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Robert P. Hanzlik,* Vimal Kishore, Robert Tullman
Department of Medicinal Chemistry
University of Kansas, Lawrence, Kansas 66045
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Articles

Mapping the Dopamine Receptor. 1. Features Derived from Modifications in Ring E of the Neuroleptic Butaclamol

Leslie G. Humber,* Francois T. Bruderlein, Adolf H. Philipp, Manfred Götz,

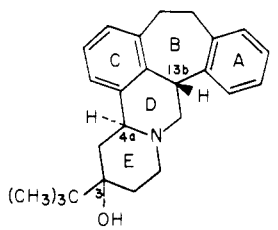
Department of Chemistry

and Katherine Voith*

Department of Pharmacology, Ayerst Research Laboratories, Montreal, Quebec, Canada H3C 3JI. *Received October 23, 1978*

Several analogues of the neuroleptic agent butaclamol, having modifications in the ring E region of the molecule, have been synthesized. Pharmacological evaluation identified two of the analogues as being equipotent to butaclamol, namely, anhydrobutaclamol (**8**) and deoxybutaclamol (**9a**). The molecular structures of both the active and inactive analogues were analyzed and the results have been used for mapping the central dopamine receptor. The existence of a previously proposed lipophilic *accessory binding site* on the receptor macromolecule has been confirmed. Its minimum dimensions, as well as its locus with respect to the *primary binding sites*, have been defined. A receptor model incorporating the above features is proposed.

Previous communications from these laboratories[1-5] have described the syntheses and psychopharmacological activities of various benzocycloheptapyridoisoquinolines related to the clinically active[6-11] antipsychotic agent butaclamol (**1**). It has been shown that in this series



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neuroleptic activity is associated with 4a,13b-trans and 3(OH),13b(H)-trans relative configurations[1,4,12] and that only the enantiomers having 3*S*,4a*S*,13b*S* absolute configurations are active.[4,5,12] We have described the qualitative and quantitative changes in neuroleptic activity which result from altering the bulky substituent at position 3,[1,2] by introducing a chlorine substitutent at various positions on rings A and C[3], and, in the following paper of this issue,[13] from making molecular modifications in the rings A/B region.

It was previously proposed[4] that the extended phenethylamine moiety of butaclamol constitutes the pharmacophore which confers neuroleptic activity on this molecule. It was further suggested that the phenyl ring and the nitrogen atom of the pharmacophore interact with primary binding sites[4] on the dopamine receptor. In the following paper in this issue[13] the nitrogen primary binding site has been redefined as a two-point system comprised of a *nitrogen location site* and a complementary *hydrogen bond donor site*. Also, the minimum dimensions of the phenyl ring primary binding site have been defined and its location relative to the above-mentioned sites has been specified.[13]

The dopamine receptor, genetically evolved to bind the endogeneous neurotransmitter dopamine, also binds butaclamol with high affinity.[14,15] Since the molecular dimensions of butaclamol are much larger than those of dopamine, we have suggested that certain structural entities of the butaclamol molecule, other than the pharmacophore, contribute to the observed affinity between ligand and receptor by interacting with accessory binding sites[4] on the dopamine receptor. Such accessory binding sites were proposed for the *tert*-butyl and the hydroxyl groups of butaclamol.

In the present study, a number of molecular modifications have been made in ring E of butaclamol involving the aforementioned groups. The potential neuroleptic activities of the resultant compounds have been determined and the results have been interpreted in terms of some detailed topographical features of the central dopamine receptor.

Chemistry. The compounds investigated fall into two groups. The first group shown in Scheme I, of which **1**[1] and **12**[16] have previously been described, is derived from the amino ketones **2** and **3**.[16]

Reduction of **2** with sodium borohydride gave a 73% yield of the secondary alcohol **4**, while reduction with lithium tri-*sec*-butylborohydride[17] afforded 66% of the epimeric alcohol **5**. The configurational assignments for

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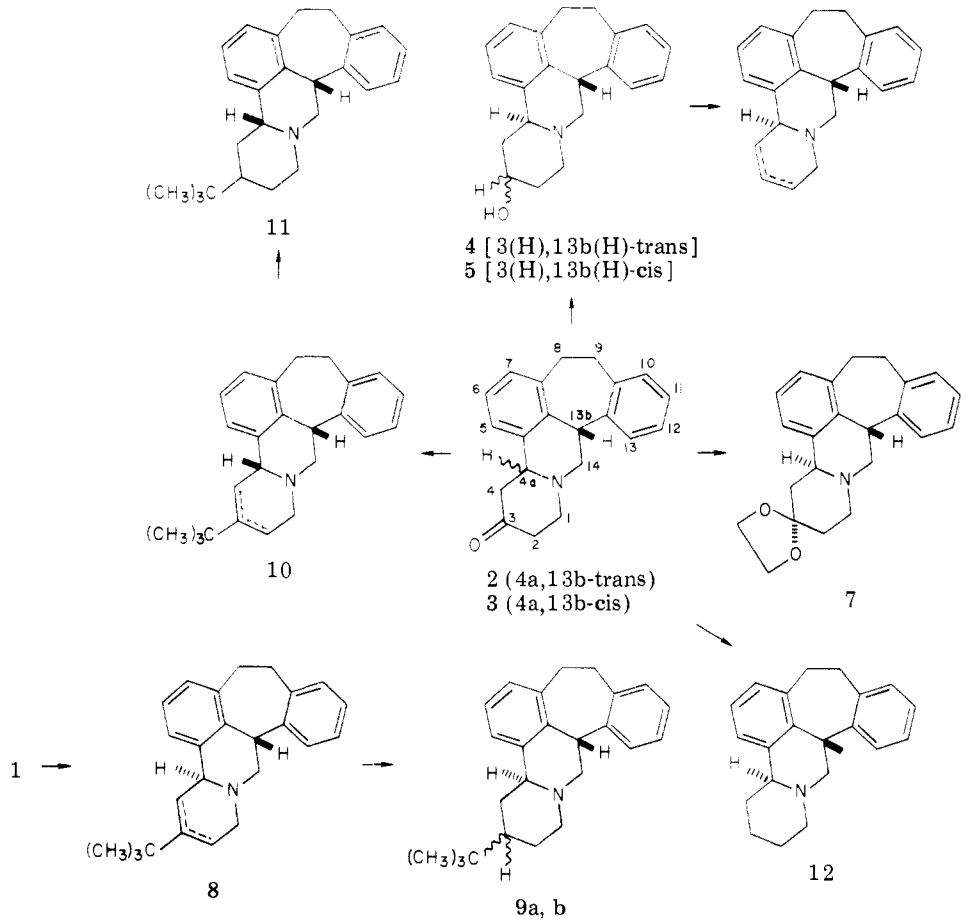
Scheme I



