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# SATURATED HETEROCYCLES—113[1]

# SYNTHESIS AND STEREOCHEMICAL INVESTIGATION OF cis- AND trans-1-SUBSTITUTED 7,8-DIMETHOXY-1,4,5,9b-TETRAHYDRO-2H-AZETO[2,1-a]ISOQUINOLINES

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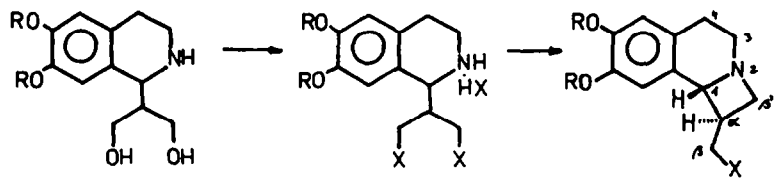
Abstract - Stereospecific and stereoselective syntheses starting from 1-[bis(hydroxymethyl)methyl]- (1) and 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) gave cis- and trans-1-chloromethyl- (10, 4a), 1-methyl- (11, 12) and 1-benzyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolines (20, 21). The steric structures of the diastereomers were determined by NMR spectroscopy.

As a continuation of our work dealing with saturated heterocycles, we recently reported simple syntheses of 6,7-dialkoxy-1-[bis(hydroxymethyl)methyl]-1,2,3,4-tetrahydroisoquinolines (1).[2,3] Compounds 1, which can be prepared conveniently and in high yields by the addition of two molecules of formaldehyde to one molecule of 1-methyl-6,7-dialkoxy-3,4-dihydroisoquinolines with subsequent reduction, possess marked anticonvulsive action, and they are suitable starting materials for the synthesis of various potential drugs, and also of model compounds for stereochemical studies.[4,5]

Although several publications[6-8] deal with the syntheses of azeto[2,1-a]isoquinolines, there are only few examples relating to the preparation of the stereoisomers and to their comparative structural investigation. In the present work the syntheses of cis- and trans-1-substituted azeto[2,1-a]isoquinolines from 1 and from 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) are described, and a comparative NMR study of the products is presented.

The hydroxy groups in 1a,b can be exchanged for halogen by treatment with $POCl_3$, $PBr_3$ or $SOCl_2$. The preparation and purification of 3a did not succeed, probably because of the instability of the product. The resulting dihalogeno derivatives 2a,b and 3b undergo ring closure in alkaline medium, as is characteristic of γ-halogenated alkylamines,[9-12] to give 1-halogenomethyl-7,8-dialkoxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolines 4a,b and 5b (Scheme 1).

As shown by the spectroscopic data, 4 and 5 are formed stereospecifically and the H-1 and H-9b atoms in these compounds occupy trans steric positions.[13] This has been substantiated by means of configurative correlations. In the course of the N → O acyl migration of the N-benzoyl derivative of 1, the products are the

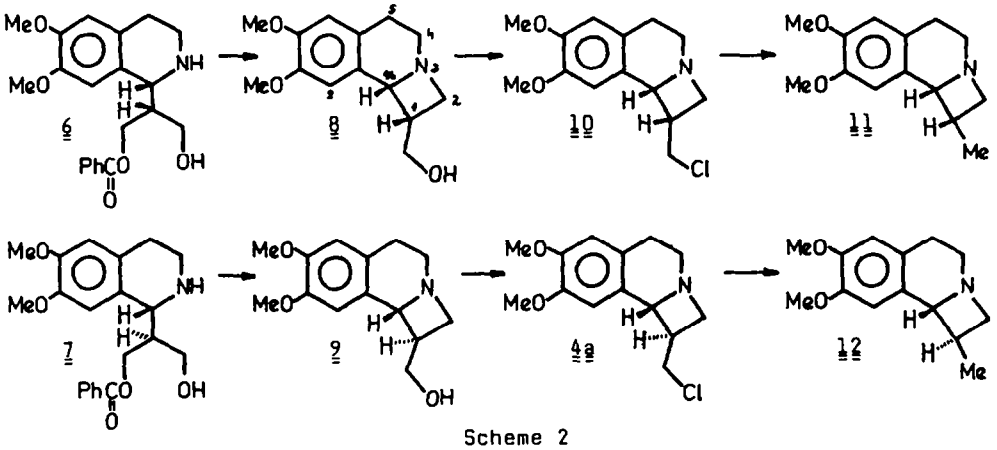


1 X = Cl: 2 X = Br: 3 X = Cl: 4 X = Br: 5
a: R = Me; b: R = Et

Scheme 1

threo (6) and erythro (7) O-benzoyl derivatives; these can be converted in three steps into the cis- and trans-1-hydroxymethylazetoisoquinoline diastereomers (8, 9).[13] The steric structures of the latter compounds have been determined by X-ray diffraction studies.[14]

