generated it will have a longer lifetime under relatively acidic conditions, due to less frequent interception by hydroxide ion. Whether alone or in concert, these circumstances with regard to **5** and **7** provide for greater probability of encountering and alkylating DNA and, in effect, represent a form of selective cross-linking.

There are significant unanswered questions which must be addressed in connection with the biologically pertinent chemistry of **5**, and our continued work in this area will employ, among other methods, multinuclear NMR techniques.

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(3) While the systematic name for compound **5** is *N,N*-bis(2-chloroethyl)phosphorodiamidic acid, we have opted for the commonly used trivial name phosphoramide mustard as a matter of convenience. Phosphorodiamidic acid mustard appears to be a less frequently used synonym for **5**.
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(16) ^{31}P NMR spectra were recorded at 40.25 MHz on a JEOL FX-100 spectrometer equipped with a 10-mm variable-temperature probe. Normal operating conditions utilized continuous broad-band ^1H decoupling, a 26-μs ($\pi/2$) pulse, 5-kHz spectral window and filter, and 8192 data points. Prior to Fourier transformation, the free-induction decay signal was zero filled with 8192 points and exponentially multiplied so as to result in an additional 1-Hz line broadening in the frequency-domain spectrum. A 2-s pulse delay time was used throughout these studies, as longer waiting periods were shown not to have a measurable effect upon relative absorption intensities. The lock signal was provided by 20% (v/v) D_2O, and chemical shifts were measured relative to an external solution of 25% (v/v) H_3PO_4 in water that was contained in a 1-mm coaxial capillary tube. A sample temperature of 37 °C was directly measured under normal operating conditions by immersion of a calibrated thermometer.
(17) Abbreviations used: Bistris, 2-[bis(2-hydroxyethyl)-amino]-2-(hydroxymethyl)-1,3-propanediol; Tris, tris(hydroxymethyl)aminomethane. The specified pH values refer to buffer solutions before the addition of 20% (v/v) D_2O and are not corrected for isotope effects [cf. R. Lumry, E. L. Smith, and R. R. Glantz, *J. Am. Chem. Soc.*, **73**, 4330 (1951)].
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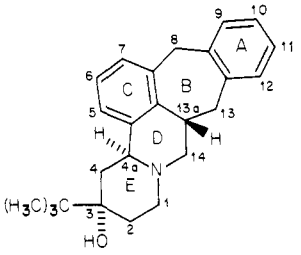
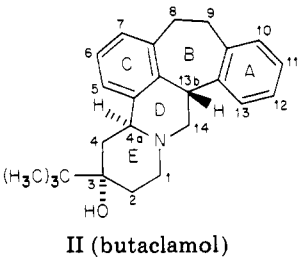
(+)-Isobutaclamol: A Crystallographic, Pharmacological, and Biochemical Study

Sir:

We have recently described[1] the synthesis and some pharmacological properties of (±)-isobutaclamol (I), a



I (isobutaclamol)



II (butaclamol)

compound having a neuroleptic profile virtually identical with that of (±)-butaclamol (II).

The activity of (±)-butaclamol, both in vivo and in vitro, has been shown to reside exclusively in the (+)-3*S*,4a*S*,-13b*S* enantiomer.[2-4] Based on a proposed model of the central dopamine receptor,[1,5] we had predicted that (±)-isobutaclamol's neuroleptic activity resides solely in its 3*S*,4a*S*,13a*S* enantiomer.

With respect to the stereochemistry of isobutaclamol at positions 3, 4a, and 13a, no chemical evidence was available to aid in the assignment of relative configurations. However, assuming a requirement for identical molecular topographies in the rings B, C, D, and E regions of both butaclamol and isobutaclamol, the latter was assigned[1] the 4a,13a-trans and 3(OH),13a(H)-trans relative configurations, shown in I, analogous to those found in butaclamol by crystallographic analysis.[6]

The purpose of the present investigation was to assess the validity of these predictions by resolving (±)-isobutaclamol, examining some aspects of the neuroleptic profile of the enantiomers, and determining relative and absolute configurations by a crystallographic analysis.

