Benzo- and Indoloquinolizine Derivatives. III. Synthesis and Structural Assignments of 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo-[*a*,*c*,*h*]quinolizine (4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-isoquino[2,1-*f*]phenanthridine).

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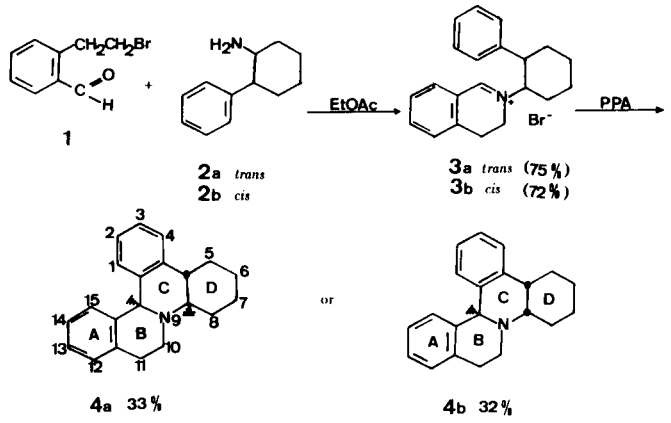
Starting from either *trans*-2-phenylcyclohexylamine or the *cis* isomer, two epimers of 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine have been synthesized. The four possible diastereoisomers of this compound were obtained by reduction of the enamine 5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine. Configuration and conformation are discussed by use of ir, 67.88 MHz cmr and 270 MHz pmr spectroscopy.

Synthesis.

Starting from isoquinolinium salts prepared according to Beke, *et al.*, (1) and Höft, *et al.*, (2), we synthesized recently 1,2-diphenyl-1,2,3,4-tetrahydroisoquinoline derivatives (3). On this basis we developed a synthesis of 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a*,*c*,*h*]-quinolizine according to Scheme 1.

SCHEME 1



Formation of both salts **3a** and **3b** was performed in ethyl acetate with a 75% and 72% yield, respectively, starting from 2-(2-bromoethyl)benzaldehyde (**1**) and the appropriate 2-phenylcyclohexylamine (**2**), already obtained by us (4,5).

After heating the corresponding salts **3a** and **3b** only one isomer **4a** was obtained in a 33% yield in the *trans* series and only one isomer **4b** in a 32% yield in the *cis* series.

Wishing to obtain the other epimers (Scheme 2, 3) enamine 5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a*,*c*,*h*]-quinolizine (**8**), synthesized according to Scheme 4, has been reduced by different methods. The results are summarized in Table I.

According to the literature (6-10) we may assume that the catalytic hydrogenation of enamine **8** will predominantly lead to *cis* addition.

The catalytic hydrogenation of enamine **8** in ethanol over platinum oxide at 4 atmospheres of hydrogen pressure, yielded two compounds in a 56/44 ratio. The isomer obtained in the higher yield was proven identical with the C/D-*cis* epimer **4b**, already prepared.

The isomer obtained in the lower yield, isomer **9**, could also be completely isomerised into **4b** in the presence of 14% (by weight) of platinum oxide at 4 atmospheres of hydrogen pressure for 24 hours (Table II). Considering isomer **9** as the kinetically controlled product we assumed a C/D *cis* ring junction for it.

From examples in the literature (7,10,12,13) we could expect a mixture of all isomers from the sodium borohydride reduction in tetrahydrofuran acetic acid solution. With an overall yield of 60%, a mixture of the four isomers was formed, which, however could not be separated on a preparative scale.

On reduction of the enamine **8** with sodium borodeuteride in tetrahydrofuran, acetic acid-d solution, we

SCHEME 2

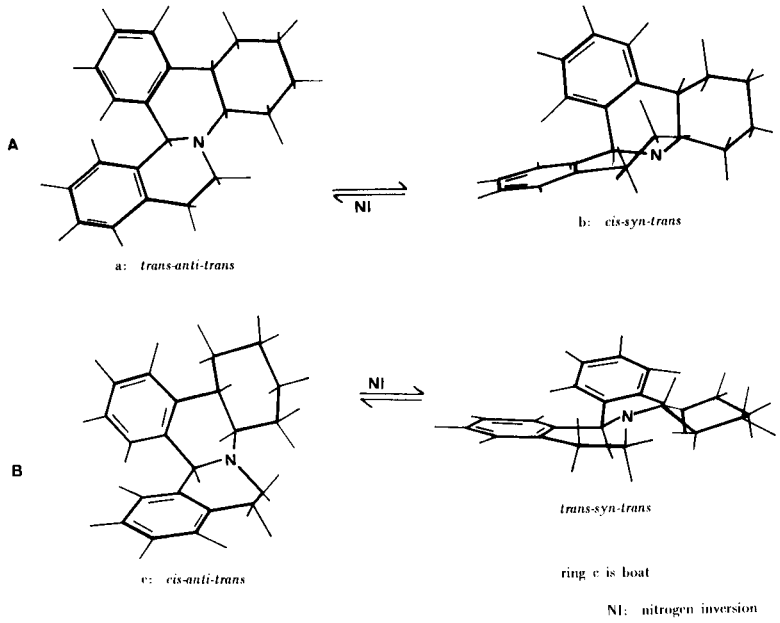


Table I

Isomer Proportion and Yields of the Reduction on Enamine 5,6,7,8,10,11-Hexahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine (**8**)

Reaction	Isomer 4b	9	4a	10	Total yield
Hydrogen/platinum oxide-ethanol 4 hours	56%	44%	--	--	52%
Lithium aluminum hydride/THF perchlorate salt	+10:6%	90%	4%	+4b:6%	72%
Formic acid	+10:19%	61%	20%	+4b:19%	36%
Lithium/ammonia	--	--	24%	76%	48%
Sodium borohydride/THF acetic acid	15%	37%	38%	10%	60%
Diborane	--	60%	40%	--	12%

were able to separate a few mg. of the 4b,8a-dideuterio analogues of isomers **4a**, **4b** and **9** (a). Reduction of **8** with sodium borohydride in tetrahydrofuran, acetic acid-d solution gave us a few mg. of the 4b-deuterio analogues of isomers **4a**, **4b** and **9** (b); whereas reduction of **8** with sodium borodeuteride in tetrahydrofuran, acetic acid solution lead to the 8a-deuterio analogues of isomers **4a**, **4b** and **9** (c). In any case, we did not succeed in extracting pure isomer **10** from the reaction mixture (Scheme 5).