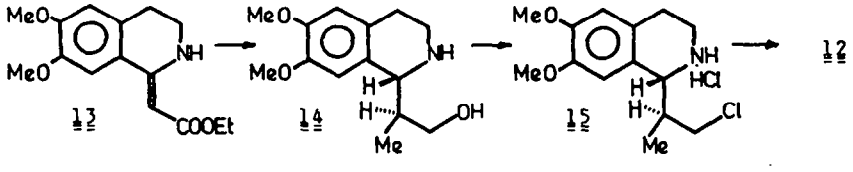
Treatment of 8 and 9 $SOCl_2$ furnished the 1-chloromethyl derivatives 10 and 4a. The product obtained from the trans compound 9 was identical with 4a prepared from 2a by alkaline treatment (Scheme 2).



Scheme 2

$LiAlH_4$ reduction of 10 and 4a gave the cis- and trans-1-methylazetidines 11 and 12. When 2a was refluxed with $LiAlH_4$ in THF, the rapid stereospecific reaction (1 h) yielded the trans-chloromethyl derivative 4a, whereas after a longer reaction time (7 h) the product was the trans-1-methylazetidine 12.

1-Methyl- and 1-benzyltetrahydroazeto[2,1-a]isoquinolines were synthesized earlier,[9] but the stereochemistry of the compounds has not been investigated. As the stereoisomeric azetoisoquinoline model compounds (4, 5, 8-12) have become available in the meantime, it seemed to be worthwhile to re-investigate the formation of these compounds.



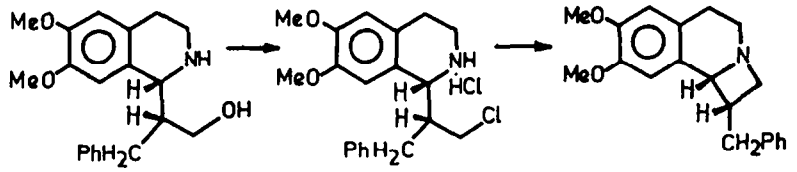
Scheme 3

The 1-ethoxycarbonylmethylene derivative 13[15] can readily be C-alkylated in the 1'-position by means of methyl iodide or benzyl chloride. When the double bond in the resulting compounds was reduced catalytically, followed by $LiAlH_4$ reduction

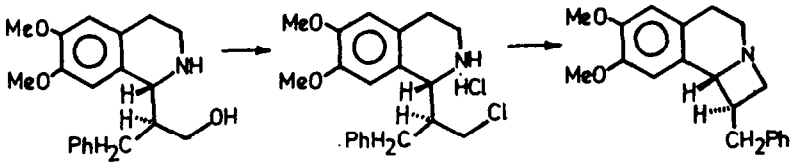
of the ester group, the stereospecific reaction gave erythro-1-[1'-(hydroxymethyl) ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 14, or stereoselective transformation resulted in the corresponding threo and erythro (16:17 = 1:3) β-phenylethyl-substituted derivatives (Schemes 3, 4).

Treatment of 14 with $SOCl_2$ gave the trans-1-methylazetidine, identical with 12 prepared as shown by the synthetic pathway in Scheme 2.

The cis- and trans-1-benzyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolines 20 and 21 were prepared from 16 and 17 in a similar way (Scheme 4).




16 18 20




17 19 21

Scheme 4

Determination of stereostructures by NMR spectroscopy[16]

The $^1H$ and $^{13}C$ NMR data on the compounds investigated (Tables 1 and 2) afford unequivocal evidence of the structures suggested. Determination of the relative configurations is simplified by the possibility of comparing the NMR data for the pairs of diastereomers 4a-10, 11-12, 16-17 and 20-21.