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Table I. Chemical, Pharmacological, and Biochemical Characteristics of Isobutaclamols

compound	mp, °C	$[\alpha]^{25}_D$,[a] deg	abs confign	antag of amphetamine stereotypy, mg/kg ip: MED[b]	inhibn of [^{3}H]haloperidol binding:[c,d] IC_{50}, nM
(±)-I·HCl	279-280 (dec)[e]			0.62	1.7
(+)-I·HBr[f]	276-278 (dec)	+222.8	3*S*,4a*S*,13a*S*	0.31	0.8
(−)-I·HBr[f]	276-278 (dec)	−221.6	3*R*,4a*R*,13a*R*	>25	0% inhibn at 1000 nM

[a] In a 2% solution in methanol. [b] Minimal effective dose. For details, see ref 1, 5, and 8. [c] For details of method, see ref 9. [d] Similar results are obtained using homogenized calf striatum and [^{3}H]spiperone as radioligand. See ref 11. [e] See ref 1. [f] $C_{25}H_{32}BrNO$. Analytical values for C, H, and N were within ±0.4% of calculated values.

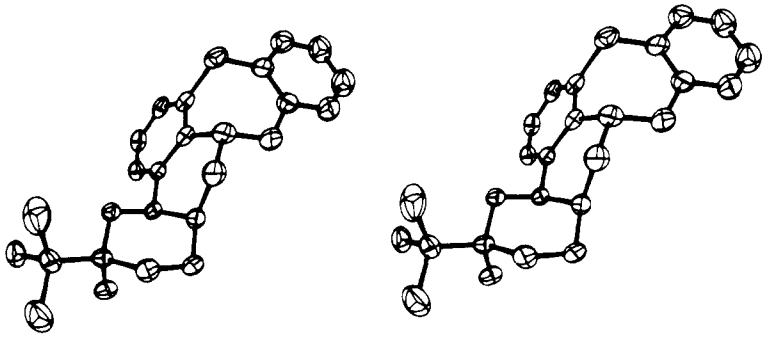

Figure 1. A stereoscopic view of (+)-isobutaclamol in the determined absolute configuration, with 50% probability thermal ellipsoids.

(±)-Isobutaclamol was resolved using (+)- and (−)-tartaric acids, as described previously[2] for the resolution of (±)-butaclamol. The (+)- and (−)-tartrate salts, obtained in 30.7 and 35.6% yields, respectively, were each crystallized twice from methanol–ether mixtures and then converted to the free bases with concentrated ammonium hydroxide in the presence of benzene. The bases were treated with methanolic hydrogen bromide, and the salts were crystallized twice from methanol–ether mixtures to afford the pure (+)- and (−)-isobutaclamol hydrobromides, whose physical constants are collected in Table I.

(+)-Isobutaclamol hydrobromide, in the form of colorless transparent prismatic crystals, was chosen for the X-ray analysis. The details of the structure determination are in press.[7] A perspective view of the molecule in the determined absolute configuration is presented in Figure 1.

The isobutaclamol enantiomers were evaluated intraperitoneally for their ability to abolish (+)-amphetamine-induced stereotyped behavior in rats. Details of the protocol used have been described recently.[1,5,8] The results, expressed as the minimal effective dose which antagonized amphetamine-induced stereotypy, are described in Table I.

The isobutaclamol enantiomers and racemate were also investigated for their ability to inhibit the specific binding of [^{3}H]haloperidol to homogenates of rat striatum. Details of the method used have been described recently.[9] The results, expressed as the nanomolar concentration required to inhibit specific binding by 50% (IC_{50}), are also shown in Table I.

The results summarized in Table I show that all of the neuroleptic activity in vivo and in vitro of (±)-isobutaclamol resides in the (+) enantiomer. Figure 1 reveals that this enantiomer possesses the expected 3*S*,4a*S*, and 13a*S* absolute configurations, as well as the assigned 4a,13a-trans and 3(OH),13a(H)-trans relative configurations.[1] Ring B is seen to exist in its conformation B (C_8 and C_{13a} hydrogens eclipsed), the conformation which we have proposed is adopted by (+)-butaclamol on interacting with the central dopamine receptor.[2] In contrast, both the (±)-butaclamol and (+)-dexclamol salts exist in the crystal in their conformations A[6] (II; C_9 and C_{13b} hydrogens eclipsed), and it was necessary to propose that they converted to their conformations B on interaction with the dopamine receptor.[2,6]

In contrast to (±)-butaclamol and (+)-dexclamol hydrobromides which exist in the crystal with transoid D,E ring fusions,[6] (+)-isobutaclamol hydrobromide has a cisoid D,E fusion with the NH bond cis to the C_{4a} hydrogen atom.

