BENZO- AND INDOLOQUINOLIZIDINE DERIVATIVES[1] XIX. THE SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME QUINOLIZIDINE DERIVATIVES, ANALOGUES OF BUTACLAMOL

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Abstract - Indenopyridoisoquinoline and benzopyridophenanthridine derivatives were synthesized as the conformationally rigid analogues of butaclamol. For both series, a unique reaction scheme has been worked out in order to obtain the desired trans-cisoid-cis conformation of the end products. In this conformation, the indenopyridoisoquinoline derivative simulates the proposed active form of butaclamol, whilst the benzopyridophenanthridine derivatives simulate the non-active form of butaclamol. The products were tested for neuroleptic activity in "in vitro" models. No significant binding was detected. In view of the pharmacological assays, we cannot decide about the correctness of the proposed structure-activity relationship in the butaclamol series. Overall topological congruence of the phenethylamine part and some flexibility of the system may be important factors for activity.

INTRODUCTION

Recently[2] the synthesis was reported of (±)-(4a,13b-trans)(3-hydroxy,13b-trans)-3-tert-butyl-2,3,4,4a,8,9,13b,14-octahydro-1H-benzo[6,7]cyclohepta[1,2,3-de]-pyrido[2,1-a]isoquinolin-3-ol (1) hydrochloride, commonly named butaclamol hydrochloride (Fig.1).

Although its structure is not related to those of the usual neuroleptics, the compound displays a remarkable antipsychotic activity[3].

The fact that only one enantiomer, namely the (+)-(3S,4aS,13bS) enantiomer, shows this activity in contrast to its antipode which is inactive[4] is also exceptional. Butaclamol acts on the dopamine receptor by blocking the site of binding, analogous to most neuroleptics[4].

Structure (1) contains the phenethylamine group, which appears also in many molecules acting on the dopamine receptor, for example dopamine itself,

TABLE 1

Parameter	Conformer A(1)[+]	Conformer B(1)[++]	Apomorphine (2)[+++]	Structure (3)[++]	Structure (4)[++]
Dihedral angle					
(1) N-C14-C13b-C13a	169°	155°			
(2) N-C6a-C7-C7a			178°		
(3) N-C9a-C14b-C14a				130°	
(4) N-C9a-C15b-C15a					170°
Deviation from perpendicularity					
(1) Ring A/C13a-C13b-C14 plane	73°	85°			
(2) Ring A/C7a-C7-C6a plane			50.35°		
(3) Ring A/C9a-C14b-C14a plane				95°	
(4) Ring A/C9a-C15b-C15a plane					70°
Ring A plane-N distance	0.19 Å	0.9 Å	1.06 Å	0.8 Å	0.2 Å
Comparison with (1)			Conformer B	Conformer B	Conformer B

\+ parameters from X-ray crystallography[5]

++ parameters from the Dreiding models

+++ parameters from X-ray crystallography[6]

(-)-apomorphine (2) and ADTN (2-amino-6,7-dioxytetrahydronaphthalene). In all these molecules the phenethylamine part is in the trans configuration. As a consequence Humber and co-workers[4] explain the pharmacological activity of butaclamol in terms of the presence of this phenethylamine group. They compare the topological parameters of butaclamol with those of (-)-apomorphine[4]. Butaclamol has a semi-rigid structure. Two conformers are possible by rotation around the C8-C9 bond (Fig.2), namely structure A (C_9-H/C_{13b}-H in eclipsed position) and structure B (C_8-H/C_{13b}-H in eclipsed position).

In table 1, we represent some parameters, describing the trans-phenethylamine geometry in (1) and (2). Structure A has been shown to be the most stable conformation by force-field calculations, in the solid state by X-ray analysis[5] and also in solution by NMR measurements.

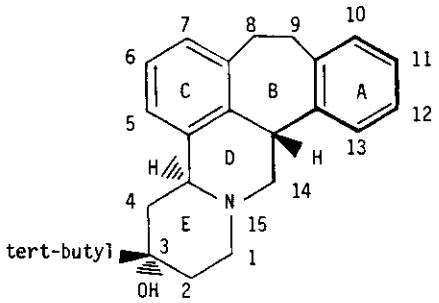
Nevertheless Humber and co-workers[4] considered the B-conformation as the biologically active one, mainly based on the fact that the distance between the N-atom and the A phenyl plane is comparable in (1) and (2). Topological coincidence of the N-atom and the A phenyl ring without coincidence of the intervening carbon atoms seems to be sufficient for pharmacological activity. Recent studies by Humber and co-workers[7] on butaclamol analogues redefine these topological considerations, and show that the nitrogen atom and the phenyl ring are part of the neuroleptic pharmacophore.

Starting from these considerations we developed the synthesis of structures with fixed geometry, simulating both A and B conformers of (1).

The selected molecules are 6-phenyl or (tert-butyl)-6-hydroxy-5,6,7,8,9a,14b-hexahydro-4bH-indeno[2,3-c]pyrido[2,1-a]isoquinoline (3) and 6-phenyl or (tert-butyl)-6-hydroxy-5,6,7,8,9a,10,11,15b-octahydro-4bH-benzo[a]pyrido[1,2-f]phenanthridine (4) with rings E/D-trans-fused, rings D/B-cis-fused and R equatorial in ring E (Fig.3). The R group is phenyl or tert-butyl, chosen for possible activity in comparison with the derivatives synthesized by Humber et al.[2]

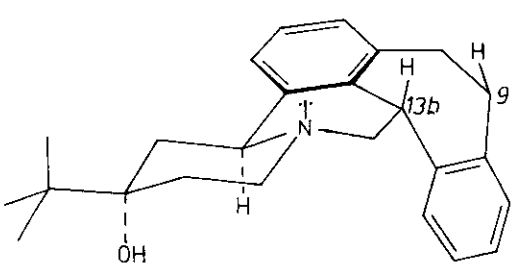
A Dreiding model study of the phenethylamine part shows that the topography of molecule (3) with a five-membered B ring is in agreement with the B conformation of (1), while the topography of molecule (4) with a six-membered B ring is in agreement with conformer A of (1), as far as we compare the distance between the N-atom and the A phenyl ring. (see table 1).