The vicinal coupling constants J(H-1,H-α) of the azetidine compounds can stand alone as definitive evidence of the cis or trans isomeric structure. These constants for 4a, 12 and 21 are 2.8-3.5 Hz, whereas for their counterparts 10, 11 and 20 the splitting is 7.5-8 Hz. According to the Karplus relation[17] for compounds with an azetidine ring, it is a general rule[18a] that $^3J(H,H)_{cis} > {}^3J(H,H)_{trans}$. Thus, the cis configurations of 10, 11 and 20 are unambiguously shown.

Further evidence is that the β-protons in the cis compounds are considerably more shielded that in the trans counterparts, since they are situated above the fused aromatic ring, whose anisotropic shielding effect[18b] is revealed in this upfield shift. The analogous shift of the methyl doublet for 11 is even more significant (-0.89 ppm) than that for the trans isomer 12.

In the benzyl compounds 20 and 21, the anisotropy of this group gives rise to upfield shifts of the H-8 atom and the C-7 methoxy signals for both isomers; however, the shift is significantly larger for the trans isomer 21, where the distance between the groups in question is smaller.

The carbon resonance spectra afford further information in support of the suggested relative configurations. The carbon atoms bearing sterically hindered groups are more shielded (steric compression shift[19]) than the analogous atoms in the isomers having the more favourable steric structure. This field effect is

Table 1. $^1$H NMR data ($\delta_{TMS}$ = 0 ppm, coupling constants in Hz) on compounds 4a,b, 5b, 10-12, 14, 16, 17, 20 and 21 in $CDCl_3$ solution at 250 MHz

| Compound | H-1 d(1H)[a] | H-3 H-4 2-4xm(4H)[b] | H-5,8 2xs(2x1H) | | $OCH_3$(6,7) 2xs(2x3H) | | H-α m(1H)[c] | H-β (2H)[d] | H-β'($NCH_2$) (2H)[e] |
|---|---|---|---|---|---|---|---|---|---|
| 4a | 4.50 | 2.4-2.5, 2.7-3.1[f] | 6.60 | 6.65 | 3.85 | 3.88 | 2.7-3.1[f] | 3.90[g], 4.67[h] | 3.16[g], 3.52[h] |
| 4b[i] | 4.48 | 2.4-2.5, 2.7-3.1[f] | 6.61 | 6.65 | 1.43 | 1.45 | 2.7-3.1[f] | 3.90, 4.1[j] | 3.15[g], 3.52[h] |
| 5b[i] | 4.45 | 2.4-2.6, 2.7-3.1[f] | 6.65 | 6.66 | 1.43 | 1.45 | 2.7-3.1[f] | 3.79[g], 3.93[h] | 3.12[g], 3.50[h] |
| 10 | 4.86 | 2.35-2.75, 2.8-3.2[f] | 6.62 | 6.67 | 3.85 | 3.88 | 2.8-3.2[f] | 3.0[f], ~3.35[j] | ~3.0[f], ~3.5[j] |
| 11 | 4.75 | 2.4[k] 2.7[k] 2.8-3.1[f] | 6.41[l] | 6.67 | 3.83 | 3.88 | 3.18 | 0.62 | ~2.95[f], 3.50[h] |
| 12 | 4.28 | 2.2[k] 2.4[k] 2.7-3.1[f] | 6.50[l] | 6.65 | 3.85 | 3.87 | 2.7-3.1[f] | 1.51 | 3.06[g], 3.51[h] |
| 14[m] | 4.09 | 2.6[k] 2.9, 3.25[k] | 6.56 | 6.60 | 3.83 | 3.85 | 2.15 | 1.21 | 3.45[g], 3.65[g] |
| 16[n] | 4.35 | ~2.3[k,o], 2.6[k,o] ~3.1[k],~3.2[k] | 6.62 | 6.73 | 3.88[f] | | 2.75-2.9[j] | ~2.45[o], 2.8[j] | 3.74[g], ~3.9[f] |
| 17[n] | 4.28 | ~2,6[k] 2.7-3.1[f] 3.1-3.3[j] | 6.49[l] | 6.60 | 3.80 | 3.85 | 2.18 | 2.9[f], 3.2[j] | 3.38[g], 3.56[g] |
| 20[n] | 4.87 | 2.3-2.5, 2.7[k]~3.5[f] | 6.26[l] | 6.69 | 3.63[p] | 3.89 | ~3.1[j] | 2.16[g], 2.87[g] | ~3.1[j], ~3.5[f] |
| 21[n] | 4.43 | 2.3-2.5, 2.6-3.1[f] | 5.72[l] | 6.58 | 3.54[p] | 3.82 | ~2.85[f] | 3.17 | 3.25[g], 3.51[h] |