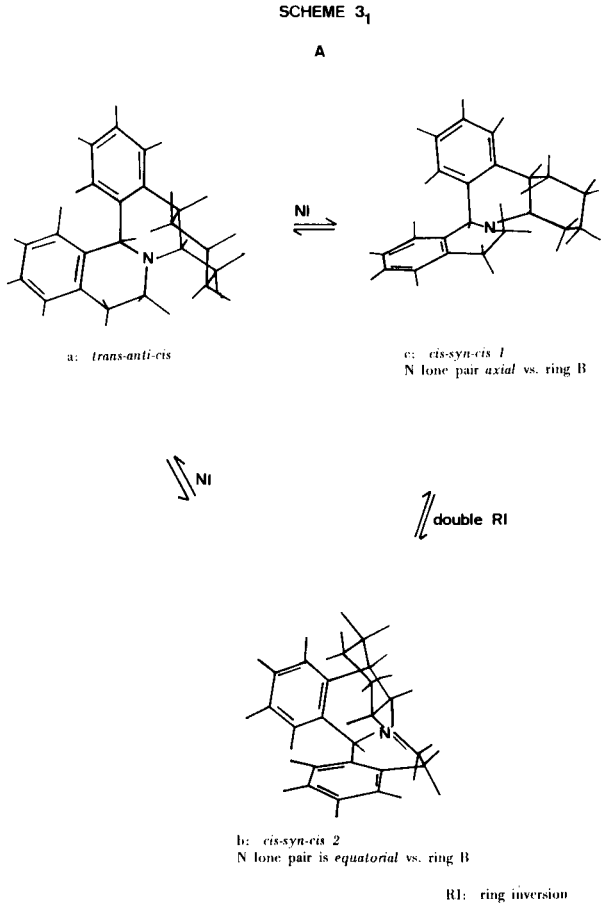
The organoborane adduct of enamine **8** was formed in a mixture diglyme, tetrahydrofuran. A very complex mixture was obtained.

Structural Assignments.

The conformational "purity" of the four diasterio-isomers was checked by comparison of their cmr spectra at 20°, -50° and -90°. Jensen, *et al.*, (14) pointed out, that measurements of the relative intensities of the stereoisomeric (exchanging) atoms at temperatures, where separate signals are given by the two forms, is the most unambiguous procedure for the determination of the relative amounts of both conformers. Schneider, *et al.*, (15) showed that for *cis*-1,4-dimethylcyclohexane, the relative abundances for identically substituted C-atoms are correctly reproduced by integration of the low-temperature ^{13}C spectrum.

For **9**, the broad band decoupled ^{13}C spectrum at 20° showed 10 peaks for the 12 aromatic C-atoms and 8 peaks for the 9 aliphatic C-atoms. At -50°, almost every peak had disappeared and it was clear, that we were near to coalesence. At -90°, we obtained 23 peaks in the aromatic part and 18 peaks in the aliphatic part of the spectrum. For both parts of the spectrum, two kinds of peaks were

SCHEME 3[1]



easily differentiated: those with low and those with high intensity. From these, an equilibrium constant of 3.0 was determined. This means that **9** is a mixture of 2 conformers in a 75/25 ratio.

In the same way, we found that **4b**, and **10** are for more than 90% conformationally "pure", whereas the conformational "purity" of **4a** exceeds 99%.

The ir spectra of the four compounds were obtained in potassium bromide, chloroform and tetrachloroethylene.

For **9**, Bohlmann bands (16) were observed in each case, whereas compounds **4b** and **4a** did not show Bohlmann bands at all. The ir spectrum of **10** (potassium bromide) showed Bohlmann bands. However, in solvent no Bohlmann bands were observed.

The pmr spectra of the four compounds were obtained in deuteriochloroform and deuteriotrifluoroacetic acid (Table III).

For **9**, two signals were obtained for H_{15b} in deuteriotrifluoroacetic acid: δ_1 = 5.85 ppm and δ_2 = 5.77 ppm (in a ratio of respectively 63/37). This result is not surprising, as we know that this isomer is a mixture of two conformers (in a ratio of approximately 75/25). In deuteriochloroform we see that in **9** H_{15b} appears at a higher field than the corresponding proton in the three other isomers. The difference in chemical shift of H_{15b} in deuteriotrifluoro acetic acid *versus* deuteriochloroform is much larger for **9** than for the three other isomers.

From these results we may postulate a *trans*-quinolizidine ring fusion for the more abundant conformer of

Table II

Catalytic Hydrogenation Study of Enamine 5,6,7,8,10,11-Hexahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine (**8**)

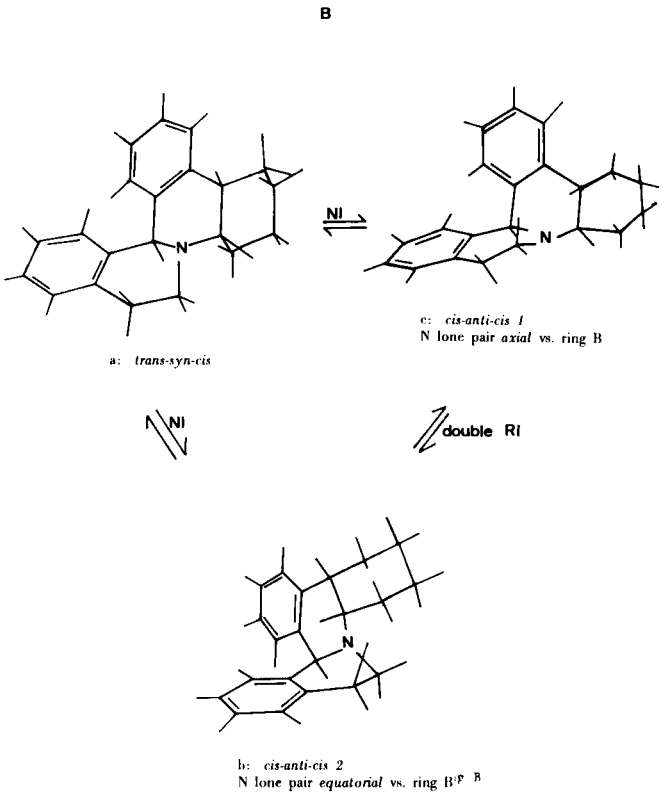
No. of Experiment	Weight (mg.) of enamine	Weight (mg.) of Platinum oxide	Percent Platinum oxide	Time (hours)	Products (%)		Total yield %
1	420	25	6	4	**9**	44	52
					4b	56	
2	420	25	6	24	**9**	0	65
					4b	100	
3	420	11	2.6	24	**9**	41	67
					4b	59	
4	423	59	14	24	**9**	0	65
					4b	100	
5	1200	8	0.7	24	**9**	94	72
					4b	6	
6	420	58	14	43	**9**	0	72
					4b	100	
7	2150	15	0.7	18	**9**	91	67
					4b	9	