5, as 3(H),13b(H)-cis (hydroxyl axial), and for 4, therefore, as 3(H),13b(H)-trans (hydroxy equatorial), are based on the report[18] that the bulky tri-*sec*-butylborohydrides reduce cyclohexanones by virtually exclusive attack by the reagent from the equatorial side to produce axial alcohols.

The olefin **6** was obtained by dehydration of the alcohol **4** with polyphosphoric acid and probably exists as a mixture of the Δ^2- and Δ^3-olefins.

The ethylene ketal derivative **7** was obtained from **2** and ethylene glycol with *p*-toluenesulfonic acid as catalyst.

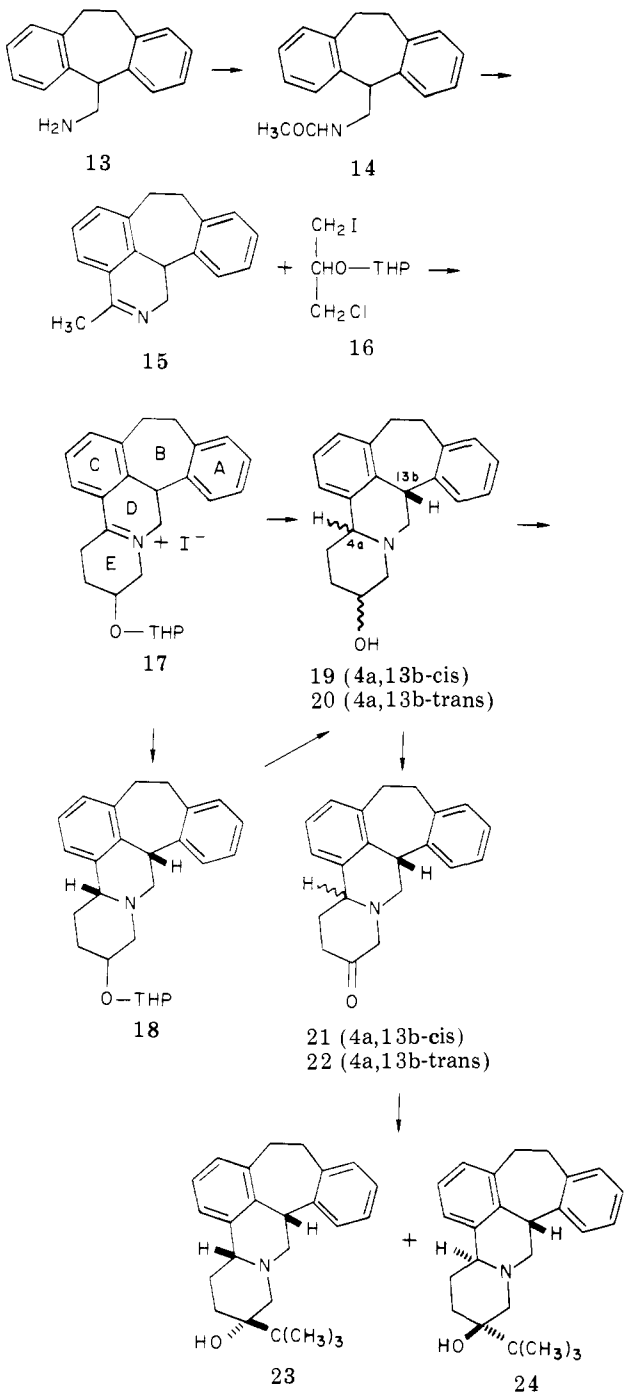
Dehydration of butaclamol hydrochloride (**1**·HCl) with thionyl chloride in chloroform afforded an inseparable mixture of Δ^2- and Δ^3-olefins **8**, as evidenced by the multiplet nature of the vinyl proton signal (δ 5.6) in the NMR spectrum. Hydrogenation of **8** under ambient conditions using platinum oxide as catalyst afforded, unexpectedly, the pair of isomers **9a** and **9b** in 34 and 30% yields, respectively. Both isomers had 4a,13b-trans relative configurations as evidenced by the triplet nature of their C_{13b} proton signals, observed at δ 4.9 for **9a** and δ 4.5 for **9b**. The reasons for the appearance of the C_{13b} proton signal as a triplet in 4a,13b-trans isomers and as a doublet in 4a,13b-cis isomers of this series have been discussed previously[16] and the validity of our conclusions has been verified by crystallographic studies of butaclamol.[12] Analysis of the splitting pattern exhibited by the C_{13b} proton signal is now used routinely to assign configurations at positions 4a and 13b in butaclamol analogues.[3] Retention of configuration at these positions during reactions cannot be assumed, as we have recorded several instances of interconversions of 4a,13b-trans and 4a,13b-cis isomers of various benzocycloheptapyridoisoquinoline derivatives.[19] In the present instance, therefore, we have considered it appropriate to further confirm the validity of the use of the splitting pattern of the C_{13b} proton signal for configurational assignments. Thus, compound **11**, a 4a,13b-cis isomer with the same constitution as the compounds **9**, was prepared.

Compound **11** was obtained from the ketone **3**[16] via the known[20] 4a,13b-cis analogue of butaclamol, which was dehydrated to afford the olefin **10**. Catalytic hydrogenation of **10** produced compound **11**. The C_{13b}-proton signal in the NMR spectrum of **11** appeared at δ 4.45 and was split into a doublet, confirming the assigned 4a,13b-cis stereochemistry.[3,16] We suggest that one of the **9a**, **9b** pair adopts a ring E boat conformation while the other adopts a chair conformation, both having their *tert*-butyl groups oriented equatorially or pseudoequatorially. Chemically, one could not distinguish between these two possibilities. However, compound **9a** was assigned a conformation in which ring E is a chair, since this compound (see below) is equally potent to butaclamol as a neuroleptic agent. Isomer **9b**, being devoid of activity, is assumed to have its ring E in a boat conformation.