[a] For 17, ~s ($\Delta\nu$ ~7 Hz), J(H-1,H-α): 2.8 (4a,b), 2.7 (5b), 7.5 (10), 7.9 (11), 3.2 (12) 7.1 (14), 2.5 (16), 8.0 (20) and 3.5 Hz (21). [b] Upfield m/m's correspond to H-3a,4a. [c] The m shows central symmetry in the cases of 11, 14 and 17, where this signal appears separately. [d] Exocyclic methylene (4a,b, 5b, 10, 20 and 21) or benzyl-methylene group (16 and 17). For 11, 12 and 14, the intensity is 3H: C-methyl d, J($CH_3$,H-α): 7.0. [e] Azetidine ring; $OCH_2$ group for 14, 16 and 17. [f,j] Overlapping signals. [g,h] A (downfield) or B part (2x1H) of an ABX spin system, dd[g] or t.[h] J(A,B): 7.3-14.2, J(A,X): 8.4-9.8, except for H-β' in 14 (2.4) and H-β in 20 (4.6) and J(B,X): 6.6 (H-β) and 3.5-4.8 (H-β'), except for H-β in 20 (8.0). For H-β in 21, d ($\delta$A ≡ $\delta$B). [i] $\delta$ $OCH_2$: 4.05, 4.08 ppm (2xqa), J = 7.0. [k] Intensity: 1H. [l] H-8. [m] Assignments were proved in DR experiments. [n] ArH: 7.0-7.35 m (5H). [o] Assignments may be reversed. [p] Pos. 7.

most pronounced on the C-α and C-β atoms, but it is also observable in the C-8a, C-3 and C-4 signals for the cis isomers. An opposite field effect is found for the C-8 and C-β' atoms. The observed upfield shift of the C-8 signal for the trans isomers is in agreement with the proton resonance data, showing that the benzyl group in 21 is compelled to approach closer to the H-8 atom and to the methoxy group in position 7 than in the cis compound.

A special problem is presented by the steric structure of the diastereomeric pair 16-17. For isomer 17, J(H-1,H-α) cannot be obtained because of the unresolved H-1 signal; further, no significant difference can be expected in theory between the diastereomers, owing to the possibility of free rotation about the C-1, C-α bond. If it is assumed that the conformation of the side-chain is fixed by hydrogen-bonding between the NH and OH groups, which is favoured because of the formation of a six-membered ring structure, then the upfield shift of 4.2 ppm of the benzyl-methylene carbon signal for isomer 16 is indicative of the axial position, and thereby of the already proved cis configuration of the azetidine derivative 20, resulting from ring closure.

Table 2. $^{13}C$ NMR chemical shifts ($\delta_{TMS}$ = 0 ppm) for compounds 4a,b, 5b, 10-12, 14, 16, 17, 20 and 21 in $CDCl_3$ solution at 20.14 or 62.89[a] MHz