Table III

Pmr Chemical Shift of H_{15b} of the 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a,c,h*]quinolizine Diasterioisomers

Compound	δ H_{15b} in deuteriochloroform (ppm)	δ H_{15b} in deuteriotrifluoro acetic acid	Δδ (ppm)
9	4.91	5.85 and 5.77	0.94-0.86
4b	5.22	5.86	0.64
4a	5.26	5.89	0.63
10	5.16	5.81	0.65

SCHEME 3_2



9 and a *cis*-quinolizidine ring fusion for **4b**, **4a** and **10** (4, 17).

At this stage, two possible structures remain for the more abundant conformer of isomer **9**: the *trans-anti-cis* (Scheme 3_1) and the *trans-syn-cis* (Scheme 3_2). In the *trans-anti-cis* conformation, H_{4b} is *axial* and H_{8a} *equatorial versus* ring D. On the other hand, in the *trans-syn-cis* conformation, one sees H_{4b} *equatorial* and H_{8a} *axial verses* ring D.

The H_{4b}-H_{5ax}, H_{5eq} coupling constants were obtained from the 270 MHz pmr spectrum of the 8a-deuterio-4b,5,6,7,8,10,11-heptahydro-15b*H*-tribenzo[*a,c,h*]quinolizine analogue of **9** and the H_{8a} - H_{8ax}, H_{8eq} coupling constants from the 270 MHz pmr spectrum of the 4b-deuterio-5,6,7,8,8a,10,11-heptahydro-15b*H*-tribenzo-[*a,c,h*]quinolizine analogue of **9** (Table IV). From the coupling constants we may conclude that the more abundant conformer of **9** has the *trans-anti-cis* conformation.

Table IV

H_{4b}-H_{5eq}, H_{5ax} and H_{8a}-H_{8eq}, H_{8ax} Coupling Constants of the 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a,c,h*]quinolizine Diasterioisomers

Compound	δ H_{4b}	δ H_{8a}	J_1	J_2
9 (b)*	--	717.8	5.8	3.1
9 (c)**	720.9	--	9.4	5.9
4b (b)	--	810.3	4.5	3.2
4b (c)	669.7	--	9.7	3.9
4a (b)	--	767.6	11.5	3.1
4a (c)	763.2	--	11.5	3.1

All values are in Hz, solvent perdeuteriobenzene. *(b) 4b-Deuterio-5,6,7,8,8a,10,11-hetahydro-15b*H*-tribenzo[*a,c,h*]quinolizine. **(c) 8a-Deuterio-4b,5,6,7,8,10,11-heptahydro-15b*H*-tribenzo[*a,c,h*]quinolizine.

Table V

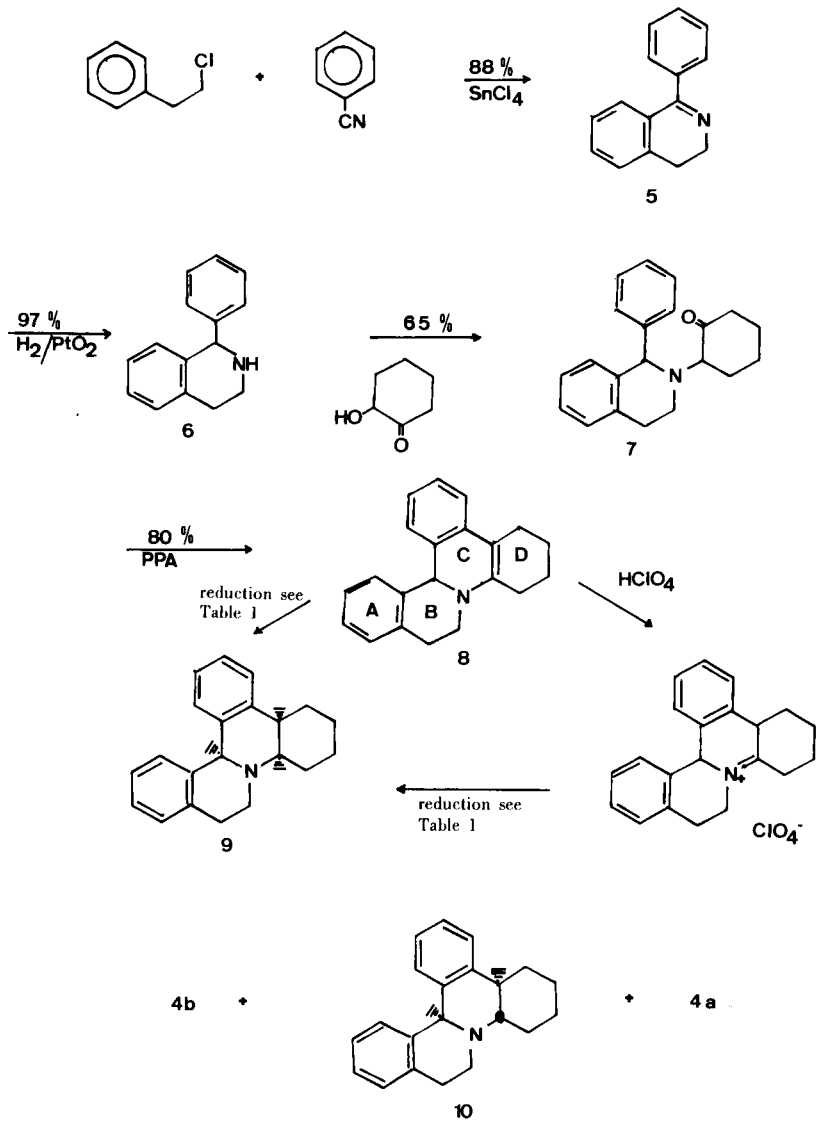
ABCD Analysis of the C_{10} and C_{11} Methylene Protons at 270 MHz. Parameters Determined by the Iterative LAME Program (Solvent Perdeuteriobenzene)

