pharmacophoric conformations. In comparing the mode of binding of various narcotic analgesics, one must consider not only the geometric disposition of pharmacophoric moieties but also take into account the role played by other groups which are not deemed essential for activity. If quite a different pattern of contributions to drug–receptor binding are made by various configurationally related analgesic molecules, the conclusions drawn from the three-point interaction concept to rationalize configurational selectivity of receptors may not necessarily be valid.

Acknowledgment.—The author gratefully acknowledges the support of this project by Public Health Service Grant NB 05192, from the National Institute of Neurological Diseases and Blindness.

Stereochemical Factors Related to the Potency of Anticholinergic Psychotomimetic Drugs

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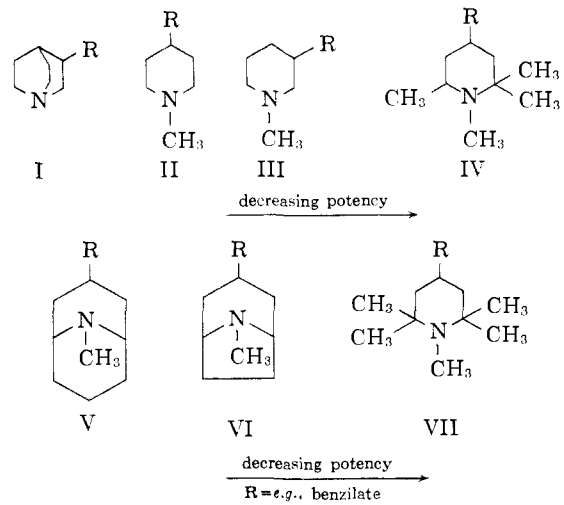
Received March 23, 1965

A group of glycolate esters of heterocyclic amino alcohols have been examined from the point of view of stereochemistry in an effort to correlate pharmacological action with molecular configuration. The examination was confined to the properties of the heterocyclic amino group and was conducted with respect to the psychotomimetic properties of the drugs. An important factor for psychotomimetic potency was the availability of the electron pair on nitrogen, which, presumably, must combine with an electrophilic center of the biological receptor site. Conformational factors were important insofar as they contributed to 1,3-diaxial interference by axial hydrogen atoms. Intramolecular interactions involving the nonbonded electron pair on nitrogen were believed to diminish potency.

Considerable interest has been focussed on the structure–activity relationships of substituted glycolate esters of heterocyclic amino alcohols which possess marked psychotogenic (*i.e.*, psychotomimetic) properties.[1,2] Previous studies were devoted largely to the piperidyl and pyrrolidyl esters, with emphasis on variation in the acid moiety of the esters. Since it was known that variations in the type of heterocyclic amino alcohol resulted in striking differences in psychotomimetic effectiveness, an opportunity was at hand to examine the possible role of the amine moiety in the pharmacological action of this series of drugs.



Pharmacology.—The drugs included in this study were evaluated for their anticholinergic potency and for their effect on those parameters of behavior which are believed to be related to the psychotomimetic action of the agents in humans. A measurement of hyperactivity in rats has been found to be a simple and effective means of evaluating the over-all action of the drugs upon the central nervous system.[1,2] A more direct measurement of the drugs' disturbance of higher central nervous function can be made by means of the swim maze and "peek" tests.[3,4] A description of these tests and their reliability in predicting the psychotomimetic action of the glycolate esters in humans has been described in detail elsewhere.[1,2] Briefly the swim maze consists of a maze which contains water in which a mouse is compelled to swim in order to escape drowning; the more centrally active drugs produce a greater number of errors in performance. The "peek" test was developed by Kosman[4] as a means of quantitating peculiar head-bobbing and head-swaying movements associated with the centrally active glycolate esters,[2] and although the significance of this test in determining the behavioral aberrations of the drugs is not too well understood, it has proved to be extremely effective in predicting psychotomimetic potency in humans. The ability of the drugs to block the acetylcholine-induced contraction of the isolated rabbit ileum was taken as a measure of anticholinergic potency.[5]

(1) L. G. Abood and J. H. Biel *Intern. Rev. Neurobiol.*, **4**, 217 (1962).
(2) L. G. Abood, A. Ostfeld, and J. H. Biel, *Arch. intern. pharmacodyn.* **120**, 186 (1959).
(3) M. E. Kosman, *Proc. Soc. Exptl. Biol. Med.*, **115**, 728 (1964).
(4) M. E. Kosman, *ibid.*, in press.
(5) H. C. Chang and J. H. Gaddum, *J. Physiol.*, **79**, 255 (1933).

