Mapping the Dopamine Receptor. 2. Features Derived from Modifications in the Rings A/B Region of the Neuroleptic Butaclamol

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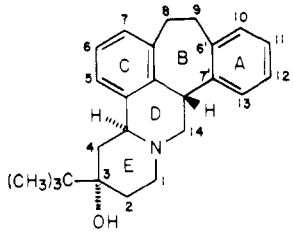
Several analogues of the neuroleptic agent butaclamol having modifications in the rings A/B region of the molecule have been synthesized. Pharmacological evaluation identified the benzo[5,6]cyclohepta analogue **2b**, isobutaclamol, as being equipotent to butaclamol. The molecular structure of this compound has been analyzed, and the results have been used for mapping the central dopamine receptor. A planar catechol *primary binding site*, composed of α and β regions, has been identified and its minimal dimensions deduced. Its locus with respect to the *nitrogen location site* and its complementary *hydrogen bond donor site* has been specified. Using a Cartesian coordinate system, a receptor model is proposed which incorporates the above-mentioned features. The receptor model has been used to rationalize the observed chirality of the central dopamine receptor.

In the preceding paper in this issue,[1] we have described the changes in neuroleptic activity that result from chemical modifications in the E ring region of the antipsychotic agent butaclamol (1). Interpretation of the



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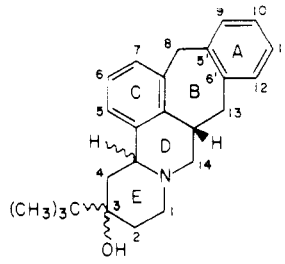

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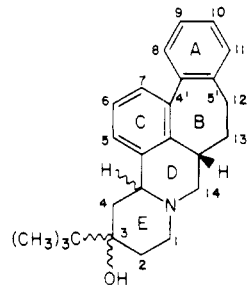

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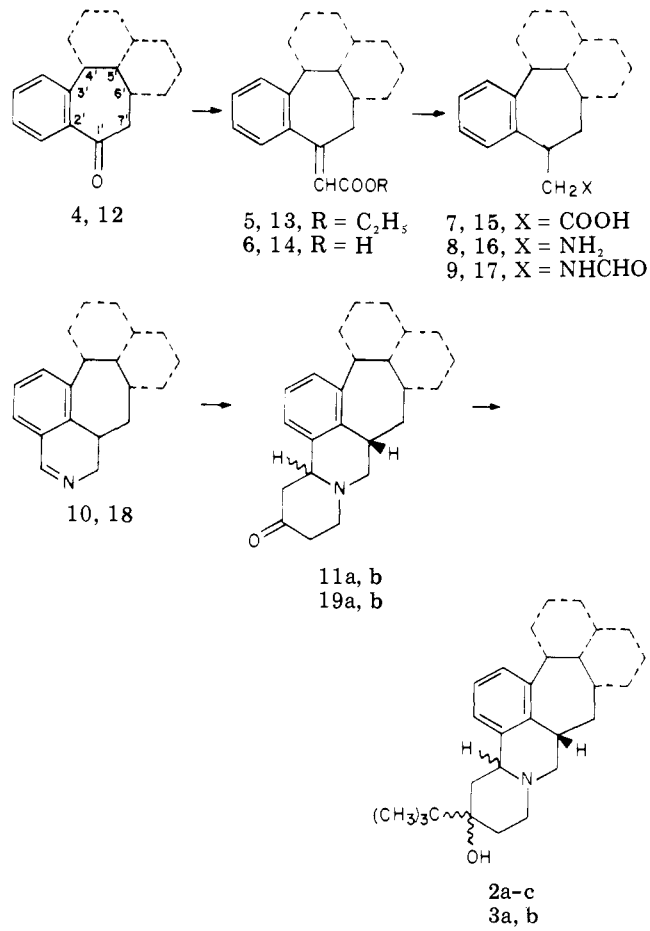
results confirmed the existence and defined the probable locus of a lipophilic *accessory binding site* on the dopamine receptor macromolecule which has a high affinity for the *tert*-butyl group of butaclamol.

The present paper explores the effect of modifying the region of the butaclamol molecule occupied by rings A and B. Butaclamol contains the benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline nucleus, and we herein report the syntheses and limited psychopharmacological evaluation of the benzo[5,6]cyclohepta analogues **2**, as well as the benzo[4,5]cyclohepta analogues **3**. Based on the results and on a study of the molecular geometries of butaclamol, **2**, and **3**, further topographical features of the central dopamine receptor are proposed.