	C_{10} and C_{11} protons of **9**		r.m.s. error = 0.313	
	Hz	ppm	Hz	
δ_1	811.3	3.00	J_{12} = 6.1	J_{24} = 7.0
2	767.1	2.84	J_{13} = 6.9	J_{34} = 6.5
3	728.2	2.70	J_{14} = -10.3	
4	685.4	2.54	J_{23} = -15.6	
	C_{10} and C_{11} protons of **4b**		r.m.s. error = 0.423	
	Hz	ppm	Hz	
δ_1	851.9	3.15	J_{12} = -14.2	J_{24} = 5.4
2	822.0	3.04	J_{13} = 6.0	J_{34} = -16.3
3	745.2	2.76	J_{14} = 2.9	
4	653.2	2.42	J_{23} = 11.1	
	C_{10} and C_{11} protons of **4a**		r.m.s. error = 0.266	
	Hz	ppm	Hz	
δ_1	799.5	2.96	J_{12} = 6.9	J_{24} = 0.9
2	736.8	2.73	J_{13} = 11.6	J_{34} = 4.4
3	716.4	2.65	J_{14} = -16.5	
4	657.3	2.43	J23 = -11.6	

Compound **4b**, which is the second isomer with the C/D *cis* ring fusion has a *cis*-quinolizidine ring structure. Two possible conformations do remain for it: the *cis-anti-cis* 1 and the *cis-anti-cis* 2 (Scheme 3_2).

In the *cis-anti-cis* 1 conformation, where the *N* lone pair is *axial versus* ring B, H_{4b} is *equatorial versus* ring D; whereas H_{8a} is *axial versus* ring D. On the other hand, in the *cis-anti-cis* 2 conformation, where the *N* lone pair is *equatorial versus* ring B, H_{4b} is *axial* and H_{8a} is *equatorial*

SCHEME 4



versus ring D.

The coupling constants were determined in the same way as for **9** (Table IV) and the *cis-anti-cis* 2 conformation is attributed to **4b**.

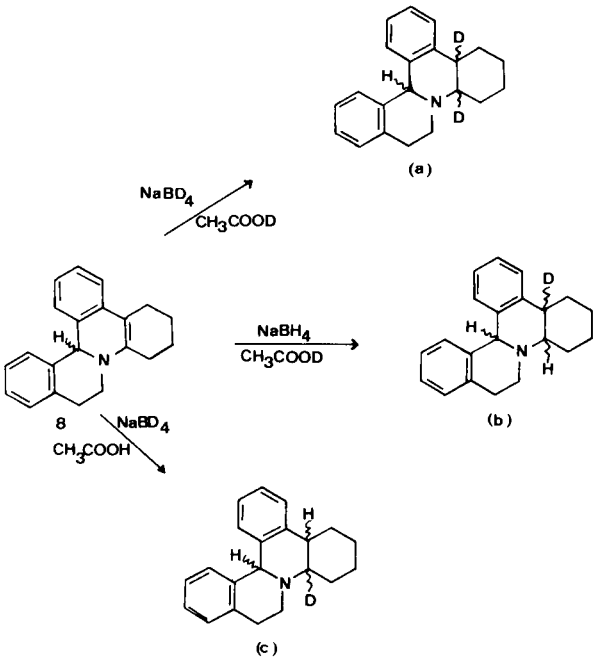
For compound **4a**, which has a *cis*-quinolizidine structure, two conformations are possible. Comparison of the *cis-syn-trans* and the *cis-anti-trans* conformation (Scheme 2) shows no difference for the coupling constants of H_{4b} and of H_{8a}. The results obtained (Table IV) confirm the C/D *trans* ring fusion for **4a**, but no conformer attribution is possible.

We also made use of the "eclipsing effect" of the *N* lone pair on the geminal coupling constant of the α-methylene group (18).

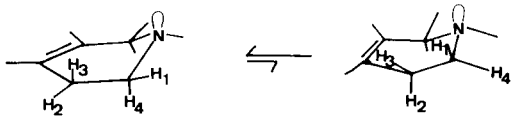
In order to determine the magnitude of the coupling constants involved, we analysed the ABCD system of the C_{10} and C_{11} methylene protons for compounds **8**, **4b** and **4a**. This spectrum analysis was carried out on the 270 MHz pmr spectra of the 4b,8a-dideuterio-5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine analogues by means of an iterative LAME program (19). Experimental and simulated spectra were matched at 270 and 90 MHz. The obtained parameters are collected in Table V.

As substituents which withdraw electrons by hpyer-conjugation (sp^2-hybridized adjacent carbon atom) add a negative increment to J_{gem} (20), this effect and the "eclipsing effect" made it quite easy to attribute the C_{10} and C_{11} protons.

SCHEME 5



SCHEME 6



For **9**, the geminal protons α to the nitrogen were attributed to H_1 and H_4, as J_{14} = -10.3 Hz and the geminal protons α to the benzoring to H_2 and H_3 as J_{23} = -15.6 Hz.

For **4b**, we attributed the geminal protons α to the nitrogen to H_1 and H_2, as J_{12} = -14.2 Hz and the geminal protons α to the benzoring to H_3 and H_4, as J_{34} = -16.3 Hz.

For **4a**, the geminal protons α to the nitrogen were attributed to H_2 and H_3 as J_{23} = -11.6 Hz and the geminal protons α to the benzoring to H_1 and H_4 as J_{14} = -16.5 Hz.

In compound **4b**, that we attributed to the *cis-anti-cis* 2 conformation where the *N* lone pair is *equatorial versus* ring B the *N* lone pair forms approximately the bissectrice of the $H_1C_{10}H_2$ angle. This orientation is in accordance with the strongly negative value of -14.2 Hz for J_{12} (5).