| Compound | C-1 | C-3 | C-4 | C-4a,8a | C-5,8 | C-6,7 | $OCH_3$[b] | C-α | C-β[c] | C-β' |
|---|---|---|---|---|---|---|---|---|---|---|
| 4a[d] | 62.2 | 44.2 | 21.9 | 126.1<br>128.8 | 109.2<br>111.5 | 147.3<br>147.9 | 55.4[e] | 43.5 | 47.6 | 49.0 |
| 4b | 62.8 | 44.9[f] | 22.5 | 126.9<br>129.6 | 112.4<br>114.6 | 147.4<br>148.3 | 14.8[e] | 44.0[f] | 47.6 | 49.7 |
| 5b | 63.9 | 44.3[f] | 22.5 | 127.0<br>129.6 | 112.5<br>114.6 | 147.7<br>148.3 | 14.9<br>15.0 | 44.8[f] | 36.8 | 50.7 |
| 10[d] | 62.1 | 43.8[f] | 21.8 | 125.0<br>127.5 | 110.7<br>111.9 | 147.7[e] | 55.6[e] | 39.2 | 43.5[f] | 50.6 |
| 11 | 63.8 | 44.2 | 22.6 | 127.7<br>128.1 | 111.4<br>112.4 | 147.8<br>148.1 | 56.1<br>56.2 | 32.1 | 15.5 | 54.6 |
| 12 | 66.2 | 45.2 | 22.9 | 126.7<br>131.1 | 109.4<br>112.2 | 147.6<br>148.3 | 55.9<br>56.0 | 36.7 | 20.2 | 53.5 |
| 14 | 61.4 | 41.8 | 29.3 | 128.4<br>129.5 | 110.7<br>112.7 | 147.7<br>148.1 | 56.1<br>56.4 | 38.4 | 15.1 | 66.1 |
| 16[g] | 60.1 | 42.6 | 29.6 | 128.6<br>129.5 | 109.4<br>112.9 | 148.1[e] | 56.1<br>56.4 | 46.9 | 31.2 | 64.4 |
| 17[g,h] | 59.5 | 42.9 | 29.9 | 128.9<br>129.0 | 110.2<br>112.6 | 148.0[e] | 56.1<br>56.5 | 46.6 | 35.4 | 62.1 |
| 20[g,h] | 63.5 | 44.2 | 22.6 | 127.1<br>129.0 | 111.4<br>112.6 | 147.8[e] | 55.8<br>56.5 | 37.6 | 36.6 | 53.0 |
| 21[g] | 63.6 | 45.4 | 23.0 | 126.6<br>130.8 | 109.3<br>112.1 | 147.6<br>148.4 | 55.8<br>56.1 | 43.6 | 41.0 | 51.7 |

[a] For compounds 5b, 11 and 20. [b] For 4b and 5b: methyl signal of the ethoxy group; $OCH_2$, 4b: 64.9[e], 5b: 65.0[e] ppm. [c] Methylene signal of the side-chain; of the benzyl group in 16 and 17 or of the methyl signal in compounds 11, 12 and 14. [d] Assignments were proved by means of proton-coupled spectra. [e] Two overlapping lines. [f] Reversed assignments may also be possible. [g] Aromatic lines of 16, 17, 20, 21: C-1', 140.0-141.4; C-2'—C-6', 125.9-129.1 ppm. [h] Assignments were proved by means of DEPT measurements.

## EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT spectrometer equipped with an Aspect 2000 computer. $^1H$ and $^{13}C$ NMR spectra were recorded at room temperature in CDCl solution in 5 and 10 mm tubes, on Bruker WM-250 ($^1H$, $^{13}C$) and WP-80 SY ($^{13}C$) FT spectrometers at 250.13 ($^1H$) and 20.14 or 62.89 ($^{13}C$) 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 and 5 or 15 kHz, pulse width 1 ($^1H$) and 3.5 or 7 ($^{13}C$) μs (~20° and ~30° flip angle), acquisition time 1.64 and 1.64 or 1.03 s, number of scans: 16 ($^1H$) and $2^8$-$2^{13}$ ($^{13}C$), computer memory 16 K. Complete proton noise decoupling (~1.5 or ~3 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).

DEPT experiments[20] were performed in a standard way,[24] using only the θ = 135° pulse to separate CH/$CH_3$ and $CH_2$ lines phased "up" and "down", respectively. Typical acquisition data were: number of scans: 128-12 K, relaxation delay for protons 3 s, 90° pulse width: 10.8 and 22.8 μs for $^{13}C$ and $^1H$, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

Physical properties and analytical data on the prepared compounds are given in Table 3.

1-[bis(Chloromethyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2a)

Method A. The salt 1a.HCl (3.0 g; 10 mmol) was added, with cooling in ice, to thionyl chloride (6 ml). The mixture was gently refluxed for 30 min. The excess of $SOCl_2$ was evaporated off in vacuum. The residue was triturated with methanol and the product was collected by filtration.