In the formation of **11**, in 44% yield from the olefin **10**, under the same conditions that afforded the isomeric pair **9a** and **9b** by hydrogenation of **8**, no isomer pair was obtained analogous to the **9a**, **9b** pair. The only other product isolable was a 20% yield of a compound in which one of the benzene rings had undergone partial reduction, as evidenced by mass spectral data. The reason for the different results during the reductions of **10** and **8** is not apparent.

The second group of compounds studied is shown in Scheme II and was synthesized from the isomeric amino ketones **21** and **22**. These ketones were obtained from 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylmethylamine (**13**),[21] via a polyphosphoric acid catalyzed cycli-

Scheme II



THP = 2-tetrahydropyranyl

zation of the cyclohepten-5-ylmethylacetamide **14** to afford the Schiff base **15**. A one-step annelation of ring E, to provide the desired oxygenation at position 2, appeared feasible in view of the demonstration by Evans[22] that the reaction of an azomethine and a dihalide generates an endocyclic enamine directly. Thus, treatment of **15** with butyllithium gave a lithio derivative which was reacted with **16**, the tetrahydropyranyl ether of 1-chloro-3-iodo-2-propanol,[23] to afford the 2-substituted quaternary salt **17**, in 67% yield. Reduction of **17** with sodium borohydride gave a quantitative yield of the 4a,13b-*cis*-isoquinoline derivative **18**, which on acid hydrolysis afforded the 4a,13b-*cis*-amino alcohol **19**. Treatment of **17** with zinc and hydrochloric acid, on the other hand, gave a mixture of the cis and trans alcohols **19** and **20** which was separated by chromatography. Oxidation of **19** and of **20** with the

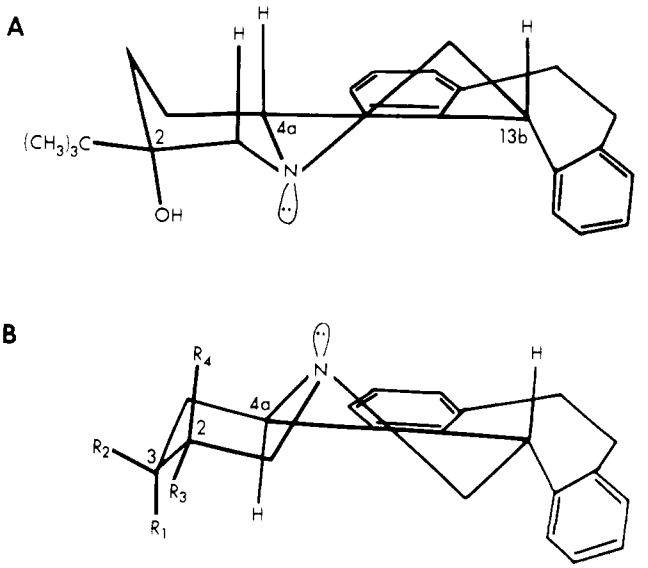


Figure 1. Structure A: compound **23**. Structure B: butaclamol, R_1 = OH, R_2 = $C(CH_3)_3$, R_3 = R_4 = H; compound **24**, R_1 = R_2 = H, R_3 = $C(CH_3)_3$, R_4 = OH.

triethylamine–sulfur trioxide complex according to the method of Parikh and von Doering[24] gave satisfactory yields of the amino ketones **21** and **22**. Reactions of these amino ketones with *tert*-butyllithium afforded the tertiary carbinols **23** and **24**.

The 4a,13b-cis relative configurations for **19**, **21**, and **23** and the 4a,13b-trans relative configurations for **20**, **22**, and **24** were assigned on the basis of an analysis of the splitting pattern of the C_{13b}-proton NMR signal.[3,16] Thus, **19**, **21**, and **23** exhibit doublets, while **20**, **22**, and **24** exhibit triplets.

The assignment of the configuration at position 2, the tertiary carbinol centers in **23** and **24**, is based on the anticipated attack on the carbonyl group by the bulky *tert*-butyl group such that it will be equatorially oriented. The complete relative configurational assignments for **24**, (4a,13b-trans)[2(OH),13b(H)-cis], and for **23**, (4a,13b-cis)[2(OH),13b(H)-trans], are illustrated in Figure 1 in comparison with butaclamol.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are corrected. Mass spectra were recorded on an LKB-9000S instrument at 70 eV and a source temperature of 250 °C. Nuclear magnetic resonance spectra were determined in $CDCl_3$ on a Model CFT-20 spectrometer at 80 MHz. All compounds were homogeneous by TLC and had NMR, IR, and UV spectra consistent with their assigned structures. Spectra and microanalyses were performed by the Ayerst Analytical Laboratory under the direction of Dr. G. Schilling. All analytical results were within ±0.4% of the calculated values.

(4a,13b-*trans*)[3(H),13b(H)-*trans*]-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol (4). To a stirred solution of ketone **2**[16] (53 g, 0.175 mol) in MeOH (1 L) was added $NaBH_4$ (5.7 g, 0.15 mol) portionwise. After refluxing for 90 min, the mixture was evaporated and the residue distributed between H_2O and EtOAc. The organic phase afforded the product: mp 157–159 °C (Et_2O–hexane); R_f (10% MeOH–EtOAc) 0.54. The HCl salt was prepared (39 g, 73%): mp 293–296 °C; NMR ($CDCl_3$) δ 4.78 (1, t, J = 6 Hz, C_{13b}-H). Anal. ($C_{21}H_{24}ClNO$) C, H, N.