For compound **4a**, the choice remains between the *cis-anti-trans* and *cis-syn-trans* conformation. In the *cis-anti-trans* conformation the *N*-one pair is *equatorial versus* ring B and forms approximately the bissectrice of the $H_2C_{10}H_3$ angle. In the *cis-syn-trans* conformation the *N* lone pair is *axial versus* ring B and the C_{10} - $H_{2(3)}$ bond *anti*-parallel with the *N* lone pair. In comparison with **4b**, we obtain a J_{gem} = -11.6 Hz, or much samller (in absolute value). This means that **4a** can be attributed to the *cis-syn-trans* conformation and **10** to the *cis-anti-trans* conformation.

The value of J_{gem} = -10.3 Hz, found for **9** is in accordance with the *trans-anti-cis* conformation for the more abundant conformer; indeed in this conformation a C_{10}-H bond is *anti*-parallel with the *N* lone pair. As the contribution to J_{gem} of the until now unidentified conformer (in abundance of approximately 25%) goes in the same sense (or a smaller coupling constant in absolute value) a possible structure for this conformer may be the *cis-syn-cis* 1 conformation (Scheme 3_1) where the *N* lone pair is *axial versus* ring B. Indeed, in this conformation a C_{10}-H bond is also *anti*-parallel to the *N* lone pair, while in the *cis-syn-cis* 2 conformation (Scheme 3_1) where the *N* lone pair is *equatorial versus* ring B, the *N* lone pair forms approximately the bissectrice of the $H_1C_{10}H_4$ angle. However, the vicinal coupling constants show nearly the same value.

This situation points out that in the second conformer, a *pseudo-axial*, respectively *pseudo-equatorial* proton of the first conformer is transformed into a *pseudo-equatorial*, respectively *pseudo-axial* proton. As the equilibrium between the *trans-anti-cis* and the *cis-syn-cis* 1 conformation takes place through an *N* inversion, it is clear that such an equilibration of the protons does not occur. So we must exclude the *cis-syn-cis* 1 conformation as the second conformer present in the equilibrium mixture of 9.

Moreover, $J_{gem}C_{10}$ protons of **9** are smaller than $J_{gem}C_{10}$ protons of **4a**. This situation points out that the contribution of the second conformer, present in the equilibrium mixture of **9**, to J_{gem} is much more smaller (in absolute value) than the contribution of a conformation, with a C-H bond *anti*-parallel *versus* the *N* lone pair. The conformation that obeys to both points is the *trans-anti-cis* conformation with the B ring in the boat conformation. Indeed if the B ring is a boat, equilibration of the protons does take place and a C-H bond eclipses the *N* lone pair (Scheme 6). So we postulate that compound **9** is a mixture of 2 conformers: approximately 75% *trans-anti-cis* (ring B in the half-chair conformation) and 25% *trans-anti-cis* (ring B in the boat conformation).

Conclusions.

We were able to obtain selectively the four diasterioisomers of 4b,5,6,7,8,8a,10,11-octahydro-15b*H*-tribenzo-[*a*,*c*,*h*]quinolizine. The stereochemistry of these isomers was elucidated mainly by use of pmr spectroscopy at 270 MHz.

Isomer **9** (+ 6% isomer **4b**) was obtained by catalytic

hydrogenation of enamine 5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a,c,h*]quinolizine. This isomer was identified as a mixture of conformers of *trans-anti-cis* (ring B in the half-chair conformation) and *trans-anti-cis* (ring B in the boat conformation) in a ratio of approximately 75/25.

Isomer **4b** (100%) was obtained by catalytic hydrogenation of enamine 5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a,c,h*]quinolizine and polyphosphoric acid cyclisation of *cis-N*-(2-phenylcyclohexyl)-3,4-dihydroisoquinolinium bromide. This isomer should predominantly exist in the *cis-anti-cis* 2 conformation, where the *N* lone pair is *equatorial versus* ring B.

Isomer **10** (+ 24% isomer **4a**) was synthesized through Birch reduction of enamine 5,6,7,8,10,11-hexahydro-15b*H*-tribenzo[*a,c,h*]quinolizine. This isomer was identified as the *cis-anti-trans* conformation.

Isomer **4a** (100%) was obtained by polyphosphoric acid cyclisation of *trans-N*-(2-phenylcyclohexyl)-3,4-dihydroisoquinolinium bromide and was attributed to the *cis-syn-trans* conformation.

EXPERIMENTAL

trans-N-(2-Phenylcyclohexyl)-3,4-dihydroisoquinolinium Bromide (**3a**).

A solution of *trans*-2-phenylcyclohexylamine (**2a**) (0.50 g., 0.003 mole) into ethyl acetate (15 ml.) was slowly dropped into a stirred solution of 50° of 2-(2-bromoethyl)benzaldehyde (**1**) (0.64 g., 0.003 mole) in ethyl acetate (15 ml.). The salt **3a** precipitated slowly (yield, 75%), recrystallisation: 90/10 ethyl acetate/ethanol, m.p. 195° (Mettler FP5 apparatus); ir spectrum (potassium bromide): iminium band: 1640 cm^{-1}; Mass Spectrum: M^+ at 290.

Anal. Calcd. for $C_{21}H_{24}BrN$: C, 68.29; H, 6.50; N, 3.79. Found: C, 68.2; H, 6.43; N, 3.76.

4b, 5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a,c,h*]quinolizine (C/D ring fusion *trans*) (**4a**).

Salt **3a** (0.32 g.) was heated at 180° under vigorous stirring for 48 hours with polypohosphoric acid (3.50 g.). The reaction mixture was put onto ice after cooling and made basic by addition of sodium hydroxide pellets. The precipitate was taken up into ether. Evaporation of the ether yielded a brown oil.

Preparative separation of the oil was performed on alumina 20 x 20 plates (type E, Merck), eluent: 90/10 petroleum ether (b.p. 40-60°)/ethyl acetate, yield, 33% of **4a**.

When repeating this reaction on a larger scale, **4a** was obtained by precipitation with ethanol followed by recrystallisation in ethanol (m.p. 135.5-136.0°, m.p. picrate 207.7°, Mettler FP5 apparatus); ir spectrum (potassium bromide) ν (cm^{-1}): 3060, 3020, 2930, 2920, 2850, no Bohlmann bands, 1600, 1480, 1445, 1115, 740; Mass spectrum: M^+ at 289; pmr spectrum (deuteriochloroform) δ (ppm): 7.39-7.09 (8 H aromatic), 5.23 (H_{15b}), 3.46-1.25 (14 H aliphatic); (deuteriotrifluoroacetic acid) δ (ppm): 5.86 (H_{15b}).