Table 3. Analytical data on compounds 2-21

| Compound | M.p. °C | Solvent | Yield[a] % | Found % C | H | N | Formula | Calculated % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| 2a[b] | 217-219 | ethanol/ether | 98 (A) | 49.46 | 6.12 | 4.16 | $C_{14}H_{20}Cl_3NO_2$ | 49.35 | 5.92 | 4.11 |
| 2b[b] | 149-155 | ethanol/ether | 89 (A) | 52.34 | 6.37 | 3.72 | $C_{16}H_{24}Cl_3NO_2$ | 52.11 | 6.56 | 3.80 |
| 3b[c] | 188-190 | ethanol/ether | 75 (B) | 38.26 | 4.92 | 2.87 | $C_{16}H_{24}Br_3NO_2$ | 38.27 | 4.82 | 2.79 |
| 4a | 103-104 | ether | 91 (C)<br>73 (D)<br>86 (E)<br>61 (F) | 62.65 | 6.58 | 5.20 | $C_{14}H_{18}ClNO_2$ | 62.80 | 6.77 | 5.23 |
| 4b | 91-93 | n-hexane | 84 (E) | 64.82 | 7.38 | 4.35 | $C_{16}H_{22}ClNO_2$ | 64.96 | 7.50 | 4.74 |
| 5a | 140-142 | n-hexane | 74 (E) | 53.72 | 5.92 | 4.63 | $C_{14}H_{18}BrNO_2$ | 53.86 | 5.81 | 4.49 |
| 5b | 93-95 | n-hexane | 71 (E) | 56.66 | 6.70 | 4.20 | $C_{16}H_{22}BrNO_2$ | 56.47 | 6.52 | 4.12 |
| 10 | 88-90 | ether | 90 (A) | 62.81 | 6.68 | 5.58 | $C_{14}H_{18}ClNO_2$ | 62.80 | 6.77 | 5.23 |
| 11 | 77-80 | n-hexane | 69 (G) | 72.20 | 8.38 | 6.09 | $C_{14}H_{19}NO_2$ | 72.07 | 8.21 | 6.00 |
| 12 | 91-92 | n-hexane | 73 (G)<br>54 (H)<br>70 (E)[d] | 72.09 | 8.44 | 6.16 | $C_{14}H_{19}NO_2$ | 72.07 | 8.21 | 6.00 |
| 14 | 119 | ether | 44[e] (I) | 67.04 | 8.59 | 5.71 | $C_{14}H_{12}NO_3$ | 66.90 | 8.42 | 5.57 |
| 15[b] | 217-218 | ethanol/ether | 81 (A) | 54.78 | 6.78 | 4.31 | $C_{14}H_{21}Cl_2NO_2$ | 54.91 | 6.91 | 4.57 |
| 16 | 133-135 | ether | 27[e] (J) | 73.27 | 7.89 | 4.53 | $C_{20}H_{25}NO_3$ | 73.36 | 7.70 | 4.28 |
| 17 | 130-131 | ether | 8[e] (J) | 73.21 | 7.78 | 4.42 | $C_{20}H_{25}NO_3$ | 73.36 | 7.70 | 4.28 |
| 18[b] | 197-202 | ethanol/ether | 83 (A) | 60.30 | 6.48 | 3.60 | $C_{20}H_{25}Cl_2NO_3$ | 60.30 | 6.33 | 3.52 |
| 19[b] | 206-207 | ethanol/ether | 89 (A) | 60.41 | 6.52 | 3.71 | $C_{20}H_{25}Cl_2NO_3$ | 60.30 | 6.33 | 3.52 |
| 20 | 127-129 | n-hexane | 78 (E) | 77.46 | 7.60 | 4.62 | $C_{20}H_{23}NO_2$ | 74.64 | 7.49 | 4.53 |
| 21 | 93 | ether | 74 (E) | 77.72 | 7.56 | 4.43 | $C_{20}H_{23}NO_2$ | 74.64 | 7.49 | 4.53 |

[a] The letter in brackets denotes the method used. [b] HCl salt. [c] HBr salt. [d] From 15. [e] Overall yield.

1-[bis(Bromomethyl)methyl]-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3b)

Method B. The salt 1a.HCl (3.5 g; 10 mmol) was suspended in benzene (30 ml). Phosphorus tribromide (10 ml) was added dropwise, with stirring, during 10 min. The reaction mixture was stirred and refluxed for 2 h. The excess benzene and $PBr_3$ were then evaporated off in vacuum. The residue was triturated with ether and the product was collected by filtration.

trans-1-Chloromethyl-7,8-dimethoxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinoline (4a)

Method C. Compound 2a (3.4 g; 10 mmol) was suspended in methanol (30 ml), and 10% aqueous sodium hydroxide solution (8 ml; 20 mmol NaOH) was added. After refluxing for 2 h, the mixture was evaporated to dryness and the residue was dissolved in ether (100 ml). Drying and concentration of the ethereal solution furnished the chloromethylazetidine 4a as a crystalline compound.