Chemistry. Compounds **2** and **3** were synthesized starting from 5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one[2] (4) and 6,7-dihydro-5*H*-dibenzo[*a*,*c*]-cyclohepten-5-one (**12**) as outlined in Scheme I. The ketones were subjected to the Wittig reaction with triethyl phosphonoacetate followed by hydrogenation and hydrolysis to afford the saturated acetic acids **7** and **15**. Curtius degradation of these gave the methylamines **8** and **16**, which were transformed to the formamides **9** and **17**. Bishler–Napieralski reactions on these formamides afforded the Schiff bases **10** and **18**, which were reacted as their hydrochloride salts with methyl vinyl ketone as described previously for the synthesis of butaclamol (1).[4,5] Thus, compound **10** afforded the 4a,13a-cis and the 4a,-13a-trans isomer pair **11a** and **11b**, and the similar isomer pair **19a** and **19b** was obtained from 18. These pentacyclic amino ketones (**11a**, **11b**, **19a**, and **19b**) were reacted with *tert*-butyllithium to generate the desired tertiary carbinols **2a–c** and **3a,b**.

Scheme I



2, 4-11, benzo[5,6]cyclohepta series
3, 12-19, benzo[4,5]cyclohepta series

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are corrected. Mass spectra were recorded on an LKB-9000S

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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 structures. Microanalyses were performed by the Ayerst Analytical Laboratory under the direction of Dr. G. Schilling. All results were within ±0.4% of the calculated values unless noted otherwise.

5,11-Dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-ylacetic Acid (7). Triethyl phosphonoacetate (45 g, 0.2 mol) was added during 15 min at 0 °C to NaH (0.2 mol, 8.4 g of a 57% suspension in mineral oil) in THF (85 mL). This mixture was added at 22 °C to a solution of 5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (**4**; 22.6 g, 0.108 mol) in THF (80 mL). After refluxing for 72 h in a N_2 atmosphere, the mixture was poured into ice–H_2O. Extraction with Et_2O, drying, and evaporation afforded an oil which was chromatographed on silica gel. Elution with C_6H_6 gave 22.4 g (74.2%) of the unsaturated ester **5**: IR ν_{max} ($CHCl_3$) 1728 cm^{-1} (COOEt). It was dissolved in EtOH (500 mL) and hydrogenated in the presence of 10% Pd on charcoal (4.0 g) for 24 h at 100 psi. The catalyst was removed by filtration, KOH (15 g) was added, and the mixture was refluxed for 1.5 h in a N_2 atmosphere. A conventional workup procedure afforded an oil which was crystallized from an Et_2O–petroleum ether mixture to give the acid **7** (14.4 g, 71%), mp 135–137 °C. Anal. ($C_{17}H_{16}O_2$) C, H.

By following the same procedure as above but using 6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-one (**12**) as starting material, there was obtained **6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-ylacetic acid (15)** in an overall yield of 85%, mp ($CHCl_3$) 187–190 °C. Anal. ($C_{17}H_{16}O_2$) C, H.

5,11-Dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-ylmethylamine Hydrochloride (8·HCl). The acetic acid **7** (61.5 g, 0.244 mol) was refluxed with $SOCl_2$ (195 mL) for 1 h. The $SOCl_2$ was removed by distillation and the acid chloride was dissolved in Me_2CO (300 mL). A solution of NaN_3 (39.1 g, 0.6 mol) in H_2O (160 mL) was added during 20 min at −10 to 0 °C. The mixture was cooled to room temperature and then poured into ice–H_2O (800 mL). Extraction with CH_2Cl_2 afforded the crude acid azide (79 g): IR ν_{max} ($CHCl_3$) 2140 cm^{-1} (CON_3). It was dissolved in toluene (400 mL), refluxed for 2 h, and then cooled to 22 °C. Concentrated HCl (80 mL) was added, and the stirred mixture was kept at 70 °C for 1 h and then refluxed for 1 h. The precipitated product was isolated by filtration, washed with Et_2O, and dried to afford 61.0 g (96%) of material, mp 229–231 °C. An analytical sample had mp (MeOH–Et_2O) 231–233 °C. Anal. ($C_{16}H_{18}ClN$) C, H, N.

By following the same procedure as above but using the acetic acid **15** as starting material there was obtained in 88.53% yield **6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-ylmethylamine hydrochloride (16·HCl)**, mp 227–229 °C, unchanged by crystallization from MeOH–Et_2O. Anal. ($C_{16}H_{18}ClN$) C, H, N.