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.20; H, 7.96; N, 4.84. Found: C, 87.0; H, 7.92; N, 4.81.

Anal. Calcd. for $C_{27}H_{26}N_4O_7$: C, 62.5; H, 5.0; N, 10.8. Found: C, 62.7; H, 5.1; N, 10.9.

4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a,c,h*]quinolizine (C/D ring fusion *cis*) (**4b**).

The procedure was almost the same as for the *trans* isomer, yield 32%; R_f = 0.38. Several recrystallisations in ethanol yielded pure **4b** (m.p. 139.0-139.5°; m.p. picrate 184-185°); ir spectrum (potassium bromide) ν (cm^{-1}): 3065, 3020, 2980, 2920, 2850, no Bohlmann bands, 1600, 1490, 1440, 1070, 740; Mass spectrum: M^+ at 289; pmr spectra (deuteriochloroform) δ (ppm): 7.28-7.03 (8 H aromatic), 5.22 (H_{15b}), 3.47-1.45 (14 H aliphatic); (deuteriotrifluoroacetic acid) δ (ppm): 5.86 (H_{15b}).

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.20; H, 7.96; N, 4.84. Found: C, 87.3; H, 7.88; N, 4.87.

3,4-Dihydro-1-phenylisoquinoline (**5**).

Tin tetrachloride (21.6 g., 0.1 mole) was slowly added to freshly distilled benzonitrile (0.1 mole) at room temperature under stirring. The complex was heated to melting (100°), and 2-phenylethylchloride (14.0 g., 0.1 mole) was slowly added. The reaction mixture was stirred for 3 hours at 110-120°. After cooling the reaction products were poured into a 20% sodium hydroxide solution. The resulting oil was worked up in the usual manner, yield of **5**, 88%; m.p. picrate 170-171°.

Anal. Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.79; H, 3.67; N, 12.84. Found: C, 57.6; H, 3.71; N, 12.87.

1,2,3,4-Tetrahydro-1-phenylisoquinoline (**6**).

3,4-Dihydro-1-phenylisoquinoline (**5**) (9.5 g.) dissolved in a mixture of ethanol (100 ml.) and acetic acid (100 ml.) were hydrogenated in a Parr apparatus at 4 atmospheres over platinum oxide, palladium on activated carbon, as catalysts. After filtration, the ethanol was evaporated *in vacuo* and the resulting liquid was neutralised by addition of sodium carbonate.

Extraction with ether and evaporation of the ether layer yielded a white-yellow powder (97%). Recrystallisation in cyclohexane gave white crystalline 1,2,3,4-tetrahydro-1-phenylisoquinoline (**6**) (yield 97%), m.p. 98-100°.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.12; H, 7.17; N, 6.69. Found: C, 86.0; H, 7.18; N, 6.64.

1,2,3,4-Tetrahydro-*N*-(2-oxocyclohexyl)-1-phenylisoquinoline (**7**).

A mixture of 1,2,3,4-tetrahydro-1-phenylisoquinoline (**6**) (6.0 g., 0.04 mole) and 2-hydroxycyclohexanone (4.25 g., 0.04 mole) in toluene was refluxed under a water separator until no further separation of water was observed (40 hours). The crude reaction products were recrystallised from ethanol (yield, 65%), m.p. 118-119°; ir spectrum (tetrachloroethylene) ν (cm^{-1}): 3055, 3010, 2930, 2850, 1720, 1605, 1495, 740 and 700; Mass spectrum: M^+ at 305.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.62; H, 7.54; N, 4.59. Found: C, 82.4; C, 7.55; N, 4.66.

5,6,7,8,10,11-Hexahydro-15b*H*-tribenzo[*a,c,h*]quinolizine (**8**).

Compound **7** (2.18 g.) was heated at 120-130° under vigorous stirring for 1 hour 15 minutes with polyphosphoric acid (21 g.). After cooling, the reaction mixture was poured onto ice. After addition of sodium hydroxide pellets the precipitate was collected on a Büchner funnel and washed with a 5% sodium bicarbonate solution. Drying under diminished pressure and sublimation of the crude product (120-130°/0.01 mm) yielded 80% of enamine **8**, m.p. 58-60°; m.p. picrate: 170.0° (Mettler FP5 apparatus).

Glc chromatogram (Becker Research Gass Chromatograph 420): 89% of **8**, t_r = 24.1 minutes and 11% of a decomposition product t_r = 18.3 minutes (column 3% JXR gas chrom Q100/120, length: 2.0 m, pyrex glass, inner diameter 4.0 mm, injector

225°, column 200°, flame ionisation detector: 250°, flow nitrogen gas 40 ml./min.); ir spectrum (tetrahcloroethylene) ν (cm^{-1}): 3060, 3025, 2930, 2860, 2835, 1620, 1500, 1480, 730; Mass spectrum: M^+ at 287; pmr spectrum (tetrachloroethylene) δ (ppm): multiplet at 7.00 (8 H aromatic), 5.11 (H_{15b}), 3.61-2.62 (4 H aliphatic), broad signal at 2.40 (4 H aliphatic), broad signal at 1.73 (4 H aliphatic).

Catalytic Hydrogenation.

Compound **8** (0.42 g.), dissolved in absolute ethanol (100 ml.) was hydrogenated in a Parr apparatus at 4 atmospheres over platinum oxide as catalyst. After filtration, the ethanol was evaporated *in vacuo*. The resulting solid product was collected on a Büchner funnel. The composition of the isomer mixture was determined by pmr spectroscopy (integration of the C_{15b} proton signals).

Preparative Separation of the *trans-anti-cis* Isomer **9** from the *cis-anti-cis* Isomer **4b**.

The solid hydrogenation products were chromatographed (column 2 cm. diameter and 25 cm. height, alumina H basic type E, for thin layer chromatography, Merck, eluent mixture 85% iso-octane, 15% ether). Two well-separated fractions were collected, and recrystallised from ethanol.