Fig. 1



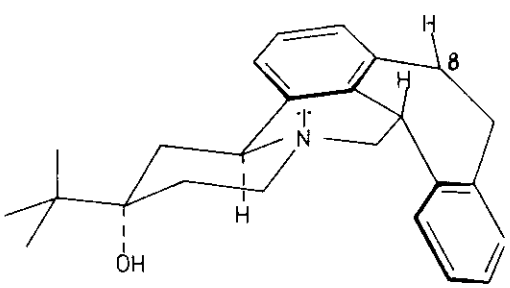
(1) (2)

Fig. 2



A

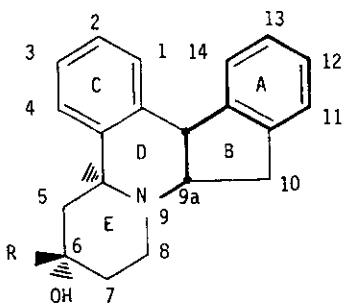
preferred



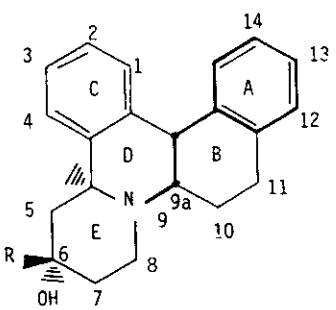
B

"active"

Fig. 3



(3)



(4)

CONFORMATION OF BUTACLAMOL IN SOLUTION

Since both conformations of butaclamol (1) differ in the relative orientation of H_8 and H_9 towards H_{13b} the distinction between the two conformations can be made by measuring the NOE effect between the interacting protons. In order to do so, the signals of H_8 and H_9 have to be assigned unambiguously. We have based this assignment upon the fact that C_8 is next to a trisubstituted aromatic ring whereas C_9 is next to a disubstituted one. Since the signals of the trisubstituted ring are well resolved in the spectrum (not shown), this spin system can easily be analysed (table 2).

TABLE 2 : 270 MHz ^1H NMR parameters of (+)-butaclamol ($CDCl_3$ soln).

Chemical shifts (ppm)		Coupling constants (Hz)	
H5	= 6.98	$^3J(5,6)$	= 7.7
H6	= 7.03	$^3J(6,7)$	= 7.9
H7	= 6.88	$^3J(5,7)$	= 1.5
H8eq	= 3.36	$^2J(8)$	= -16.8
H8ax	= 3.02	$^3J(8eq,9eq)$	= 5.0
H9eq	= 2.81	$^3J(8eq,9ax)$	= 4.9
H9ax	= 3.61	$^3J(8ax,9eq)$	= 5.0
		$^3J(8ax,9ax)$	= 12.5
		$^2J(9)$	= -14.5
		$^5J(13b,8eq)$	= 1.5
		$^5J(13b,8ax)$	= 1.1

The correlation between these aromatic protons and the benzylic C_8 protons was made by removing the small long range benzylic coupling between H_7 and the C_8 protons. Since these couplings are too small to be resolved in the spectrum, their effect appears as a line broadening of the corresponding signals.
This is particularly evident in the resolution-enhanced spectrum (fig.4a). On irradiating the H_7 signal, this broadening is removed, which allows the assignment of the H_8 signals (fig.4b). The interbenzylic couplings with H_{13b} are now resolved.

Fig. 4

(a) resolution-enhanced 270 MHz ^1H spectrum of the aliphatic protons (except H_{13b}) of butaclamol (1).

(b) idem, but on irradiating the H7 signal at 6.88 ppm to remove the benzylic couplings with the C8 protons.