5,11-Dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-ylmethylformamide (9). The cyclohepten-10-ylmethylamine **8**, obtained from the HCl salt (16 g, 0.062 mol), was treated for 20 h at 22 °C with formic anhydride–acetic anhydride prepared by heating Ac_2O (14.6 g, 0.14 mol) with HCOOH (6.6 g, 0.14 mol) at 60 °C for 2 h. The mixture was poured into ice–H_2O, made alkaline with 10% aqueous NaOH solution, and extracted with Et_2O to afford a solid product (14.0 g, 90.6%), mp 105–108 °C. An analytical sample had mp (Et_2O) 109–111 °C. Anal. ($C_{17}H_{17}NO$) C, H, N.

By following the same procedure but using the amine hydrochloride **16**·HCl as starting material there was obtained a 78% yield of **6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-ylmethylformamide (17)**, mp 104–107 °C. An analytical sample had mp ($CHCl_3$–Et_2O) 107–109 °C. Anal. ($C_{17}H_{17}NO$) C, H, N.

1,7,12,12a-Tetrahydrobenzo[5,6]cyclohepta[1,2,3-*de*]isoquinoline (10). The formamide **9** (6.7 g, 0.027 mol) was stirred with polyphosphoric acid (50 g) for 3.5 h at 155–160 °C and then poured into ice–H_2O. After stirring for 30 min, the solution was made alkaline with 30% aqueous NaOH solution. Extraction with $CHCl_3$ gave a residue which was chromatographed on neutral alumina (Woelm, activity II). Elution with C_6H_6–EtOAc (19:1) gave 5.79 g of a semisolid. Crystallization from Et_2O yielded the pure product (4.05 g, 65%): mp 91–93 °C; IR ν_{max} ($CHCl_3$) 1629 cm^{-1} (C=N). Anal. ($C_{17}H_{15}N$) C, H, N. The hydrochloride salt **10**·HCl had mp (MeOH–Et_2O) 285–295 °C. Anal. ($C_{17}H_{16}ClN$) C, H, N.

By following the above procedure and using the formamide **17** as starting material there was obtained, after elution with C_6H_6 from a neutral alumina column, an 83% yield of the benzo[4,5] analogue **18**. It was an amorphous solid softening at 100–103 °C and good elemental analyses could not be obtained: IR ν_{max} ($CHCl_3$) 1634 cm^{-1} (C=N), MS *m/e* 233 (M_r 233).

1,2,4,4a,8,13,13a,14-Octahydro-3*H*-benzo[5,6]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ones 11a and 11b. The Schiff base hydrochloride **10**·HCl (23.5 g, 0.087 mol) and methyl vinyl ketone (200 mL) were combined and heated at 100 °C for 1.5 h. On cooling to 20 °C a solid precipitated. It was isolated by filtration and distributed between $CHCl_3$ and 10% aqueous NaOH solution. The $CHCl_3$ phase afforded a semisolid which was a mixture of two compounds detectable by TLC. It was chromatographed on silica gel using C_6H_6–EtOAc (6:1) as eluant.

The first compound eluted weighed 19.4 g. Crystallization from C_6H_6–hexane yielded 13.4 g (50.7%) of product **11a**: mp 192–194 °C; IR ν_{max} ($CHCl_3$) 1706 cm^{-1} (CO). Anal. ($C_{21}H_{21}NO$) C, H, N.

Continued elution afforded, after crystallization from C_6H_6, product **11b** (4.33 g, 16.4%): mp 217–219 °C, IR ν_{max} ($CHCl_3$) 1702 cm^{-1} (CO). Anal. ($C_{21}H_{21}NO$) C, H, N.

1,2,4,4a,12,13,13a,14-Octahydro-3*H*-benzo[4,5]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ones 19a and 19b. The Schiff base hydrochloride **18**·HCl was reacted with methyl vinyl ketone as described above to afford a mixture of isomers, which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (12:1) gave in 20% yield the product **19a**: mp (C_6H_6–pentane) 172–174 °C; IR ν_{max} ($CHCl_3$) 1710 cm^{-1} (CO). Anal. ($C_{21}H_{21}NO$) C, H, N.

Continued elution with the same solvent mixture afforded a 39% yield of product **19b**, mp (C_6H_6–pentane) 197–203 °C. Anal. ($C_{21}H_{21}NO$) C, H, N.

3-*tert*-Butyl-1,2,4,4a,8,13,13a,14-octahydro-3*H*-benzo[5,6]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ols 2a–c. To a solution of *tert*-butyllithium in pentane (50 mL of a 1.8 M solution) was added, during 30 min at 0–10 °C, the amino ketone **11a** (3.03 g, 0.01 mol) dissolved in C_6H_6 (120 mL). The reaction mixture was kept at 10 °C for 1.5 h and then at 22 °C for 16 h. After the addition of 10% aqueous NH_4Cl (50 mL) to the mixture, the organic phase was separated, dried, and evaporated to afford a gum, which was chromatographed on neutral alumina (Woelm, activity II). Elution with C_6H_6–hexane (1:1) afforded 85 mg (2.3%) of the product **2c**: mp (EtOH) 163–165 °C; IR ν_{max} ($CHCl_3$) 3370 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.96 [9, s, $C(CH_3)_3$]. Anal. ($C_{25}H_{31}NO$) C, H, N.