Fraction 1 was crystals with m.p. 113.5-114°; m.p. of picrate, 168-169°. The glc chromatogram (same conditions was for enamine **8**) had one peak with t_r = 15.4 minutes. High pressure liquid-solid chromatogram (Water Associates type ALC 201, equiped with a RI detector) had one peak with t_r = 14.8 minutes (column alumina neutral type E Merck scratched from tlc sheets, 0.037-0.053 μ, length 70 cm, inner diameter 2.0 mm, pyrex glass, pressure 200 psi, system, hexane/ethyl acetate 98/2); ir spectrum (potassium bromide) ν (cm^{-1}): 3070, 3020, 2940, 2850, Bohlmann bands at 2800 and 2750, 1600, 1485, 1450, 1070, 750 and 725; ir spectrum (tetrachloroethylene) ν (cm^{-1}): Bohlmann bands at 2790 and 2740; Mass spectrum: M^+ at 289; pmr spectra (deuteriochloroform) δ (ppm): 7.28-7.06 (8 H aromatic), 4.91 (H_{15b}), 3.25-1.16 (14 H aliphatic), (deuteriotrifluoroacetic acid) δ (ppm): 5.89 and 5.77 in a ratio of 63/37, total integration 1 H (H_{15b}).

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.20; H, 7.96; N, 4.84. Found: C, 87.1; H, 7.95; N, 4.85.

Fraction 2 gave crystals with m.p. 139.0-139.5°; ir spectrum (potassium bromide): identical with the ir spectrum (potassium bromide) of the C/D *cis* epimer **4b**; glc chromatogram (same conditions as enamine **8**) had one peak, t_r = 16.9 minutes. High pressure liquid-solid chromatogram (same conditions as **9**) had one peak, t_r = 26 minutes.

Isomerisation of **9** to **4b**.

The same procedure as for the hydrogenation of enamine **8** has been used. The composition of the reaction mixtures was determined by pmr spectroscopy (integration of the C_{15b} proton signals).

Lithium Aluminum Hydride Reduction.

The perchlorate of enamine **8** was prepared by adding 70% perchloric acid dissolved in a 50/50 mixture of ether and ethanol to a solution of enamine **8** in hot ethanol. The perchlorate salt precipitated as white crystals. The salt could be recrystallised from an acetonitrile/ether mixture, m.p. 186-187°.

The perchlorate salt (0.45 g., 0.0012 mole) and lithium aluminium hydride (0.45 g., 0.0012 mole) were suspended in dry, freshly distilled tetrahydrofuran (50 ml.) and refluxed for 20 hours. After cooling the reaction mixture, 10 ml. of water was carefully added, followed by addition of 10% sodium hydroxide (10 ml.). Extraction with ether and evaporation of the ether layer yielded 0.27 g. of a yellow oil.

Tlc on alumina (type E, Merck), eluent benzene, showed five spots, R_f = 0.70 (enamine **8**), R_f = 0.57 (**9**), R_f = 0.38 (**4b**), R_f = 0.31 (fourth isomer **10**) and R_f = 0.22 (**4a**); glc chromatogram (same conditions as enamine **8**), peak t_r = 8.4 minutes, 1.3%?, peak t_r = 11.7 minutes, 2.2%?, peak t_r = 15.5 minutes, 81.8% **9**, peak t_r = 17.1 minutes, 5% **4b** and **10**, peak t_r = 22.0 minutes, 4.1% **4a** and peak t_r = 25.1 minutes, 4.5% **8**. Total yield of isomers, 72%. High pressure liquid-solid chromatogram (same conditions as **9**) gives one peak with t_r = 14.5 minutes, **9**.

Formic Acid Reduction.

Enamine **8** (1.20 g.) was heated at 80-85° with 2 ml. of 98% formic acid during 16 hours. After cooling, the reaction products were added to 20 ml. of a 20% sodium hydroxide solution. The resulting dark brown gum was taken up in chloroform. Tlc on alumina (type E, Merck), eluent benzene, showed the same five spots as above together with a spot that did not migrate; glc chromatogram (slightly different conditions as enamine **8**) peak t_r = 7.5 minutes, 2.3%?, peak t_r = 10.5 minutes, 3.9%?, peak t_r = 13.9 minutes, 21.9% **9**, peak t_r = 15.4 minutes, 7.1% **4b** and **10**, peak t_r = 16.4 minutes, 52.3%?, peak t_r = 19.6 minutes, 6.8% **4a** and peak t_r = 16.3 minutes, 5.8% **8**, total yield of isomers, 36%.

Birch Reduction (**11**).

Enamine **8** (1.02 g., 0.0036 mole) dissolved in dry ether (100 ml.) was slowly added to a stirred solution of lithium (0.17 g., 0.024 mole) in liquid ammonia (300 ml.), and stirred for 5 hours. After addition of ammonium chloride, the ammonia was allowed to evaporate. Addition of water and extraction with ether yielded after evaporation, a brown oil, which after column chromatography (silica gel Merck 0.5-0.02 mesh, eluent 85% hexane, 15% acetone) gave 0.43 g. of non-separated isomers.

Tlc on alumina (type E, Merck), eluent benzene, showed two spots, R_f = 0.31 (fourth isomer **10** and R_f = 0.22 (**4a**); glc chromatogram (same conditions as enamine **8**), peak t_r = 11.8 minutes, 2.2%?, peak t_r = 17.4 minutes, 71.2% **10**, peak t_r = 21.8 minutes, 22.1% **4a**. High pressure liquid-solid chromatography (same conditions as **9**) showed one peak t_r = 26 minutes, 79.8% **10** and one peak t_r = 43 minutes, 20.2 % **4a**, total yield of isomers 48%.

The mixture was put on tlc 20 x 20 plates of alumina G (type E, Merck) and eluted with a mixture of 98% hexane, 2% ethyl acetate. Two impure isomers were obtained in a yield of 92 mg. and 63 mg. Both isomers were separately chromatographed on a tlc plate (same plates as above). From the mixture in the lower quantity, 41 mg. of white crystals was obtained, which were recrystallised from ethanol, m.p. 135-136°.

A mixed melting point with the C/D *trans*-epimer **4a** showed no depression of melting point. Tlc on alumina (type E, Merck), eluent benzene, showed one spot with R_f = 0.22 (same as R_f C/D *trans*-epimer **4a**). The ir spectrum was identical with the ir spectrum of the C/D *trans*-epimer **4a**.