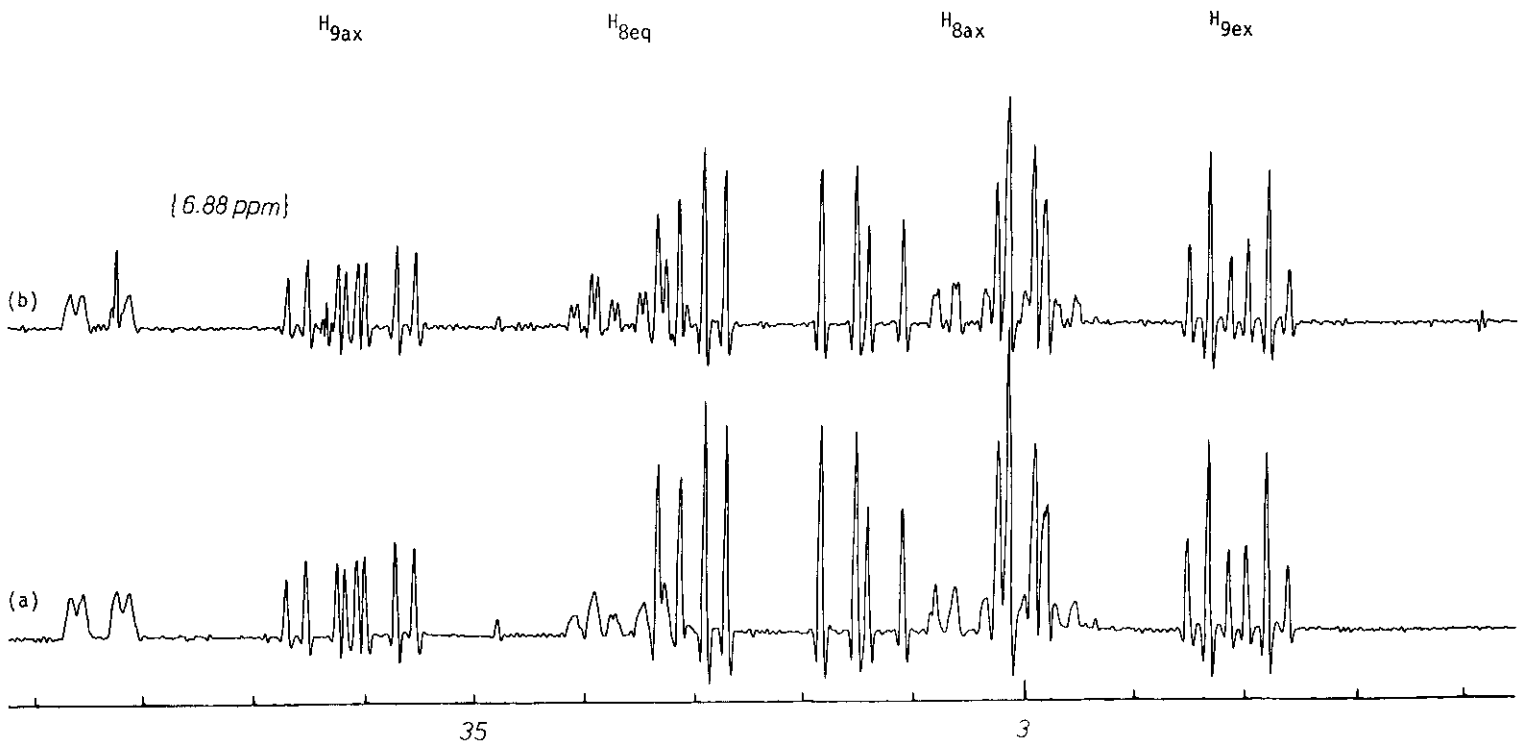
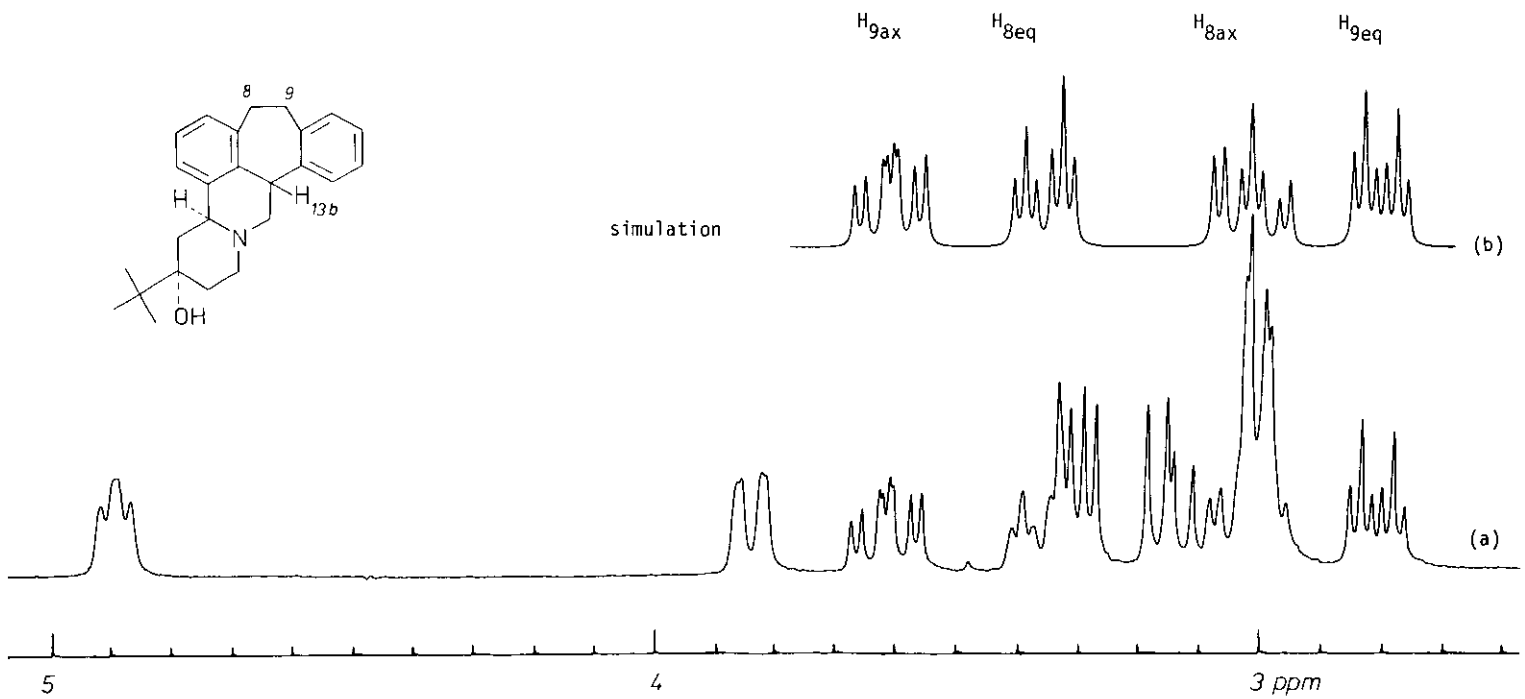
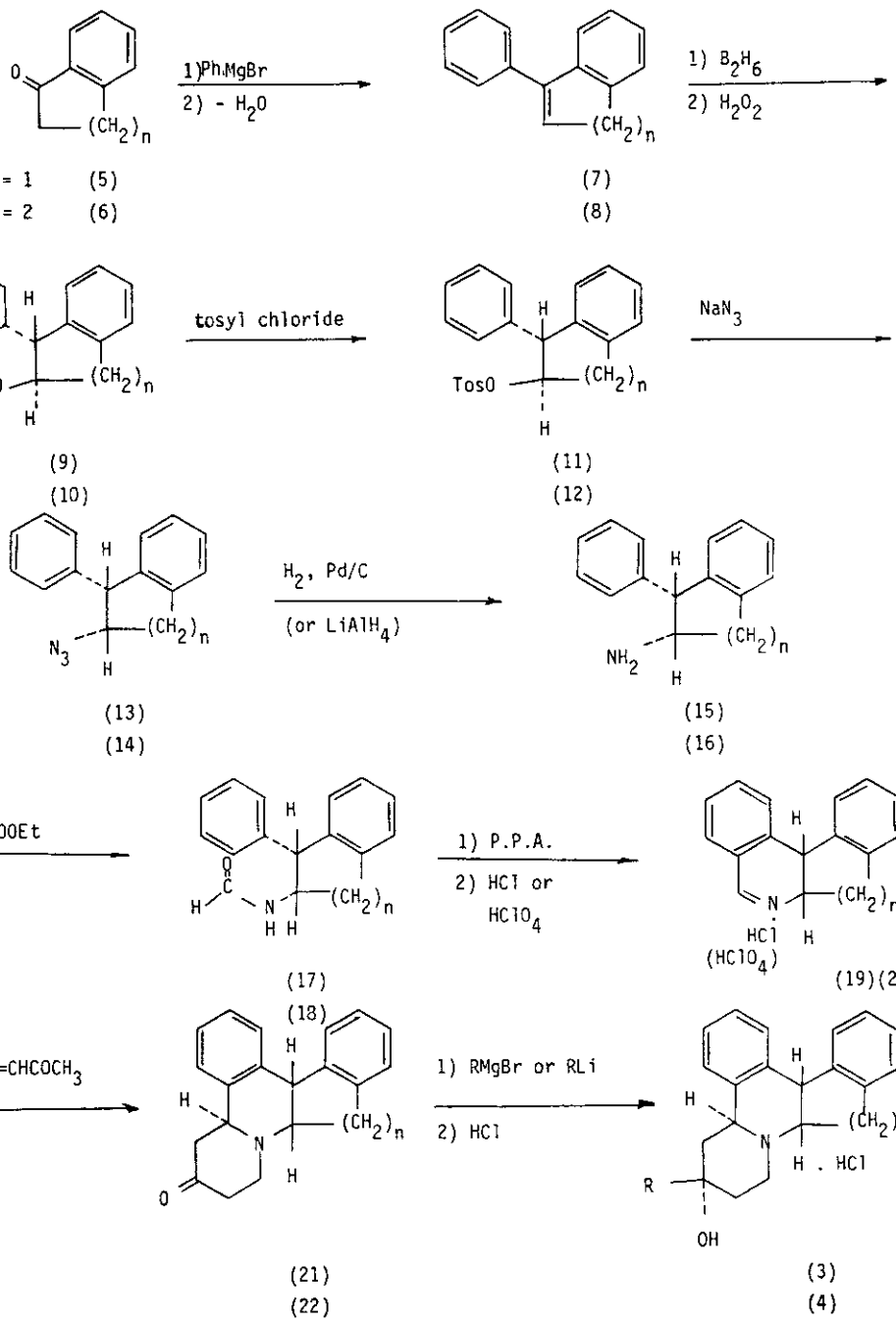