Further elution with C_6H_6–EtOAc (9:1) afforded 1.48 g (41%) of the isomer **2a**: NMR ($CDCl_3$) δ 0.95 [9, s, $C(CH_3)_3$]. The hydrochloride salt **2a**·HCl had mp (2-PrOH–Et_2O) 295–298 °C. Anal. ($C_{25}H_{31}NO$) C, H, N.

Following the procedure described above, the amino ketone **11b** was reacted with *tert*-butyllithium to afford a gum. After three crystallizations from $CHCl_3$–Et_2O, the product, isomer **2b**, was obtained in 30% yield: mp 180–182 °C; IR ν_{max} ($CHCl_3$) 3620 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.96 [9, s, $C(CH_3)_3$]. Anal. ($C_{25}H_{31}NO$) C, H, N. The hydrochloride salt **2b**·HCl had mp (MeOH–Et_2O) 279–280 °C. Anal. ($C_{25}H_{32}ClNO$) H, N; C: calcd, 75.44; found, 74.97.

3-*tert*-Butyl-1,2,4,4a,12,13,13a,14-octahydro-3*H*-benzo[4,5]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ols 3a and 3b. Following the procedure described below, the amino ketone **19a** was reacted with *tert*-butyllithium to afford a 21.5% yield of the product **3a**, eluted from an alumina column with C_6H_6–EtOAc (9:1): IR ν_{max} ($CHCl_3$) 3615 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.00 [9, s, $C(CH_3)_3$]. It was converted to the hydrochloride salt **3a**·HCl which had mp (MeOH–Et_2O) 276–279 °C. Anal. ($C_{25}H_{32}ClNO$) C, H, N.

In a similar manner, amino ketone **19b** was reacted with *tert*-butyllithium to afford a 64% yield of the product **3b**: IR ν_{max} ($CHCl_3$) 3615 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.91 [9, s, $C(CH_3)_3$]. The hydrochloride salt **3b**·HCl had mp (MeOH–Et_2O) 305–307 °C. Anal. ($C_{25}H_{32}ClNO$) C, H, N.

Table I. Pharmacological Comparisons of Butaclamol (1a) and Isobutaclamol (2b)

compd	amphet-induced stereotyped behav: MED[a]	condit avoid. resp: ED_{50}[b]	epinephr-induced mortal. ED_{50}[c]	catalepsy, % of max[d]	isolat-induced fight behav: ED_{50}[e]
1	0.62	0.64 ± 0.13	15 ± 3	60	1.9 ± 0.16
2b	0.62	1.0 ± 0.67	10 ± 4	45	2.0 ± 0.30

[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}, 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] Catalepsy was evaluated at a 5 mg/kg dose, which was approximately tenfold the dose that antagonized amphetamine-induced stereotyped behavior. [e] ED_{50} (mg/kg, ip), defined as the dose which abolished the fighting behavior in 50% of the pairs tested.

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 the 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.[6]

***d*-Amphetamine-Induced Stereotyped Behavior in Rats.** Details of the methodology and scoring system were recently described.[7] 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 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[8] 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.[9] 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.[10] was followed. Groups of six or more rats (220–250 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.[11] The compounds were administered ip, to groups of six rats, at a 5 mg/kg dose, which was 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.[12] 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.[13] The isolation-induced aggressive behavior, manifested as fierce fighting, appeared 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.[7]

The present experiments have established that the compounds **2a** and **2c** of the benzo[5,6]cyclohepta series and **3a** and **3b** of the benzo[4,5]cyclohepta series do not antagonize the amphetamine-induced stereotyped behavior at 20 mg/kg, which was the highest dose tested. In contrast, the isomer **2b**, isobutaclamol,[14] was very similar to butaclamol (Table I), both qualitatively and quantitatively, under the experimental conditions used. At low doses, the compound strongly antagonizes amphetamine-induced stereotypy, suppresses the conditioned avoidance response in rats, and exerts a taming effect in isolated fighting mice. At a slightly higher dose catalepsy is induced, while still higher doses are required to antagonize epinephrine mortality. Under clinical conditions, isobutaclamol (**2b**) would therefore be expected to be a potent antipsychotic drug with a clinical profile very similar to that of butaclamol.[1]

With respect to the stereochemistry of **2b** and also of **2a** and **2c**, no chemical evidence could be obtained regarding the relative configurations at positions 3,4a, and 13a. It is apparent, however, that of the four possible racemic isomers of **2** only one can have a molecular structure in which the region occupied by rings B, C, D and E will have an identical topography to the same region of butaclamol. Examination of Dreiding models (Figure 1), as well as direct superimposition of molecular structures using the MMS-X molecular graphics system,[15] reveals that that isomer of **2** must have 4a,13a-trans and 3(OH),13a-(H)-trans relative configurations. This stereochemistry is assigned to isomer **2b** in view of the virtually identical psychopharmacological profiles of butaclamol and isobutaclamol.