(4a,13b-*trans*)[3(H),13b(H)-*cis*]-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol (5). A solution of ketone **2** (9 g, 0.03 mol) in THF (120 mL) was added at −50 °C to a solution of lithium tri-*sec*-butylborohydride in THF[17] (30 mL of a 1 M solution). The mixture was allowed to come to room temperature and, after 15

min, a solution of 10% aqueous HCl was added. The solution was made alkaline with 10% aqueous NaOH and extracted with Et_2O to afford an oil which was chromatographed on silica gel. Elution with EtOAc gave the product (6.6 g, 66%): mp (Et_2O–hexane) 168–170 °C; R_f (10% MeOH–EtOAc) 0.44; NMR ($CDCl_3$) δ 5.0 (1, t, J = 6 Hz, C_{13b}-H). Anal. ($C_{21}H_{23}NO$) C, H, N.

2,4a,8,9,13b,14- and 4,4a,8,9,13b,14-Hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolines 6. A mixture of 4·HCl (2.8 g, 0.008 mol) and polyphosphoric acid (52 g) was stirred for 30 min at 160–165 °C and then poured into a 25% aqueous NaOH solution at 0 °C. Extraction with EtOAc gave the crude product as an oil. It was converted to the HCl salt and, after three crystallizations from MeOH–Et_2O, pure 6·HCl (0.6 g, 23%; mp 277–280 °C) was obtained as an inseparable mixture of the Δ^2- and Δ^3-olefins: NMR ($CDCl_3$) δ 4.75 (1, t, J = 6 Hz, C_{13b}-H), 5.8 (2, m, H_2H_3 and H_3H_4); MS m/e 287. Anal. ($C_{21}H_{22}ClNO·0.5H_2O$) C, H, Cl, N.

(4a,13b-*trans*)-1,2,4,4a,8,9,13b,14-Octahydrospiro[3*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline-3,2′-[1,3]dioxolane] (7). The ketone **2** (2.0 g, 0.006 mol), *p*-toluenesulfonic acid (0.2 g), ethylene glycol (2.0 g, 0.04 mol) and C_6H_6 (200 mL) were combined and refluxed for 24 h in a flask fitted with a H_2O separator. The reaction was worked up in a conventional manner to afford the product (1.5 g, 65.5%): mp (Et_2O) 176–177 °C; NMR ($CDCl_3$) δ 4.8 (1, t, J = 6.5 Hz, C_{13b}-H). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

(4a,13b-*trans*)-3-*tert*-Butyl-2,4a,8,9,13b,14- and (4a,13b-*trans*)-3-*tert*-Butyl-4,4a,8,9,13b,14-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolines 8. A suspension of butaclamol hydrochloride[1] (1·HCl; 3.0 g, 0.007 mol) in $CHCl_3$ (60 mL) and $SOCl_2$ (10 mL) was refluxed for 90 min. The resulting solution was evaporated and the residue was distributed between $CHCl_3$ and 10% aqueous Na_2CO_3 solution. The $CHCl_3$ phase was dried and concentrated to give the crude product as an oil. It was converted to the HCl salt, which was obtained as a pure mixture of Δ^2- and Δ^3-olefins after two crystallizations from EtOAc (1.6 g, 56%): mp 252–256 °C; NMR of the free base ($CDCl_3$) δ 5.05 (1, t, J = 6 Hz, C_{13b}-H), 5.6 (1, m, H_2 and H_4). Anal. ($C_{25}H_{30}ClN$) C, H, N.

By following the same procedure as above but using the 4a,13b-cis isomer of butaclamol hydrochloride[1] as starting material there was obtained a 51% yield of **(4a,13b-*cis*)-3-*tert*-Butyl-2,4a,8,9,13b,14- and (4a,13b-*cis*)-3-*tert*-Butyl-4,4a,8,9,13b,14-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolines 10:** NMR ($CDCl_3$) δ 4.52 (1, d, J = 4 Hz, C_{13b}-H); HCl salt mp (2-PrOH–Et_2O) 219–225 °C; MS m/e 343. Anal. ($C_{25}H_{30}ClN$) C, H, Cl, N.

(4a,13b-*trans*)-3-*tert*-Butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]isoquinolines 9a and 9b. The mixture of olefins **8**, as their HCl salts (5.0 g, 0.013 mol), was dissolved in EtOH (100 mL) in the presence of PtO_2 (0.6 g) and agitated at 22 °C in a hydrogen atmosphere. After 4 h, hydrogen uptake was complete. The catalyst was removed by filtration and the solvent by distillation in vacuo. The residue was distributed between $CHCl_3$ and a 10% aqueous NaOH solution. The $CHCl_3$ phase yielded an oil (4.6 g), which was a mixture of two compounds as shown by TLC. It was chromatographed on silica gel. Elution with C_6H_6–$CHCl_3$ mixtures gave the least polar isomer **9a** as an oil: HCl salt (1.7 g, 34%) mp (CH_3CN–Et_2O) 250–253 °C; NMR ($CDCl_3$, free base) δ 4.9 (1, t, J = 7 Hz, C_{13b}-H); MS m/e 345. Anal. ($C_{25}H_{32}ClN$) C, H, N.

Continued elution with the same solvent mixture gave a more polar isomer **9b**, as an oil: HCl salt (1.6 g, 30%) (MeCN–Et_2O) mp 295 °C; NMR ($CDCl_3$, free base) δ 4.5 (1, t, J = 7 Hz, C_{13b}-H); MS m/e 345. Anal. ($C_{25}H_{32}ClN$) C, H, N.

(4a,13b-*cis*)-3-*tert*-Butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]isoquinoline (11). The mixture of olefins **10** (0.8 g, 0.002 mol) as their HCl salts was hydrogenated in EtOH (40 mL) using PtO_2 (0.3 g) as catalyst. A conventional workup procedure gave an oil (650 mg), which was a mixture of two compounds as shown by TLC. It was chromatographed on silica gel. Elution with benzene afforded the product as an oil (350 mg, 44%): NMR ($CDCl_3$) δ 4.45 (1, d, J = 3.8 Hz, C_{13b}-H); HCl salt mp (2-PrOH–Et_2O) 240–244 °C; MS m/e 345. Anal. ($C_{25}H_{32}ClN$) C, H, N.

Further elution with benzene gave 150 mg (20%) of an oil, which was homogeneous by TLC: MS m/e 351.