FIG.5

(a) : 270 MHz proton spectrum of the aliphatic protons of butaclamol (1) and simulation (trace(b)) of the C8-C9 spin system.



Scheme 1


1) PhMgBr
2) - H2O
1) B2H6
2) H2O2
n = 1 (5)
n = 2 (6)
(7)
(8)
tosyl chloride
NaN3
HO
TosO
(9)
(10)
(11)
(12)
H2, Pd/C
(or LiAlH4)
(13)
(14)
(15)
(16)
HCOOEt
1) P.P.A.
2) HCl or
HClO4
(17)
(18)
(19)(20)
CH2=CHCOCH3
1) RMgBr or RLi
2) HCl
(21)
(22)
(3)
(4)

The complete four-spin system of the C_8-C_9 bridge was then analyzed by spectrum simulation (fig.5, table 2).

The NOE experiment gives an enhancement of ca. 12% of the H_9 signal on irradiating H_{13b}. This experiment proves the predominance of conformer A in the chloroform solution.

SYNTHESIS AND STRUCTURE OF ANALOGUES (3) and (4)

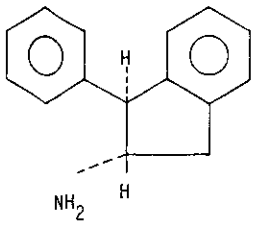
The synthesis of (3) and (4) has been performed according to Scheme 1. The proposed configuration was incorporated in two stages. First constructing the D/B-cis ring fusion is followed by annelation of the E-ring on this part in a stereoselective way.

The assignment of the trans configuration of the alcohols (9) and (10) was based on the cis addition mechanism of the diborane reaction and the ^{1}H-NMR data for structure (10). Owing to the nature of the five-membered ring, the NMR coupling constants do not permit a straightforward assignment of the configuration of (9). The expected inversion at the reaction centre in the synthesis of the azido derivatives was proved by ^{1}H-NMR study on structure (14) (the coupling constant of the hydrogen at the phenyl-substituted carbon decreases from 12 Hz for X=OH to 5 Hz for $X=N_3$). Comparison of the ^{1}H-NMR spectra of amine (15) with those of the trans-amine (23)(Fig.6) proved the proposed cis configuration for the five-membered ring azide (13) and amine (15) and consequently the trans configuration of alcohol (9) and tosylate (11). In the NMR spectrum of the product (23) with amino and phenyl substituent trans we noted a coupling constant of 8 Hz for the hydrogens on the corresponding carbon atoms and a coupling constant of 6.5 Hz in the product with cis configuration (15). In the six-membered ring amine (16) the corresponding coupling constant was 6 Hz.

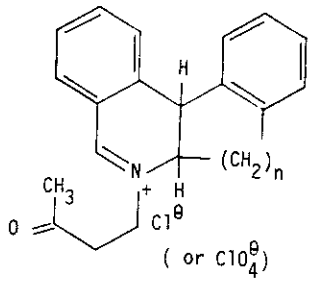
As for the ring fusion of the cyclized products (19) and (20) we obtained coupling constants of 8 Hz for (19) and 6 Hz for (20) in the ^{1}H-NMR, proving the D/B-cis ring fusion.

The annelation of the E ring was performed on compounds (19) and (20) by reaction with methyl vinyl ketone followed by cyclization of the intermediates (24) and (25). The intermediates were purified by salt formation (hydrochloride or perchlorate). The cyclisation step was performed on these salts. In the case of the six-membered ring the hydrochloride (25) was cyclized on an Al_2O_3 column by elution with ether in 70% yield. Only one isomer was obtained.

Fig. 6



(23)



(24)
(25)

Fig. 7

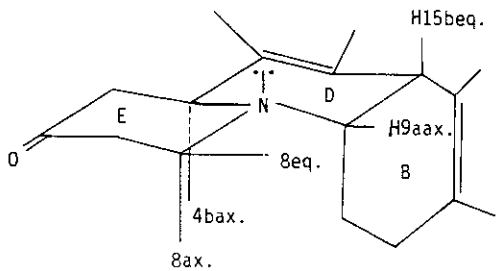
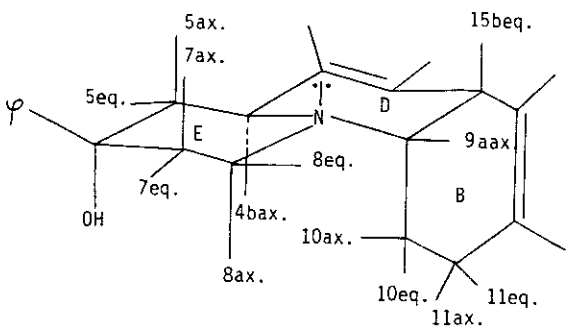


Fig. 8



^{1}H-NMR data proved that the product (22) is in the trans-cisoid-cis configuration (E/D/B ring system) in comparison with analogous structures obtained in our laboratory (Fig.7)[8].

The coupling constants of H15b (doublet, 4.5 Hz, ax-eq with H10a) and of H9a (double triplet: 11.5 Hz, ax-ax with H10ax; 4.5 Hz, ax-eq with H10eq; 4.5 Hz with H15b) prove a D/B-cis ring fusion with H15b equatorial and H9a axial in ring B.