Compound **11b**, the precursor amino ketone of **2b**, is consequently assigned the same relative configurations at positions 4a and 13a. The isomeric amino ketone **11a**, as well as the derived tertiary carbinols **2a** and **2c**, have, therefore, 4a,13a-cis relative configurations. The reaction of the 4a,13a-*cis*-amino ketone **11a** afforded **2a** and **2c** in yields of 41.5 and 2.3%, respectively. The unique shape of the molecule **11a** favors attack by the *tert*-butyl anion on the carbonyl group from the least-hindered face, i.e., equatorially.

Consequently, the product obtained in high yield, **2a**,

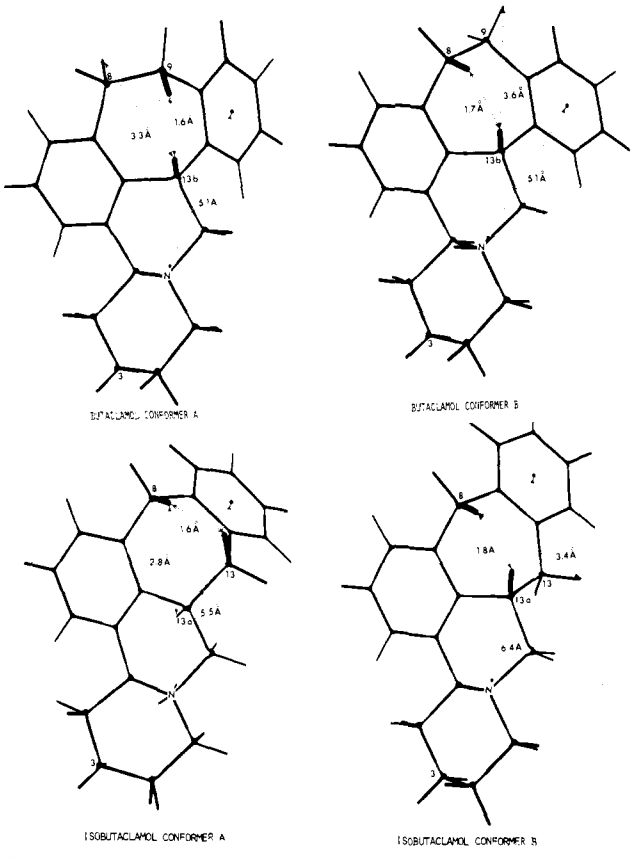

Figure 1.

is assigned a 3(OH),13a(H)-trans relative configuration, and **2c** must be the 3(OH),13a(H)-cis isomer.

The fact that the activity of isobutaclamol (**2b**) is very similar to that of butaclamol is the most interesting finding of this study. From an analysis of the molecular structure of isobutaclamol, it is apparent that the rings C-D-E region constitutes a completely rigid system, assuming only that ring E adopts a chair conformation with its *tert*-butyl group oriented equatorially. On the other hand, because of the possibility of rotation about the C_{13}–C_{13a} bond, the cycloheptane ring B can adopt the two conformations shown in Figure 1. In one, designated conformer A, the hydrogens at C_8 and C_{13} are eclipsed (a flagpole–bowsprit type interaction), while in conformer B, C_8 and C_{13a} hydrogens are eclipsed.

The butaclamol nucleus can also adopt two conformations due to the flexibility of the cycloheptane ring. They have been designated[16] conformer A (C_9-H and C_{13b}-H eclipsed) and conformer B (C_8-H and C_{13b}-H eclipsed) and are depicted in Figure 1.

In the crystal structure of butaclamol, it is the conformer A that exists.[19] There is, however, no a priori reason why a conformation detected by X-ray crystallography, even of a semirigid molecule such as butaclamol, should be assumed to be the conformation in which a ligand binds to a biological receptor. In fact, we have proposed[16] that it is butaclamol's conformer B which interacts with the central dopamine receptor, and we present now additional evidence supportive of this contention.