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylmethylacetamide (14). A mixture of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-ylmethylamine (**13**; 48 g, 0.22 mol), pyridine (250 mL), and Ac_2O (30 mL) was heated at 100 °C for 20 h. A conventional workup procedure gave the product (43 g, 75%): mp (C_6H_6–hexane) 139 °C; NMR ($CDCl_3$) δ 1.8 (3, s, CH_3CO), 6.0 (1, s, NH). Anal. ($C_{18}H_{19}NO$) C, H, N.

2-Methyl-1,7,8,12b-tetrahydrobenzo[1,2]cyclohepta[3,4,5-*de*]isoquinoline (15). A stirred mixture of polyphosphoric acid (150 g) and the cycloheptene-5-ylmethylacetamide **14** (43 g, 0.16 mol) was heated at 150 °C for 2 h, then cooled, and poured into a 20% aqueous NaOH solution. Extraction with EtOAc afforded the product (29 g, 72%): mp (C_6H_6–hexane) 130–132 °C; IR ($CHCl_3$) ν_{max} 1625 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.35 (3, s, CH_3). Anal. ($C_{18}H_{17}N$) C, H, N.

1-Chloro-3-iodo-2-[(2-tetrahydropyranyl)oxy]propane (16). Epichlorohydrin (186 g, 2 mol) was added with stirring at 0–10 °C during 30 min to a freshly prepared solution of MeMgI (2 mol) in Et_2O (500 mL). The reaction mixture contained a heavy gray precipitate. It was poured onto crushed ice with vigorous stirring, saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O. The extracts were washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo to afford **1-chloro-3-iodo-2-propanol** (457 g) as a light yellow oil, which was homogeneous by TLC. It was mixed with an excess of dihydropyran (235 g, 4 mol), the mixture was cooled to 0 °C, and concentrated HCl (0.2 mol) was added with stirring. After 20 h at 22 °C, H_2O was added and the mixture was extracted with Et_2O. The extracts were washed with aqueous $NaHCO_3$, dried, and evaporated in vacuo at 20–40 °C to afford a light yellow oil (550 g). Chromatography of 50-g batches on silica gel and eluting with C_6H_6–EtOAc (19:1) gave the product as a colorless oil (374 g, 67.5% based on epichlorohydrin): NMR ($CDCl_3$) δ 1.67 [6, m, $(CH_2)_3$], 3.46 (2, m, CH_2I), 4.80 (1, m, OCHO), MS m/e 304, 306.

2-[(2-Tetrahydropyranyl)oxy]-1,2,3,4,8,9,13b,14-octahydrobenzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolinium Iodide (17). To a solution of the Schiff base **15** (74.2 g, 0.3 mol) in THF (700 mL) at −65 to −70 °C was added *n*-butyllithium (0.3 mol; 130.5 mL of a 2.3 M solution in hexane) during 10 min under a N_2 atmosphere. The mixture was stirred at −75 °C for 2 h and then the 1-chloro-3-iodo-2-propanol derivative **16** (91.5 g, 0.3 mol) was added during 5 min while keeping the temperature below −50 °C. The mixture was stirred at −75 °C for 2.5 h, allowed to come to room temperature, and then heated at reflux for 2 h, during which time a heavy precipitate formed. After cooling, the solid was collected, washed with cold THF (−20 °C), and dried to afford the product as a yellow solid (103.5 g, 67%): mp 207–209 °C; IR (Nujol) ν_{max} 1642 cm^{-1} (C=N$^+$). Anal. ($C_{26}H_{30}INO_2$) C, H, N.

(4a,13b-*cis*)-2-[(2-Tetrahydropyranyl)oxy]-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]-pyrido[2,1-*a*]isoquinoline (18). The isoquinolinium iodide **17** (21.2 g, 0.04 mol), MeOH (350 mL), and $NaBH_4$ (6 g) were stirred and heated at reflux for 30 min. The MeOH was evaporated and the residue was distributed between C_6H_6 and H_2O. The C_6H_6 phase afforded the product (15.8 g, 100%) as a solid. A sample crystallized from Me_2CO had mp 150–153 °C. Anal. ($C_{26}H_{31}NO_2$) C, H, N.

(4a,13b-*cis*)-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-ol (19). Compound **18** (15.8 g) was dissolved in a mixture of Me_2CO (200 mL), H_2O (50 mL), and concentrated HCl (3.5 mL) and heated at reflux for 20 min. A conventional workup procedure afforded the product (8.23 g, 67.4%): mp (C_6H_6–hexane) 161–164 °C; NMR ($CDCl_3$) δ 4.50 (1, d, J = 4.0 Hz, C_{13b}-H). Anal. ($C_{21}H_{23}NO$) C, H, N. The HCl salt had mp (MeOH–Et_2O) 262–264 °C. Anal. ($C_{21}H_{24}ClNO$) C, H, N.

(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-ol (20). To a stirred suspension of the isoquinolinium iodide **17** (103.5 g, 0.20 mol) in EtOH (500 mL), H_2O (375 mL), concentrated HCl (375 mL), and Zn dust (103 g) were added in portions while refluxing for 3 h. The EtOH was evaporated, made basic with concentrated NH_4OH, and extracted with C_6H_6 to afford a yellow solid (66 g), which was chromatographed on silica gel. Elution

with C_6H_6–EtOAc (5:1) gave first the 4a,13b-cis isomer **19** (25.4 g, 41.5%) and then the product **20** (6.5 g, 10.6%): mp (C_6H_6–hexane) 162–164 °C; NMR ($CDCl_3$) δ 4.91 (1, t, J = 8 Hz, C_{13b}-H). The HCl salt had mp (MeOH–Et_2O) 253–258 °C. Anal. ($C_{21}H_{24}ClNO$) C, H, Cl, N.

(4a,13b-*cis*)-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-one (21). To a solution of the isoquinolin-2-ol **19** (4.4 g, 0.014 mol) in Me_2SO (10 mL) and Et_3N (15 mL) was added a solution of $Et_3N{\cdot}SO_3$ (7.84 g, 0.044 mol) in Me_2SO (20 mL). The mixture was stirred for 20 h at 22 °C and then poured into ice–H_2O. The resultant precipitate was washed with H_2O, dried, and chromatographed on neutral alumina (Woelm, activity II). Elution with $CHCl_3$ afforded the product (3.46 g, 79%): mp ($CHCl_3$–MeOH) 197–199 °C; IR ν_{max} ($CHCl_3$) 1712 cm^{-1}; NMR ($CDCl_3$) δ 4.50 (1, d, J = 4 Hz, C_{13b}-H). Anal. ($C_{21}H_{21}NO$) C, H, N.