The coupling constants of H4b (double doublet: 12 Hz, ax-ax with H5ax; 2 Hz, ax-eq with H5eq) prove an axial position in ring E.

The chemical shifts of H4bax (3.93 ppm) and H8eq (3.24 ppm) and the geminal coupling constants of the protons at position 8 (-11.5 Hz) are consistent with a trans-quinolizidine structure (effects induced by the nitrogen lone pair and the substituents). Cyclization of (25) in basic medium afforded only 30% of the isomer (22) and a major by-product, identified as the free base of (20). Cyclization of the salt (24), the hydrochloride or the perchlorate, on a column in basic or in acid medium produced the ketone (21) in low yields (20 to 30% maximum). The NMR data are also consistent with a trans-cisoid-cis configuration. (trans-quinolizidine structure and a D/B-cis ring fusion).

Introduction of the phenyl group was performed by the Grignard reaction on compounds (21) and (22), in yields of 25% and 60%, respectively. The end products were purified as their HCl salts. Introduction of tert-butyl group was performed by reaction with tert-butyllithium. We obtained the desired compound (4) with R = tert-butyl in 20% yield as the HCl salt. In the case of the derivative of (3) we obtained a compound which formed a HCl salt but was not identified until now.

Evidence of equatorial attack of the bulky phenyl and tert-butyl groups on the carbonyl (R group equatorial, OH axial) was proved by the complete ^{1}H-NMR analysis of product (4) with R = phenyl. The relative configuration of the end products is shown in fig.8.

The trans-cisoid-cis configuration of the end products is evident from the chemical shifts and coupling constants similar to those for the ketone derivatives, shown in Fig.7. [compound (4) : H15b at 4.4 ppm, equatorial in ring B; H4b at 4.15 ppm, axial in ring E; H9a at 3.40 ppm, axial in ring B].

The equatorial position of the phenyl ring and the axial position of the hydroxyl group in ring E are clear from the fact that this configuration produces an approach of the chemical shifts of H5ax versus H5eq and H7ax versus H7eq.

The normal chemical shift difference (0.5 ppm) between the equatorial and the

axial protons on carbon atoms 5 and 7 is reduced by introducing an equatorial phenyl substituent at carbon atom 6. In this case the difference is 0.3 to 0.4 ppm.

In the alternative configuration (phenyl in axial position and hydroxyl in equatorial position) the chemical shift difference will be increased.

IN VITRO BINDING ASSAYS

The compounds were tested in two different in vitro models : ^{3}H-haloperidol binding assay in rat striatum and ^{3}H-spiperone binding assay in rat frontal cortex[9].

No activity was detected for (3, R = phenyl) and (4, R = tert-butyl).

The IC_{50} values (concentration of drug needed for 50% inhibition) are approximately $2x10^{-6}$M versus $2x10^{-9}$M for haloperidol and $2x10^{-5}$M versus $2x10^{-9}$M for spiperone.

In comparison the values for butaclamol are : 1.6×10^{-8}M versus haloperidol and $4x10^{-8}$ *versus spiperone*.

Derivative (4, R = phenyl) showed some in vitro activity (IC_{50}: 2.8×10^{-7} versus haloperidol and 1.3×10^{-6} versus spiperone).

CONCLUSIONS

Starting from the topological considerations by Humber et al.[4] for butaclamol, we have synthesized butaclamol mimics (3) and (4). In these structures we fixed two possible conformations of butaclamol. Structure (3) represents then the B conformation and the assumed active form of butaclamol (1), whilst structure (4) represents the A conformation. In view of the pharmacological assays on (3) and (4), we cannot decide for the correctness of the proposals of Humber et al.[4] The activity of structure (4, R = phenyl) can probably be explained by the overall topological congruence of the whole phenethylamine part among (4, R = phenyl), butaclamol (1) (A-conformer) and apomorphine (2). This is not the case with structure (3), where the N-atom and the A-phenyl are congruent with the configuration in butaclamol (1)(B-conformer) and apomorphine (2), but where the C-atoms between them are not superimposable. Those facts are in favour of the A conformation of butaclamol (1).

Flexibility of the system may be also an important factor. This flexibility exists in structure (4). Structure (3) is completely rigid. No satisfactory argument

explains the inactivity of molecule (4, R=tert-butyl) in comparison with butaclamol (1).

EXPERIMENTAL

IR spectra were determined on a Perkin-Elmer 257 spectrometer. NMR spectra were obtained with a Varian T60 or a Bruker HX 270 apparatus. The reported chemical shifts refer to the centre of the multiplets (TMS as internal reference). The mass spectra were obtained with an AEI-MS 902 S spectrometer. The intensity of the fragments is expressed as the percentage of the base peak. Melting points were taken on a Büchi 510 apparatus. GC-MS were performed on a Finnigan 3200 apparatus. The purity of the products was controlled by thin-layer chromatography and GC-MS analysis. The elemental composition was investigated by peak matching of the important mass peaks in the MS spectra.

3-Phenylindene (10)

To a solution of phenylmagnesium bromide (prepared from 66 g, 0.42 mol of bromobenzene and 10 g, 0.42 mol of magnesium) in ether, 50 g (0,38 mol) of 1-indanone (5) in 200 ml of ether were added in small portions. The mixture was stirred and refluxed for 1 h. The excess of the Grignard reagent was destroyed by slowly adding the mixture to a stirred saturated solution of ammonium chloride in water (500ml). The organic phase was separated, dried and evaporated. The crude product was poured into a mixture of 120 ml of acetic acid and 30 ml of conc. H_2SO_4. After 30 min two layers were formed.
The product was poured into 400 ml of water and 250 ml of ether. The organic phase was dried, the solvent was evaporated and the product distilled.
Yield : 49.5 g, 0.26 mol, 68%; bp 100-105°C/0.1 Torr.

1-Phenyl-3,4-dihydronaphthalene (11)

Prepared as described for (7), starting from α-tetralone (50 g, 0.34 mol)(6).
Yield : 43.4 g, 0.21 mol, 62%; bp 111-113°C/0.07 Torr.

trans-2-Hydroxy-1-phenylindane (9)

3-Phenylindene (7) (19.2 g, 0.1 mol) dissolved in 150 ml of freshly distilled THF was put into a 3-necked, round-bottomed flask equipped with a mechanical stirrer, diborane gas inlet and condenser. Diborane gas, prepared from $NaBH_4$ (7.5 g) and

BF_3 etherate (30 ml) in diglyme, was bubbled through the solution (kept at 0°C) for 1 h. The mixture was then stirred for 16 h at room temperature. The solution was cooled to 0°C and an excess of water (50 ml) was added slowly. Then 100 ml of 10% NaOH was added in one portion. An excess of 30% H_2O_2 (100 ml) was dropped into the solution, which was then stirred for 6 h. After an additional part of water had been added, the product was exhaustively extracted with ether, dried and distilled.