Superimposition of the molecular models of the conformers A and B of both butaclamol and isobutaclamol reveals (Figure 2) that only with the conformers B are all the atoms of the two molecules coincident, with the exceptions of C_{9-11} of isobutaclamol, C_{11-13} of butaclamol, and their appended hydrogen atoms. It is evident that the topographical features that these ligands share in common

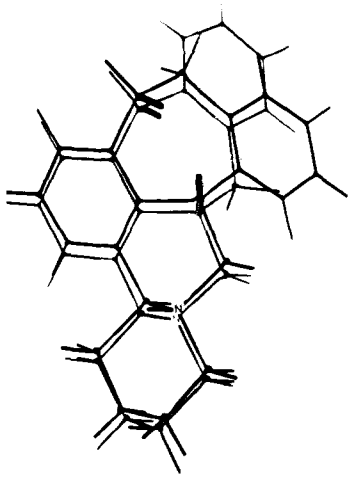

Figure 2. Superimposition of Dreiding models of the nuclei of butaclamol and isobutaclamol in their conformations **B**.

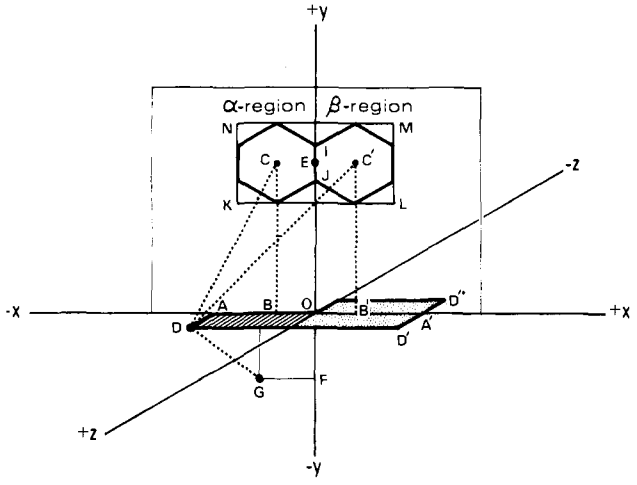

Figure 3. A representation of primary binding sites on the dopamine receptor derived from measurements of Dreiding models of the conformers B of butaclamol and isobutaclamol (see text). The figure is drawn to a scale of 1 cm = 1 Å. Key distances are: $O-E = B-C = B'-C' = 4.7$, $A-D = A'-D' = A'-D'' = 0.9$, $A-B = A'-B' = 2.0$, $A-B' = 4.4$, $D-C = 5.1$, $D-C' = 6.4$, $D-G = 2.6$, $A-O = A'-O' = 3.2$, $K-L = M-N = 4.8$, $N-K = M-L = 2.4$, $O-F = 1.8$, $F-G = 1.7$

are prerequisite for recognition by the dopamine receptor. That they exist only in the conformers B is regarded as compelling evidence that isobutaclamol, and butaclamol as previously proposed,[16] interact with the dopamine receptor in their conformations B.

The nonsuperimposable regions of the conformers B of isobutaclamol and butaclamol, the sextets of atoms referred to above, are parts of their benzene rings A. It is apparent (Figure 2) that these benzene rings lie in a common plane and are immediately adjacent to each other with C_{9a}–C_{10} and the C_{12}–C_{12a} bonds of butaclamol and isobutaclamol, respectively, being coincident.

On the basis of our studies with butaclamol and apomorphine,[16] we proposed that there exists a *primary binding site* on the dopamine receptor which is occupied by the phenyl ring A and by the catechol ring, respectively, of these ligands. It is clear from the present study that this planar binding site must have the dimensions of at least two adjoining benzene rings, i.e., about 4.8 × 2.4 Å, and it appears to be of no consequence to the receptor whether the α or β region of this site is occupied (Figures 2 and 3).

It was further suggested[16] that the dopamine receptor

Table II. Distances Defining Relative Positions of the Nitrogen and Ring A in Butaclamol and Analogues[a]

	$B-C=$ $B'-C'$	$A-B$	$A-B'$	$A-D$	$D-C$	$D-C'$
1 B	4.7	2.0		+0.9	5.1	
2b B	4.7		4.4	+0.9		6.4
1 A	4.7	1.5		−0.19	5.1	
2b A	4.7		1.1	+3.1		5.8
3-*X*	4.7	4.3		+1.0	6.5	
3-*Y*	4.7	1.5		+3.5	6.0	

[a] These distances are illustrated in Figure 3 and were measured with the molecule oriented in a Cartesian Coordinate system as specified in the text.

also has a primary binding site which accommodates the nitrogen atom of butaclamol and that it was situated at 0.9 Å from the plane in which phenyl ring A is located. Table II shows this distance, as well as other relevant distances, between certain points in Dreiding models of conformers A and B of (+)-(3*S*,4a*S*,13b*S*)-butaclamol and of the isobutaclamol enantiomer with 3*S*,4a*S*,13a*S* absolute configurations,[17,18] while Figure 3 illustrates these points in a Cartesian coordinate system of three mutually perpendicular planes, calibrated in angstrom units.