By following the same procedure but using the isoquinolin-2-ol **20** as starting material there was obtained **(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-one (22)** in 48.8% yield: mp 162–164 °C (C_6H_6), IR ν_{max} ($CHCl_3$) 1712 cm^{-1}; NMR ($CDCl_3$) δ 4.74 (1, t, J = 5.5 Hz, C_{13b}-H). Anal. ($C_{21}H_{21}NO$) C, H, N.

(4a,13b-*trans*)[2(OH),13b(H)-*cis*]-2-*tert*-Butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-ol (24). Powdered amino ketone **20** (0.86 g, 0.0028 mol) was added to *tert*-butyllithium in pentane (15 mL of a 2.3 M solution) at −70 °C with stirring under a N_2 atmosphere. After 1 h at −70 °C, toluene (30 mL) was added. The mixture was kept at −70 °C for 2 h and then allowed to come slowly to room temperature. Aqueous NH_4Cl solution was added, and the mixture was extracted with C_6H_6. The extract was concentrated and the residue was chromatographed on neutral alumina (Woelm, activity II). Elution with C_6H_6–petroleum ether (1.5:1) gave the product (0.455 g, 44.3%) as a gum: IR ν_{max} ($CHCl_3$) 3480 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.02 (9, s, *tert*-butyl), δ 4.95 (1, t, J = 8 Hz, C_{13b}-H). The HCl salt had mp (MeOH–Et_2O) 237–242 °C. Anal. ($C_{25}H_{32}ClNO$) C, H, N.

By following the same procedure as above but using amino ketone **19** as starting material, there was obtained a 27.7% yield of **(4a,13b-*cis*)[2(OH),13b(H)-*trans*]-2-*tert*-butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-2-ol (23)**: mp ($CHCl_3$–MeOH) 205–207 °C; IR ν_{max}($CHCl_3$) 3480 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.05 (9, s, *tert*-butyl), 4.58 (1, d, J = 4 Hz, C_{13b}-H). Anal. ($C_{25}H_{32}ClNO$) C, H, Cl, N.

Pharmacology Methods. Animals. Experiments were performed on male Sprague–Dawley rats and male Swiss albino mice. The animals were housed in air-conditioned quarters and had free access to food and water until the start of the experiment.

Materials. The doses used were calculated as the free base. The compounds were dissolved in distilled water or suspended in distilled water with a few drops of Tween 80 (2–3 drops/10 mL). Fresh solutions were prepared on the day of the experiment. In addition to test compounds, the following drugs were used: *d*-amphetamine sulfate (K & K Laboratories) and epinephrine bitartrate (Sigma Chemical Co.).

Statistics. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[25]

***d*-Amphetamine-Induced Stereotyped Behavior in Rats.** Details of the methodology and scoring system were recently described.[26] Groups of four or more rats (160–180 g) were injected ip with *d*-amphetamine, 10 mg/kg, followed 15 min later by an ip injection of graded doses of the test compounds or the vehicle. The highest dose evaluated was 20 mg/kg. Observations were made at 15-min intervals for a period of 4 h after the injection of amphetamine, and the behavior of the rats was scored from 0 to 2, "0" referring to normal, "1" to excited, and "2" to stereotyped behavior.

The results are expressed as the minimal effective dose (MED), arbitrarily defined as the lowest dose which antagonized all the behavioral effects of amphetamine.

Conditioned Avoidance Behavior in Rats. The method of Morpurgo[27] was followed. Rats were trained to leave the starting chamber and move into one of two exit compartments, which was lighted. Failure to leave the starting chamber within 10 s was punished with shock. Details of our three-chambered discrimination box and training procedure was described in a previous paper.[28] On the day of the experiment, groups of six or more rats (250–400 g) were tested in a control session of two trials prior to drug administration to ensure an accurate response. Graded doses of the test compounds were administered ip to groups of six or more rats, and the drug effect was evaluated in ten trials 30 min after injection. The "active avoidance failure", i.e., failure to leave the starting chamber prior to the onset of the shock, was recorded, and the mean number of failures per group was calculated as a percent of the total number of trials. The results are expressed as the ED_{50} values, defined as the dose of a compound that caused a 50% failure in the active avoidance response.

Epinephrine-Induced Mortality in Rats. The method of Janssen et al.[29] was followed. Groups of six or more rats (220–225 g) were injected ip with graded doses of the compounds, followed 1 h later by an iv injection of epinephrine bitartrate, 0.25 mg/kg. This dose of epinephrine is lethal to nontreated rats. Mortality was determined over a 24-h period. The results are expressed as protective ED_{50} values.

Catalepsy in Rats. The assessment of catalepsy in rats (160–180 g) was based upon the method of Morpurgo.[30] The compounds were administered ip, to groups of six rats, at a 5 mg/kg dose, approximately tenfold the dose that antagonized amphetamine-induced stereotyped behavior. Catalepsy was evaluated after 1, 2, 4, 6, and 24 h according to stages III and IV of Wirth et al.[31] The mean cataleptic scores were calculated and the highest one was expressed as a percent of the maximum attainable score.

Isolation-Induced Fighting Behavior in Mice. Albino mice (14–16 g) were isolated for 4–5 weeks according to the method of Valzelli et al.[32] The isolation induced aggressive behavior, manifested as fierce fighting, whenever two isolated mice were placed in the same cage for a period of 5 min. The animals were observed during a control session in the morning to ascertain if maximal fighting occurred in both members of the pair. They were then injected ip with the compounds and tested again 30 min and 3 h later. Drug effect was evaluated on an "all or none" basis, i.e., the compound was considered effective when no fighting episode occurred during the 5-min observation period.