Yield : 14.5 g, 0.069 mol, 69%; bp 130-132°C/0.1 Torr.

IR (NaCl-film) : (free OH) : 3520 cm^{-1}, (bound OH): 3320 cm^{-1}.

MS : 211 (13.6), 210 (100), 192 (88.9), 191 (26.0), 181 (48.3), 179 (39.8), 178 (35.4), 167 (45.6), 166 (32.9), 165 (52.1), 91 (51.3), 77 (33.1).

NMR ($CDCl_3$) : 7.35-6.93 ppm (m's; 9H); 4.46 ppm (q, 1H); 4.15 ppm (d, 1H); 3.28 ppm (q, 1H); 2.92 ppm (q, 1H).

trans-2-Hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (10)

The same procedure as that for (9) by starting from (8) (20.6 g 0.1 mol) was used. In the next reaction, the product was used without purification. During attempted distillation (over a range of 130-170°C at 0.01 Torr) by-products were formed.

IR (NaCl-film) : ν (free OH) : 3530 cm^{-1}, ν(bound OH): 3450 cm^{-1}.

MS : 225 (0.5), 224 (5.8), 207 (13.8), 206 (92.2), 180 (63.8), 179 (100), 178 (55.2), 165 (37,3), 91 (37.5).

NMR ($CDCl_3$) : 9.37-6.75 ppm (m's, 9H); 4.06 ppm (m, 1H), 3.95 ppm (d, 1H; J=12 Hz : trans configuration); 3.02 ppm (m, 2H); 2.18 ppm (m, 1H); 1.90 ppm (m, 1H).

O-Tosyl-2-hydroxy-1-phenylindane (11)

To a solution of 10.5 g (0.05 mol) of (9) in 100 ml of dry pyridine, 19 g (0.1 mol) of p-toluenesulfonyl chloride was added in small portions at 0°C. The solution was stirred for 1 h at 0°C for 7 days. An excess of water was then added. The precipitated tosylate was crystallized from ether-hexane.

Yield : 15.5 g, 0.042 mol, 85%; mp 118-118.5°C.

O-Tosyl-2-hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (12)

The same procedure as that for (11) by starting from (10). Crystallization from benzene-ether.

Yield (calculated from (8)):18.9 g, 0.05 mol, 50%; mp 108.5-109°C.

cis-2-Azido-1-phenylindane (13)

To a solution of 11 g (0.03 mol) of tosylate (11) in 100 ml of DMF, a solution of 5 g (0.07 mol) of sodium azide in 10 ml of water was added in small portions and the reaction mixture was heated for 48 h at 90-100°C. An excess of water was added and the solution extracted with ether. The azide was used without further purification.

IR (NaCl-film) : ν (N_3) : 2100 cm^{-1}.

MS : 207 (23.2), 206 (79.4), 180 (31.5), 179 (100), 178 (56.2), 165 (33.8), 89 (49.6), 76 (29.1).

NMR ($CDCl_3$) : 7.40-7.10 ppm (m's, 9H), 4.57 ppm (d, 1H); 4.43 ppm (m, 1H), 3.27 ppm (q, 1H), 3.11 ppm (q, 1H).

cis-2-Azido-1-phenyl-1,2,3,4-tetrahydronaphthalene (14)

The same procedure as that for (13) by starting from (12). In the reaction mixture elimination products were detected.

IR (NaCl-film) : ν (N_3) : 2100 cm^{-1}.

MS : 222 (14.3), 221 (36.4), 220 (28.0), 208 (39.2), 207 (27.0), 206 (100), 205 (35.7), 204 (40.3), 203 (37.1), 202 (32.1), 194 (22.0), 191 (35.0), 180 (41.2), 179 (54.7), 178 (47.1), 165 (30.0).

NMR ($CDCl_3$) : 7.56-6.82 ppm (m's, 9H), 4.36 ppm (d, 1H; J = 5Hz, cis-configuration); 4.00 ppm (m, 1H), ≃ 2.9 ppm (m, 2H); ≃ 2.1 ppm (m, 2H).

cis-2-Amino-1-phenylindane (15)

Five grams (0.021 mol) of azide (13) in dry ether (50 ml) were slowly dropped into a stirred suspension of 7.5 g (0.2 mol) of $LiAlH_4$ in 50 ml of dry ether. The mixture was stirred for 6 h at room temperature. The excess $LiAlH_4$ was destroyed with 10% NaOH. The product was extracted with ether. The extract was dried, evaporated and distilled.

Yield (calculated from (11): 31 g, 0.015 mol, 70% ; bp 130-140°C/0.2 Torr.

IR (NaCl-film) : ν(NH_2) : 3350 cm^{-1}.

MS : 210 (20.4), 209 (100), 208 (19.2), 192 (69.2), 191 (35.0), 179 (39.6), 178 (33.6), 165 (35.4), 91 (25.3).

NMR ($CDCl_3$) : 7.62-7.08 ppm (m, 9H), 4.41 ppm (d, 1H, J = 6.5 Hz),

3.91 ppm (q, 1H), 3.21 ppm (q, 1H), 2.80 ppm (q, 1H).

cis-2-Amino-1-phenyl-1,2,3,4-tetrahydronaphthalene (16)

Method A : The same procedure as that for (15) by starting from (14). The major products in this reaction were elimination products. Only 20% to 30% yield of (16) was obtained.

Method B : Seventeen grams (0.07 mol) of (14) were reduced with H_2 over Pd/C at 4 atm and 25°C in isopropanol for 8 h. Acid-base extraction produced 14.75 g of (16) (0.066 mol). The purity was > 95% (NMR-data and GC). The product was not stable for distillation.

Yield (calculated from tosylate (12)) : 14.75 g, 0.066 mol, 40%.

IR (NaCl-film) : $\nu(NH_2)$: 3370 cm^{-1}.

MS : 224 (7.5), 223 (35.0), 207 (42.5), 180 (77.5), 179 (100), 178 (67.5), 165 (56.3), 161 (40.0), 115 (35.0), 91 (50).