For obtaining measurements, the models were oriented in the coordinate system such that the centers of rings A were located at points *C* or *C'*, a distance above the *X* axis proportional to 4.7 Å, and with the nitrogen atom located in the −X, +Z plane. With this orientation of (+)-butaclamol, conformer B, and of (3*S*,4a*S*,13a*S*)-isobutaclamol, conformer B, C_{9a} and C_{12a} of the rings A of these two ligands lie at point *J* on the *Y* axis, C_{10} and C_{12} lie at point *I*, while the rings A of the two ligands lie in the −X, +Y plane and the +X, +Y plane, respectively.

The identical *A* − *D* distance of +0.9 Å in both butaclamol and isobutaclamol in their conformations B suggests that that value is critical for defining the neuroleptic pharmacophore. The distance *A* − *D* along with the distances *A* − *B* and *A* − *B'* define the *X*, *Y*, *Z* coordinates of the nitrogen atom with respect to the centers of the phenyl rings A of these two ligands. The different *A* − *B*, *A* − *B'* values (2.0 and 4.4 Å) and *D* − *C*, *D* − *C'* values (5.1 and 6.4 Å) for the conformers B of butaclamol and isobutaclamol reflect the circumstance that the phenyl ring binding site has the dimensions of at least two adjacent benzene rings (*M* − *N* = 4.8 Å, *N* − *K* = 2.4 Å) and that the phenyl ring can bind to either the α or β region of that site.

The nitrogen atom of butaclamol (and of isobutaclamol) binds to a site on the dopamine receptor. The nature of the binding is suggested from the following considerations. (+)-Butaclamol has a pK_a of 5.9,[20] and homogenized rat caudate nucleus, which is rich in dopamine receptors, has a pH of 7.3.[21] Thus, on interaction of this ligand with its receptor, the nitrogen atom exists almost exclusively in the deprotonated form. This rules out the notion that the nitrogen, through a charged protonated form, might bind with a group on the receptor via an ionic interaction. We suggest instead that the nitrogen lone-pair electrons participate in hydrogen-bond formation with another electronegative atom. Hydrogen-bond formation is effective when the distance between the electronegative atoms involved is between 2.5 and 2.7 Å and when the three atoms involved are linearly aligned.[22] Consequently, we suggest that an electronegative atom is located at point *G*, 2.6 Å from the nitrogen atom. Because of the rigidity of the butaclamol nucleus, the nitrogen lone-pair electrons have a unique directional vector, which is fully defined by the value of 45° for the angle *GDD'* in Figure 3. The point *G* has the coordinates −2.0*X* and −1.8*Y* and is located at the intersection of the −X, −Y plane, and a perpendicular −X,+Z plane which is 1.8 Å (the distance *OF*) below the plane in which the nitrogen atom is located.

Figure 3 illustrates the essential relationships between the positions of the phenyl rings A, the nitrogen atom, and the complementary electronegative atom with which it forms a hydrogen bond. These relationships are derived from a study of specific conformations of the pharmacologically active enantiomers of butaclamol and isobutaclamol. The nitrogen atom and the phenyl rings A of these ligands are part of the neuroleptic pharmacophore and must interact with complementary features on the dopamine receptor. Thus, Figure 3 can be considered as a representation of the dopamine receptor itself, showing the phenyl ring primary binding site with its minimum dimensions and the previously designated[16] nitrogen atom primary binding site, which must now be viewed as being composed of a nitrogen location site D and a complementary hydrogen bond donor site *G*.

This receptor representation also accounts for the chirality of the receptor. Thus, if the pharmacologically inactive (−) enantiomer of butaclamol is oriented to the receptor with its ring A bound to the β region of the phenyl ring binding site, it requires the existence of a nitrogen atom location site at position *D'* (+3.2*X*, +0.9*Z*). It would appear that either no such site exists at *D'* or that the molecule would have to occupy "disallowed" space in the +*Z* octants of the coordinate system in which the receptor is oriented.

We have chosen, in Figure 3, to orient the phenyl rings A of (+)-butaclamol and of (3*S*,4a*S*,13a*S*)-isobutaclamol, both in conformation B, on the *X*, *Y* plane such that the nitrogen atoms are situated on the +*Z* side of the *X*, *Y* plane. Inspection of models of these ligands reveals the remarkable circumstance that, with the exception of five hydrogen atoms of the former ligand (those attached to $C_{1,8,9,13b}$ and C_{14}) and the similar hydrogen atoms of the latter (attached to $C_{1,8,13,13a}$ and C_{14}), all the other 53 atoms of the molecules lie either on the *X*, *Y* plane or in the +*Z* side of that plane. This observation suggests that the *X*, *Y* plane of the receptor represents an essentially flat membrane surface of which the phenyl ring primary binding site is a part.