From the mixture in the higher quanity, 70 mg. of a colorless oil was obtained which solidified upon standing (the crystals were not recrystallised), m.p. 91-92°, m.p. picrate, 149.5-150.5°.

Tlc on alumina (type E, Merck), eluent benzene, showed one spot with R_f = 0.31; ir spectrum (potassium bromide): 3060,

3020, 2920, 2850. Bohlmann bands at 2780 and 2740, 1600, 1475, 1450, 1440, 1085, 750, 730; ir spectrum (chloroform): no Bohlmann bands; Mass spectrum: M^+ at 289; pmr spectra (deuteriochloroform) δ (ppm): 7.28-6.74 (8 H aromatic), 5.16 (H_{15b}), 3.11-1.25 (14 H aliphatic), (deuteriotrifluoroacetic acid) δ (ppm): 5.81 (H_{15b}).

Anal. Calcd. for $C_{27}H_{26}N_4O_7$: C, 62.55; H, 5.02; N, 10.81. Found: C, 62.8; H, 5.22; N, 10.63.

Sodium Borohydride Reduction.

Enamine **8** (1.01 g., 0.004 mole) and sodium borohydride (1.0 g., 0.024 mole) were put into freshly distilled tetrahydrofuran (60 ml.). Acetic acid (20 ml.) was carefully dropped into the stirred supension and the mixture was refluxed for 3 hours. The reaction mixture was diluted with water (100 ml.) and neutralized by addition of a 10% sodium hydroxide solution. After extraction with ether and evaporation of the ether layer a yellow oil was left. Tlc on alumina (type E, Merck), eluent benzene, showed five spots, R_f = 0.70 (**8**), R_f = 0.57 (**9**), R_f = 0.38 (**4b**), R_f = 0.31 (**10**), and R_f = 0.22 (**4a**); glc chromatogram (same conditions as enamine **8**) peak t_r = 8.2 minutes, 2.8%?, peak t_r = 11.5 minutes, 5.0%?, peak t_r = 15.2 minutes, 30.4% **9**, peak t_r = 16.7 minutes, 22% **4b** and **10** and peak t_r = 21.3 minutes, 37%. High pressure liquid-solid chromatography (same conditions as **9**) gave peak t_r = 8 minutes, 5.3%?, peak t_r = 15 minutes, 35.3% **9**, peak t_r = 26 minutes, 14.2% **4b**, peak t_r = 26 minutes, 9% **10**, peak t_r = 42.5 minutes 36.5% **4b**, total yield of isomers, 60%.

Pure isomers were obtained by preparative tlc on alumina 20 x 20 plates (type E, Merck), eluent benzene of the reactionmixture.

Diborane Reduction.

Enamine **8** (1.12 g.) dissolved in 100 ml. of freshly distilled tetrahydrofuran was put into a 250 ml. three-necked, round bottom flask, equiped with a mechanical stirrer, diborane gas inlet and condensor. Diborane gas, prepared from sodium borohydride (1.5 g.), was led into the reaction vessel (kept at room temperature) for 1 hour.

The reaction mixture was refluxed for 1 hour and cooled for 2 hours. Destruction of excess diborane was effected by dropwise addition of 20 ml. of ethanol. After evaporation of the solvents, a white glass was obtained. Treatment for 30 minutes on a steam-bath with concentrated hydrochloric acid yielded after basification with a 20% sodium hydroxide solution, extraction with ether and evaporation of the ether layer *in vacuo*, 0.38 g. of a green-yellow oil. The undissolved residue of the glass was taken up in acetic acid and treated as above; 0.89 g. of a green oil was obtained.

Tlc on alumina (type E, Merck), eluent benzene, hydrochloric acid extract gave one spot R_f = 0.57 (**9**) and one spot R_f = 0.22 (**4a**), and one spot that did not migrate. Glc chromatogram (same conditions as enamine **8**) gave hydrochloric acid extract, peak t_r = 11.6 minutes, 6.1%?, peak t_r = 15.0 minutes, 24.6% **9**, peak t_r = 16.4 minutes, 14.4%?, peak t_r = 21.0 minutes, 17.0% **4a**, peak t_r = 24.3 minutes, 24.0% **8** and peak t_r = 26.1 minutes, 11%?, and acetic acid extract, peak t_r = 12.4 minutes, 9.8%?, peak t_r = 18.9 minutes, 3.8%?, peak t_r = 21.3 minutes, 2.9% **4a**, peak t_r = 24.2 minutes, 62.9% **8**, total yield of isomers, 12%.

Spectra.

Ir spectra were taken on a Perkin Elmer 257 and the mass spectra on an A.E.I. MS 902S apparatus. Elemental analyses were carried out by Mr. Socquet, from U.C.B., Division Pharmaceutique Belgium, to who we are indebted.

Nmr Spectra.

60 MHz ^1H spectra were taken on a Varian A60 and a Varian T60 apparatus and 90 MHz ^1H spectra were obtained on a Bruker HX90E using the Fast Fourier Transform method (FFT) (stabilization on the deuteron signal of hexadeuterio-benzene) while 270 MHz ^1H spectra were recorded on a Bruker HX270 MHz apparatus by continuous wave or FFT (stabilization on the deuteron signal of deuteriochloroform or hexadeuteriobenzene). In each case we used 5 mm O.D. sample tubes and added TMS as the internal reference. All chemical shifts are expressed as δ values in ppm. The pulse interferograms were accumulated and Fourier transformed with a Nicolet Instrument Computer, model 1080 (8 K, 20 bit) for the 90 MHz ^1H spectra and model 1085 (20 K, 20 bit) for the 270 MHz ^1H spectra. The 270 MHz ^1H spectra were analysed by the LAME program (LOACOON with magnetic equivalence, build upon the frame work of the program LOACOON 3 by Bothner and Castellano (19), written in FORTRAN IV) with a PDP 15 computer.

Cmr spectra were recorded at 67.88 MHz on the Bruker HX270 MHz apparatus using the FFT method. Sample tubes of 10 mm O.D. were used. Each compound (250 mg.) was dissolved in 2.5 ml. of carbon disulfide and 1.0 ml. of methyl alcohol-d_4 was added as external stabilization.

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