NMR ($CDCl_3$) : 7.36-6.90 ppm (m's, 9H); 4.24 ppm (d, 1H; J = 6 Hz cis configuration); ~3.9 ppm (m, 1H); 3.34 ppm (m, 2H); 3.03 ppm (m, 2H); 1.80 ppm (m, 2H).

cis-2-(N-Formylamino)-1-phenylindane (17)

Five grams (0.028 mol) of aminoindane (15) were refluxed in ethyl formate with a few drops of acetic acid for 16 h. After evaporation of the ethyl formate, the product was recrystallized from benzene/hexane.

Yield : 5.3 g, 0.022 mol, 80%; mp 104-107°C.

IR (KBr) : ν(NH) : 3400 and 3290 cm^{-1} - ν(C=O) : 1665 cm^{-1}.

MS : 237 (0.04), 193 (15.6), 192 (100), 191 (27.5), 165 (9.2).

NMR ($CDCl_3$) : 7.94 ppm (s; 1H); 7.41-7.10 ppm (m's, 9H); 5.27 ppm (NH); 5.10 ppm (m, 1H); 4.10 ppm (d, 1H); 3.33 ppm (q, 1H); 2.88 ppm (q, 1H).

cis-2-(N-Formylamino)-1-phenyl-1,2,3,4-tetrahydronaphthalene (18)

The same procedure as that for (17) by starting from (16). Recrystallization from benzene/hexane.

Yield : 4.4 g, 0.018 mol, 80%; mp 173-176.5°C.

IR (KBr) : ν (NH) : 3400 cm^{-1} and broad band between 3300-3200 cm^{-1}.

ν(C=O) : 1680 cm^{-1}.

MS : 251 (1.0), 207 (16.3), 206 (100), 205 (9.4), 180 (11.8), 179 (43.4), 178

(29.2), 165 (16.3), 91 (20.9).

NMR ($CDCl_3$) : 8.09 (s, 1H); 6.85-7.40 (m's, 9H); 5.20 ppm (NH); 4.60 ppm (m, 1H); 4.40 ppm (d, 1H); 3.02 ppm (m, 2H); 1.82 ppm (m, 2H).

cis-5a, 11b-Dihydroindeno[2,3-c]isoquinoline (19)

Five grams (0.021 mol) of (17) were heated for 6 h at 150°C with polyphosphoric acid (50 g). The reaction mixture was poured onto ice, basified and extracted with ether. The product was purified by column chromatography (Al_2O_3 Act I/benzene) and recrystallization from n-hexane was carried out.

Yield : 3.79 g, 0.017 mol, 80%; mp 120-123°C.

mp(HCl salt) 225-229°C (recryst. from EtOH/ether).

mp($HClO_4$ salt) 208-212°C (recryst. from EtOH/ether).

IR (KBr) : ν(C=N) : 1630 cm^{-1}.

MS : 220 (12.3), 219 (86.6), 218 (100), 217 (49.3), 216 (19.5), 109 (33.9).

NMR ($CDCl_3$) : 8.20 ppm (s, 1H); 7.51-6.94 (m's, 8H); 4.69 ppm (broad s, 1H); 4.20 ppm (d, 1H); 3.58 ppm (q, 1H); 3.40 ppm (q, 1H).

cis-6a,7,8,12b-Tetrahydrobenzo[a]phenanthridine (20)

The same procedure as that for (19) by starting from (18). Recrystallization from cyclohexane was carried out.

Yield : 3.7 g, 0.016 mol, 80%; mp 116-119°C; mp(HCl-salt) 208-213°C.

IR (KBr) : ν(C=N) : 1625 cm^{-1}.

MS : 234 (11.8), 233 (76.0), 232 (86.8), 218 (33.8), 217 (40.5), 216 (72.0), 215 (65.1), 130 (100), 115 (22.3), 109 (29.4).

NMR ($CDCl_3$) : 8.32 ppm (s, 1H), 7.43-7.04 ppm (m's, 8H); 4.16 ppm (m, 1H), 4.08 ppm (d, 1H, J = 14 Hz); 3.04 ppm (m, 1H), 2.89 ppm (m, 1H), 9.10 ppm (m, 2H).

5,6,7,8,9a,14b-Hexahydro-4bH-indeno[2,3-c]pyrido[2,1-a]isoquinolin-6-one (21)

Method A

One gram of the hydrochloride of (19) (0.0039 mol) was heated for 30 min under reflux in methyl vinyl ketone, and the mixture was treated with 10% NaOH. After extraction with ether, drying and evaporating the resulting extract, the product was purified by column chromatography (Al_2O_3 Act I/ether). One isomer of (21) was obtained in crystalline form. Attempts to recrystallize the product were

unsuccessful. The NMR data proved the purity (95%) and the trans-cisoid-cis configuration.

Yield : 340 mg, 0.0012 mol, 30%.

IR (KBr) : ν (C=O) : 1710 cm^{-1}.

MS : 290 (22.2), 289 (80.7), 288 (100), 246 (72.1), 219 (60.9), 218 (80.2), 217 (42.5), 203 (27.2), 202 (21.8).

NMR ($CDCl_3$) : 7.58-7.04 ppm (m's, 8H); 4.52 ppm (d, 1H); 4.14 ppm (q, 1H); 4.00 ppm (q, 1H); 3.32 ppm (m, 1H); 3.07-1.58 ppm (m's, other protons).

The same procedure for the perchlorate. Here the intermediate (24) crystallized by cooling of the methyl vinyl ketone solution.

Method B

The intermediate (24) was passed through an Al_2O_3 Act I column with CH_2Cl_2 as solvent. The obtained cyclized product was further purified as described in method A.

Yield : 30%.

5,6,7,8,9a,10,11,15b-Octahydro-4bH-benzo[a]pyrido[1,2-f]phenanthridin-6-one (22)

The same procedure as that for (21) by starting from (20) (1 g, 0.0042 mol).

Method A

Yield of the trans-cisoid-cis isomer : 380 mg, 0.0013 mol, 30%.

Method B

Yield of the trans-cisoid-cis isomer : 890 mg, 0.0029 mol, 70%.

IR (KBr) : ν (C=O) : 1705 cm^{-1}.

MS : 304 (18.7), 303 (73.4), 302 (100), 260 (50.4), 233 (50.9), 232 (70.1), 231 (34.7).

NMR ($CDCl_3$) : 7.37-7.06 ppm (m's, 8H); 4.35 ppm (d, 1H; J = 4.5 Hz); 3.93 ppm (q, 1H; J = 2 and 12 Hz); 3.48 ppm (double triplet, 1H; J = 4.5 and 11.5 Hz); 3.24 ppm (double triplet, 1H; J = 2,7 and 11.5 Hz); 3.00 ppm (m, 2H); ≈2.75 ppm (m, 3H); ≈2.50 ppm (m, 2H); 1.94 ppm (m, 1H); 1.67 ppm (m, 1H).