The ligands discussed above could, alternatively, have been oriented with their phenyl rings A bound to a complementary site on the *X*, *Y* plane but with the nitrogen atoms located at position *D''* in the −*Z* side of that plane. This alternative is identical with the first as long as no information is available concerning the nature of the proposed membrane that is represented by the *X*, *Y* plane. However, we consider it improbable that a receptor membrane would be so undifferentiated that specific ligand binding could occur, indiscriminately, on either face.

Table II also shows key distances for the conformers A of (+)-butaclamol and (3*S*,4a*S*,13a*S*)-**2b**. The *A* − *D* values of −0.19 and + 3.1 Å are inconsistent with the above definition of the structural requirements for receptor affinity and is taken as additional evidence that these ligands interact with the dopamine receptor exclusively in their conformations B.

It was the presence of an extended phenethylamine moiety in butaclamol that prompted a comparison of its topography with that of the same grouping in apomorphine and which led to the detection of common topographical features in the two ligands.[16] Isobutaclamol does not contain such an extended phenethylamine moiety but rather a phenylpropylamine group constrained within a

semirigid ring system. A priori, one might not have expected isobutaclamol to be capable of interacting with the receptor genetically designed for the phenethylamine neurotransmitter dopamine. However, because of the dimensions of the planar phenyl ring primary binding site and because isobutaclamol has the required $A - D$ distance, it possesses the essential features required for recognition by the dopamine receptor. This constitutes a unique instance where a phenylpropylamine grouping functions topographically as a phenethylamine.

For the compounds of the benzo[4,5]cyclohepta series, **3a** and **3b**, there is also no chemical evidence available regarding the stereochemistry at positions 3,4a and 13a. Since neither compound possessed any butaclamol-like activity, no stereochemical conclusions could be made on the basis of knowledge of the structural requirements for interaction with the dopamine receptor. However, it is evident that the precursors of **3a** and **3b**, the amino ketones **19a** and **19b**, constitute the 4a,13a-cis and 4a,13a-trans pair of isomers. On reaction of these amino ketones with *tert*-butyllithium, each affords a single tertiary carbinol which is assumed to have its *tert*-butyl group oriented equatorially. Compounds **3a** and **3b** would then constitute the pairs of isomers having (4a,13a-trans)[3-(OH),13a(H)-trans] and (4a,13a-cis)[3(OH),13a(H)-trans] relative configurations.

Inspection of a molecular model of the (4a,13a-trans)-[3(OH),13a(H)-trans] isomer of **3** shows that the rings CDE region superimposes exactly with the same region of butaclamol. It is further seen that that isomer of **3** can exist in two conformations due to rotation about the C_{12}–C_{13} bond of the cycloheptane ring.

The key distances for these two conformers, designated **3**-*X* and **3**-*Y*, have been measured on models and are collected in Table II. It is apparent that the large value of the distance $A - D$ for **3**-*Y* (3.5 Å) disqualifies it as a candidate dopamine receptor ligand. On the other hand, the $A - D$ distance for **3**-*X* is 1.0 Å, close to the optimum required for interaction with the dopamine receptor. However, inspection of models of **3**-*X* and butaclamol with rings C, D, and E superimposed shows that ring A of **3**-*X* does not lie in the same plane as ring A of butaclamol. In fact, it lies in a plane which makes an angle of almost 90° to the plane occupied by ring A of butaclamol. Thus, although **3**-*X* possesses one of the required recognition features, this is insufficient since its phenyl ring A is so situated that it is incapable of binding to the phenyl ring binding site on the receptor.

The same conclusion is reached by stating that the coordinates of its nitrogen atom ($-3.5X$, $+1.0Z$), when the phenyl ring A is bound to the α region of the phenyl ring binding site, are inconsistent with the position of the nitrogen atom location site on the dopamine receptor.

Recent evidence for multiple types of dopamine receptors has been cited in the preceding paper in this issue,[1] and the proposals put forward herein for a map of a central dopamine receptor should not be restricted only to the classical type of postsynaptic receptor.

In summary, this study has led to the identification of isobutaclamol, **2b**, as a potent neuroleptic which should be a clinically active antipsychotic agent. In addition, studies of the molecular geometries of this agent and of butaclamol allow considerable progress in mapping topographical features of the central dopamine receptor.

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