 ± 16.75 | 6.53 | 2.66 |
| 500 | 504.33 ± 7.09 | 1.41 | 0.87 |
| 1000 | 1099.44 ± 4.24 | 0.39 | 9.94 |
| Mean | | 7.19 | 2.35 |

**Table II.** System suitability test of the GC-RD system: results of multiple (n = 5) injections of a 200 ng mL$^{-1}$ concentration $^3$H-deramciclane standard solution.

| Concentration ng mL$^{-1}$ | Response for $^3$H-deramciclane (cps) mean ± SD | RSD% |
|---|---|---|
| 200 | 487.54 ± 8.70 | 1.78 |

**Table III.** Comparison of the pharmacokinetic parameters of deramciclane calculated from plasma concentration-time data obtained with different bioanalytical methods, after 10 mg kg$^{-1}$ single oral administration of $^3$H-deramciclane in dogs.

| Measured moiety | Method | $AUC_{0-\infty}$ (ng h mL$^{-1}$) | $C_{max}$ (ng mL$^{-1}$) | $t_{max}$ (h) | MRT (h) | $t^{\beta}_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| Deramciclane | GC-NPD | 12861.3 | 1018.3 | 2.5 | 9.9 | 7.68 |
| $^3$H-deramciclane | GC-RD | 10252.8 | 967.8 | 2.9 | 11.5 | 7.57 |
| Total radioactivity | LSC | 269000.0 | 3480.0 | 2.9 | 138.0 | 97.30 |

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