Results and Discussion

The pharmacological effects of the analogues were evaluated in animal models which either indicate neuroleptic activity or predict the liability to cause side effects. The significance of the models and their probable mechanisms have been discussed previously.[26]

Compounds **4–12**, **23**, and **24** were evaluated for their capacity to antagonize amphetamine stereotypy. Compounds **4**, **8**, and **9a** antagonized the amphetamine-induced abnormal behavior, while the remaining compounds were inactive at 20 mg/kg, the highest dose tested. However, the potencies of the three active compounds varied greatly; anhydrobutaclamol (**8**)[33] and deoxybutaclamol (**9a**)[33] abolished the amphetamine-induced behavioral changes at 0.62 mg/kg, thus being equipotent to butaclamol. Their onset of effect was slower than that of butaclamol but lasted throughout the 4-h experimental period. In contrast, **4**, the secondary axial alcohol, exerted a short-lasting (45 min) antagonism at the 20 mg/kg dose level, thus being more than 30 times less potent than butaclamol or compounds **8** and **9a**. The latter two agents also depressed conditioned avoidance behavior in rats, fighting behavior in isolated mice, and antagonized the epinephrine-induced mortality in rats at doses very similar to those of butaclamol, while both compounds were more cataleptic than butaclamol (Table I).

The absence of neuroleptic activity with the analogues **6** and **12** which lack substituents at position 3, the inac-

Table I. Pharmacological Comparisons of Butaclamol (1), Anhydrobutaclamol (8), and Deoxybutaclamol (9a)

compd	amphet-induced stereotyped behav: MED[a]	condit avoid. resp: ED_{50}[b]	epinephr-induced mortal: ED_{50}[c]	isolat-induced fight. behav: ED_{50}[d]	catalepsy, % of max[e]
1	0.62	0.64 ± 0.13	15.0 ± 3.0	1.9 ± 0.16	60
8	0.62	0.76 ± 0.10	14.2 ± 4.7	3.0 ± 0.40	100
9a	0.62	0.80 ± 0.13	19.0 ± 7.6	2.1 ± 0.11	93

[a] MED = minimal effective dose (mg/kg, ip), defined as the dose which antagonized all the behavioral effects of amphetamine (10 mg/kg, ip) during the entire 4-h experimental period. [b] ED_{50} (mg/kg, ip), defined as the dose which caused a 50% failure in the active avoidance response. [c] ED_{50} (mg/kg, ip), defined as the dose which protected 50% of the rats against the lethal effect of epinephrine. [d] ED_{50} (mg/kg, ip), defined as the dose which abolished the fighting behavior in 50% of the pairs tested. [e] Catalepsy was evaluated at a 5 mg/kg dose, which was approximately tenfold the dose that antagonized amphetamine-induced stereotyped behavior.

tivity of the secondary equatorial alcohol **5**, and the borderline activity of the secondary axial alcohol 4 indicate that high neuroleptic activity in this series is critically dependent on the presence of a *tert*-butyl or similar bulky group[1,2] attached equatorially at position 3 of the butaclamol nucleus.

In the olefin mixture **6**, rings E exist as half-chairs because of the Δ^2 and Δ^3 double bonds. These half-chair conformations are not, per se, incompatible with high neuroleptic potency, since the same ring E conformations are adopted in the Δ^2- and Δ^3-olefin mixture **8**, the 3-*tert*-butyl analogues of **6**, which is equipotent to butaclamol (Table I).

Inspection of models of butaclamol and anhydrobutaclamol (**8**) reveals that rings E of the Δ^2- and Δ^3-olefinic isomers can each adopt only a single half-chair conformation. In both of these conformations, the locus of the volume in space occupied by the *tert*-butyl groups is very similar to that of the same group of butaclamol, and the groups overlap to a considerable degree. In contrast, if the isomers **8** adopt the less stable ring E half-boat conformations, the locus of the volumes occupied by the *tert*-butyl groups barely overlaps with that of butaclamol's *tert*-butyl group. We conclude that the isomers **8** adopt the more stable half-chair conformation, and that high neuroleptic potency is retained because the *tert*-butyl groups are still able to occupy and bind effectively with a complementary accessory binding site on the dopamine receptor.

The locus of the volume occupied by the *tert*-butyl group of the deoxybutaclamol (**9a**), which was assigned an equatorial orientation on a ring E chair, is identical with that of the same moiety in butaclamol. Compound **9a** is equipotent to butaclamol (Table I), and this observation is consistent with the above conclusion, i.e., that occupancy of this lipophilic accessory binding site is essential for high neuroleptic activity. In contrast, inspection of a model of the inactive isomer **9b**, whose *tert*-butyl group was assigned a pseudoequatorial orientation on a ring E boat, shows that the centrum of the volume occupied by that group is located at more that 1 Å from the centrum of butaclamol's *tert*-butyl group and is apparently incapable of effectively occupying the lipophilic accessory binding site on the dopamine receptor.

The lack of activity of **10** and **11**, the 4a,13b-cis analogues of **8** and **9a**, was not unexpected in view of their molecular shape which is known to be inconsistent with neuroleptic activity in this series.[1]

The inactive ethylene ketal derivative **7** was studied since it has an oxygen atom at the same coordinates as does butaclamol. However, the oxyethylene portion of the spiro system, though equatorially fused, evidently is not an effective surrogate for even the ethyl or *n*-propyl groups, which when present at position 3 of the butaclamol nucleus result in compounds with neuroleptic activity.[1]

In the analogues **23** and **24**, the *tert*-butyl and hydroxyl groups of butaclamol have been transposed from position 3 to 2. The inactivity of **23** is not surprising in view of its unfavorable 4a,13b-cis stereochemistry. The 4a,13b-trans analogue **24**, however, possesses a nuclear shape identical with that of butaclamol (Figure 1). Inspection of models of butaclamol and **24** revealed that the centra of the volume occupied by their *tert*-butyl groups are separated by almost 3 Å. Thus, the inactivity of **24** is ascribed to the inability of its *tert*-butyl group to effectively occupy the lipophilic accessory binding site on the dopamine receptor.