6-Phenyl-5,6,7,8,9a,14b-hexahydro-4bH-indeno[2,3-c]pyrido[2,1-a]isoquinolin-6-ol Hydrochloride (3)

From the classical Grignard reaction on isoquinoline derivative (21) (300 mg, 0.001 mol) with an excess of phenylmagnesium bromide, we obtained a mixture,

which was treated with HCl-gas. The formed salt was recrystallized from ethanol/ether.

Yield : 67 mg, 0.00025 mol, 25% ; mp(HCl-salt) : decomposition starts at 180°C.

Spectroscopic studies were performed on the free base :

IR (KBr) : ν(OH) : broad band in the range of 3400-3300 cm^{-1}.

MS : 368 (5.0), 367 (21.1), 366 (13.3), 233 (42.5), 220 (75.0), 219 (62.5), 218 (100), 217 (46.8), 105 (25.0), 77 (25.8).

Peak matching on peak 367 proved the composition $C_{26}H_{25}NO$. The configurational analysis is discussed in the text.

6-Phenyl-5,6,7,8,9a,10,11,15b-octahydro-4bH-benzo[a]pyrido[1,2-f]phenanthridin-6-ol Hydrochloride (4; R = phenyl)

The same procedure as that for (3) by starting from (22) (600 mg, 0.002 mol). Recrystallization of the HCl-salt from ethanol/ether.

Yield : 475 mg, 0.0018 mol, 60%; mp(HCl-salt): decomposition above 210°C

Spectroscopic studies on free base :

IR (KBr) : ν (OH) : broad band between 3400-3300 cm^{-1}.

MS : 382 (19.8), 381 (73.5), 380 (50.7), 364 (35.1), 363 (31.7), 276 (35.8), 260 (67.5), 247 (100), 232 (65.3), 218 (35.6), 217 (57.0), 216 (79.7), 215 (57.3), 144 (49.1), 130 (56.2), 117 (48.8), 115 (41.7), 105 (65.2), 103 (30.2), 91 (76.0), 78 (48.4), 77 (95.7).

Peak matching on peak 381 proved the composition $C_{27}H_{27}NO$.

NMR ($CDCl_3$) : 7.60-7.00 (m's, 13H); 4.37 ppm (d, 1H, J = 4.5 Hz); 4.16 ppm (broad d, 1H, J = 11 Hz); 3.36 ppm (double triplet, 1H; J = 4 Hz and J = 11 Hz); 3.28 ppm (q, 1H, J = 2 Hz and J = 12 Hz); ≈ 2.80 ppm (m, 3H); 2.42 ppm (m, 1H); 2,28 ppm (q, 1H); 2,08 (q, 1H); ≈ 1.83 ppm (m, 3H).

The configurational analysis is discussed in the text.

6-tert-Butyl-5,6,7,8,9,10,11,15b-octahydro-4bH-benzo[a]pyrido[1,2-f]phenanthridin-6-ol Hydrochloride (4, R = tert-butyl)

To a solution of tert-butyllithium in hexane (2 ml of 1.6 M solution, 0.003 mol) at 0°C was added dropwise 200 mg of (22) (0.0007 mol) in 10 ml of benzene. The temperature was kept at 5-10°C during the addition and for 60 min thereafter. The reaction mixture was treated with 10% aqueous NH_4Cl solution. The organic phase was dried and evaporated. The product was dissolved in ether and treated

with HCl-gas. The crude HCl salt was recrystallized from ethanol/ether.

Yield : 63 mg, 0.000175 mol, 25%; mp(HCl salt) > 200°C (decomp.)

Spectroscopic studies on the free base :

IR (KBr) : ν(OH) : broad band between 3400-3300 cm^{-1}.

MS : 362 (7.3), 361 (27.8), 360 (19.0), 305 (23.6), 304 (100), 260 (37.6), 232 (20.5).

Peak matching on peak 361 proved the composition $C_{25}H_{31}NO$. The configurational analysis is discussed in the text.

trans-2-Amino-1-phenylindane (23)

trans-2-Amino-1-phenylindane was obtained by reduction of 5 g (0.020 mol) of the oxime of 1-phenyl-2-indanone[12] with an excess of Na (10g) in 100 ml of ethanol. The reaction mixture was refluxed for 1 h and then stirred for 24 h at room temperature. After elimination of the excess of Na, the product was purified by acid-base extraction. The NMR data of the product shows a ratio of 80% trans- to 20% cis-amine. The pure trans-amine was obtained by recrystallization of the hydrochloride salt from ethanol/ether.

Yield : 2.5 g, 0.012 mol, 60%.

IR (NaCl) : ν(NH_2) ; 3350 cm^{-1}.

mp(HCl-salt) 217.5-220°C.

NMR ($CDCl_3$) 7.36-6.86 ppm (m, 9H); 3.87 (d, 1H, J = 8 Hz); 3.63 (q, 1H), 3.26 (q, 1H), 2.76 (q, 1H).

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REFERENCES

1. F. Vlaeminck and G. Van Binst, Heterocycles, 12, 329 (1979).
2. F. T. Bruderlein, L. G. Humber and K. Voith, J. Med. Chem., 18, 185 (1975).
3. K. Voith and F. Herr, Psychopharmacologica, 42, 11 (1975).
4. L. G. Humber, F. T. Bruderlein and K. Voith, Mol. Pharmacol., 11, 833 (1975).
5. P. H. Bird, F. T. Bruderlein and L. G. Humber, Can. J. Chem., 54, 2715 (1976).
6. J. Giesecke, Acta Cryst., B29, 1785 (1973).
7. L. G. Humber, F. T. Bruderlein, A. H. Philipp, M. Götz and K. Voith, J. Med. Chem., 22, 761 (1979).
   A. H. Philipp, L. G. Humber and K. Voith, J. Med. Chem., 22, 768 (1979).
8. G. Van Binst and G. Laus, Org. Magn. Res., 9, 467 (1977).
9. P. Laduron and J. Leysen, Biochem. Pharmac., 26, 1003 (1977).
10. W. E. Parham and C. D. Wright, J. Org. Chem., 22, 1473 (1975).
11. R. Weiss, "Organic Syntheses" Coll. Vol. III, 729 (1955).
12. A. T. Blomquist and E. J. Moriconi, J. Org. Chem., 26, 3761 (1961).

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