Method D. Compound 2a (3.4 g; 10 mmol) was dissolved in ethanol (50 ml). Triethylamine (5 ml) was added and the mixture was allowed to stand for 3 days at room temperature. The reaction mixture was evaporated to dryness, the residue was mixed with water (30 ml) and the mixture was extracted with ether (3x50 ml). After drying, concentration of the ethereal solution furnished 4a as an off-white product.

Method E. Compound 2a (3.4 g; 10 mmol) was dissolved in methanol (50 ml) containing NaOH (1 g) and the solution was refluxed for 1 h. After evaporation, the residue was mixed with water (20 ml) and the mixture was extracted with chloroform (3x20 ml). Drying and evaporation of the extract furnished 4a.

Method F. $LiAlH_4$ (1.14 g; 30 mmol) was suspended in dry THF (100 ml). With stirring and cooling in ice, compound 2a (1.7 g; 5 mmol) was slowly added to the suspension. After refluxing for 1 h, the reaction mixture was decomposed by the addition of 2 ml of water while cooling in ice. The usual workup gave the chloromethylazetidine 4a.

cis-1-Chloromethyl-7,8-dimethoxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinoline (10)

This compound was prepared from the salt 8.HCl by Method A. The base was liberated from the salt 10.HCl (m.p. 207-209 °C, from ethanol), by means of aqueous $Na_2CO_3$.

trans-1-Methyl-7,8-dimethoxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinoline (12)

Method G. $LiAlH_4$ (0.38 g; 10 mmol) was suspended in THF (50 ml). Compound 4a (1.34 g; 4 mmol) was added to the stirred suspension. After stirring and refluxing for 4 h, the reaction mixture was decomposed by the addition of water (1 ml), and it was worked up in the usual way. The azetidine 12 was obtained in crystalline form.

Method H. $LiAlH_4$ (1.9 g; 50 mmol) was suspended in dry THF (50 ml). The suspension was stirred and cooled in an ice-bath, while compound 2 (1.7 g; 5 mmol) was slowly added to it. After stirring and refluxing for 7 h, the mixture was decomposed with water (4 ml); the usual workup gave the azetidine 12.

Erythro-1-[1'-(hydroxymethyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14)

Method I. 1-Ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) (11.08 g; 40 mmol) was dissolved in ethanol (50 ml), and methyl iodide (8.52 g; 60 mmol) was added to the solution. It was allowed to stand for 3 days at room temperature, and was then evaporated to dryness. The residue was taken up in ethanol (100 ml) and reduced in hydrogen atmosphere under normal conditions for 30 min, in the presence of pre-hydrogenated platinum oxide (0.2 g). The catalyst was removed by filtration. On evaporation of the ethanol, 1-(1'-ethoxycarbonylethyl)-1,2,3,4-tetrahydroisoquinoline hydroiodide was obtained as a crystalline compound (m.p. 165-166 °C). The base was liberated from the hydroiodide by means of $Na_2CO_3$. (No erythro isomer could be detected in the $^1H$ NMR 60 MHz spectrum of the crude product.) The crude base was added, in portions, to a suspension of $LiAlH_4$ (2 g) in THF (200 ml). Stirring and refluxing of the mixture for 2 h, followed by the usual processing, gave the required compound 14.

Threo and erythro-1-(1'-hydroxymethyl-2'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (16, 17)

Method J. 1-Ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) (11.08 g; 40 mmol) in ethanol (20 ml) was refluxed for 4 h with benzyl chloride (6.5 g; 50 mmol). Evaporation of the reaction mixture furnished a yellow crystalline product, m.p. 166 °C, which was reduced in hydrogen atmosphere under normal conditions in ethanol (100 ml) in the presence of pre-hydrogenated platinum oxide (0.2 g). After 30 min the catalyst was removed by filtration and the filtrate was evaporated to dryness. From the resulting 1-(1'-ethoxycarbonyl-2'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride mixture (m.p. 208-209 °C) the bases were liberated. $^1H$ NMR (60 MHz) measurements indicated a threo-erythro isomer ratio of 1:3. Reduction was effected with $LiAlH_4$ (Method I).

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