The principal conclusions regarding the topography of the dopamine receptor that can be drawn from this study are, firstly, that the previously proposed[4] hydroxyl accessory binding site plays only a minor role, if any, in the binding of butaclamol to the dopamine receptor, since its removal generates a compound with a remarkably similar psychopharmacological profile. Secondly, the data presented herein provide conclusive evidence for our previous contention[4] that a lipophilic accessory binding site uniquely located on the dopamine receptor macromolecule does exist and it can effectively accommodate the *tert*-butyl groups of butaclamol, of anhydrobutaclamol (**8**), and of the deoxy analogue **9a**. The dimensions of the lipophilic accessory binding site cannot, at this stage, be precisely defined. From our previous studies it is known that an equatorially oriented group as small as ethyl[1] or as large as a substituted phenyl ring[2] will confer neuroleptic activity on the resultant analogue. The *tert*-butyl group has dimensions close to those of a benzene ring. However, the high potency of the Δ^2- and Δ^3-olefin mixture **8**, obtained by dehydration of butaclamol, suggests that the locus of the volume in space occupied by the *tert*-butyl group can be displaced, within limits, either above or below the plane in which the lipophilic accessory binding site is located (Figure 2). Taking these possible displacements into consideration, it would appear that this accessory binding site is considerably larger than, simply, the volume occupied by a *tert*-butyl group.

The lipophilic accessory binding site, therefore, might be viewed as a uniquely shaped cavity on a membrane surface having a minimum diameter of 2.5 Å (Figure 2). Measurements on a model oriented in a Cartesian coordinate system calibrated in angstrom units shows that it is centered at the point *H* (+4.0*Z*, −5.0*X*, −2.5*Y*) in a −*X*, +*Z* plane parallel to that in which the nitrogen atom is located.[13] The receptor representation in Figure 2 shows that it is 4.5 Å (*D* − *H*) from the nitrogen location site *D*, 6.5 Å (*H* − *G*) from the hydrogen bond donor site (*G*), and 9.6 Å (*H* − E) from the center of the phenyl ring binding site (*E*).

These key distances and coordinates involving the lipophiphilic binding site *H*, along with the distances and coordinates related to the nitrogen location site *D*, the hydrogen bond donor site *G*, and the α and β regions of

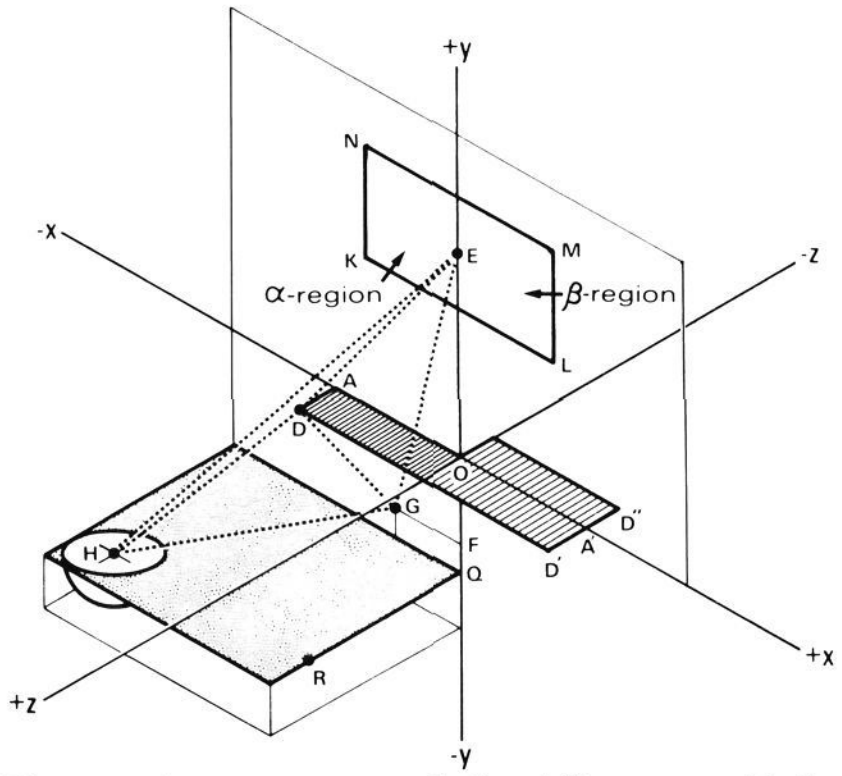


Figure 2. A representation of the lipophilic *accessory binding site* and the *primary binding sites* on the dopamine receptor (see text). The figure is drawn to a scale of 1 cm = 1 Å. Key distances are: $O - E = 4.7$, $A - D = 0.9$, $D - E = 5.7$, $A - O = 3.2$, $D - G = 2.6$, $H - E = 9.6$, $D - H = 4.5$, $O - F = 1.8$, $O - Q = 2.5$, $H - G = 6.5$, $Q - R = 5.0$, $H - R = 4.0$, $F - Q = 0.7$, $N - K = M - L = 2.4$, $K - L = M - N = 4.8$.

the phenyl ring binding site discussed in our accompanying report[13] represent a comprehensive preliminary description of the topography of the dopamine receptor.

In conclusion, from the study on the relationship between neuroleptic activity and detailed molecular structure in certain analogues of butaclamol, it has been possible to gather compelling evidence for the existence of a lipophilic accessory binding site on the central dopamine receptor, to define its probable dimensions, and to specify its locus with respect to the catechol and the nitrogen atom primary binding sites.

Recent experimental evidence points to the existence of presynaptic dopamine receptors,[34-36] in addition to the classical type of postsynaptic receptors. Furthermore, Cools and van Rossum[37] have suggested that dopamine-rich structures in the mammalian brain contain two populations of dopamine receptors which are excitation mediating and inhibition mediating. The present experiments were not aimed at establishing which dopamine receptor(s) butaclamol and its analogues interact with. Although, in the animal models used, neuroleptics are believed to elicit their pharmacological effects through blockade of postsynaptic receptors, the proposals put forward for a map of a central dopamine receptor should not be restricted to these postsynaptic receptors.

Apart from these insights regarding topographical features of the central dopamine receptor, we have also identified in the present study compounds **8**[33] and **9a**[33] as potent neuroleptics with profiles similar to that of butaclamol. It is predicted that these compounds would exert antipsychotic activity in man.

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