We have suggested that at the receptor site(s) the biologically active butaclamol and isobutaclamol enantiomers exist predominantly in the deprotonated form.[1] In this form the rings D,E cisoid and transoid species are readily interconvertible through nitrogen inversions. The receptor model we have proposed[1,5] will accommodate only the transoid forms of butaclamol and isobutaclamol. The model also accommodates the rigid and semirigid dopamine receptor ligands (−)-apomorphine and (+)-octoclothepin, respectively, which have topographical features in common only with the transoid forms of butaclamol and isobutaclamol.[10] Consequently, we suggest that it is the rings D,E transoid form of (+)-isobutaclamol which interacts with the dopamine receptor(s).

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Articles

N-Alkyl Derivatives of (±)-α-Methyldopamine

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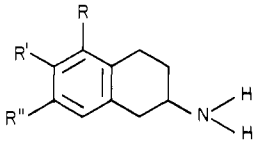
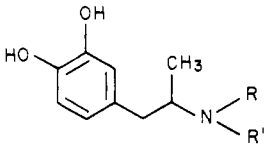
A series of N-alkylated α-methyldopamine derivatives has been prepared for comparison of their biological effects with those of semirigid dopamine congeners derived from 2-aminotetralin systems. All of the α-methyldopamine derivatives were inert as dopaminergic agonists in a variety of animal assays, both centrally and peripherally, although certain compounds produced powerful and prolonged locomotor hyperactivity on intra-accumbens injection in mice, by indirect mechanism(s). A rationalization, based upon conformational analysis, is presented for the lack of direct dopaminergic agonist activity of α-methyldopamine derivatives.

The pronounced dopaminergic agonist activity reported[1,2] for (±)-5,6-dihydroxy- (**1a**) and 6,7-di-



1a, R = R' = OH; R'' = H
1b, R = H; R' = R'' = 2-OH



2, R, R' = combinations of H, CH_3, C_2H_5, n-C_3H_7, 2-C_3H_7, n-C_4H_9

hydroxy-2-aminotetralins (**1b**) and their N-substituted derivatives prompted an investigation of central and peripheral effects in a variety of animal experimental models of an extended series of N-substituted congeners of (±)-α-methyldopamine **2** which, like the aminotetralins, bear the amino group on a secondary carbon, rather than on a primary carbon as in dopamine.

Accounts of biological testing of α-methyldopamine, a few N-alkylated derivatives, and some ether derivatives have indicated that some of these compounds exhibit "epinephrine-like" activity,[3] sympathomimetic effects,[4] β-adrenergic activity,[5] possible stimulation of release-inhibiting α-adrenoceptors in renal hypertensive rats,[6] weak positive inotropic effects,[7] and CNS stimulant effects (via an indirect mechanism).[8] However, the literature revealed only a few reports of investigation of dopamine-like effects of α-methyldopamine systems.[9-11] Noteworthy among these is the reported inability of both enantiomers of α-methyldopamine to produce vasodilatation of the renal artery[11] and the report[9] of a lack of consistent activity spectrum in (±)-α-methyldopamine and its *N*-methyl- and *N,N*-dimethyl homologues in oxotremorine antagonism, reserpine antagonism, and hypothermia assays.

Preparation of the compounds based on **2** involved reductive amination of 3,4-dimethoxyphenylacetone and, when appropriate, subsequent N-alkylation of the amine product. The Experimental Section describes representative types of alkylation procedures employed for the target compounds which are listed in Table I. Spectral (IR and NMR) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Results. None of the compounds inhibited the positive inotropic or chronotropic response induced by field stimulation of cat atria. Compounds **8**, **15**, **9**, **12**, **2c**, and **2e** (Table I) increased heart rate and inotropic responses following field stimulation. The minimal effective dose for these compounds was 20 μg/L. Compounds **2f**, **2i**, and **2j** increased resting heart rate in doses of 50 μg/L. With these agents there was no increase in the inotropic responses. The very weak inotropic response reported by Tuttle and Mills[7] for *N*-isopropyl-α-methyldopamine (**2a**) was not observed here. The influence of the compounds on heart rate and blood pressure was evaluated in ten dogs anesthetized with sodium

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