Chemistry.—Inasmuch as it would be highly improbable for any of the glycolate esters to exhibit a mode of action on the molecular level different from the others, a rationalization of this mode of action may be attained by a consideration of the physicochemical properties of the most potent drug. It is readily apparent upon examination of the structures of the amino alcohols that the most potent of the esters (I) has an amino alcohol group, *viz.*, 3-(±)-quinuclidinol, which is a rigid structure formally related to the "boat" form of cyclohexane. The atoms making up this bridged, bicyclic ring are incapable of changing their relative positions *via* rotation about the axes of the bonds involved in ring formation.

Since the acyl portion of the ester and the nonbonded pair of electrons of the amino group are directed away from each other (because of the rigidity of this structure), the possibility of intramolecular hydrogen bonding, chelation, and similar neighboring-group, electronic interactions becomes remote. It can, therefore, be concluded that involvement of the electron-pair on nitrogen in these stated intramolecular interactions does not play a significant role in the mode of action of these drugs. Indeed, the occurrence of such intramolecular interactions in the glycolate esters of the other amino alcohols probably detracts from their psychotogenic efficacy.

TABLE I

BEHAVIORAL AND ANTICHOLINERGIC EFFECTS OF BENZILIC ACID ESTERS OF VARIOUS HETEROCYCLIC AMINO ALCOHOLS

Compd.	Activity cage[a]	Swim maze[b]	Peek test[c]	Anticholinergic ED_{50}[d]	BDI[e]
I	5.2	5.8	5.2	70	16.2
I-CH_3[f]	4.2	4.0	4.4	250	12.6
II	5.1	5.6	5.1	300	15.8
III	4.4	4.5	2.9	300	11.8
IV	4.0	4.4	4.0	150	12.4
V	4.4	3.7	3.5	350	11.6
VI	3.5	3.7	2.9	350	10.0
VI-benzyl[g]	1.5	2.6	2.7	1	6.8
VII	1.8	2.9	2.7	100	7.4
Saline	0.6	2.6	2.5		5.7

[a] Activity cage values (rats) are expressed as oscillations/3 × 10^{-2} min. [b] Swim maze values (mice) are in terms of errors on the fourth trial: ref. 3. [c] Peek test values (mice) are in terms of total number of peeks. The dose in all tests was 1 mg./kg. i.p. [d] Anticholinergic potency was expressed in terms of the ED_{50} *vs.* acetylcholine; *i.e.*, the dilution of the drug (parts per million) necessary to produce a 50% inhibition of acetylcholine-induced spasms. [e] Behavioral disturbance index (an arithmetical sum of activity cage, swim maze, and peek test values). [f] Methyl substituent on C-2. [g] Benzyl group in place of a methyl group on nitrogen.

It may be further readily inferred that the "boat" form type of geometry displayed by the bicyclooctane system of 3-(±)-quinuclidinol is not in itself necessary for psychotogenic activity. For although the esters of the other amino alcohols are capable of existing in "boat" form conformations, the extent to which this conformation would be present in the piperidyl esters (excluding the effect of intramolecular, electronic interactions) is exceedingly small.[6]

The most unique differentiating feature of the bridgehead nitrogen of 3-(±)-quinuclidinol is the accessibility of its nonbonded electron pair. Quinuclidine (VIII) has been found to react with methyl iodide over 50 times as rapidly as triethylamine.[7] The difference becomes even more pronounced if a larger, more hindered substrate is employed. Nucleophilic substitution of isopropyl iodide with quinuclidine is over 700 times as rapid as substitution with triethylamine.[7] The alkyl substituents on the nitrogen atom of quinuclidine are restrained, allowing very little steric interference with the substrate, whereas the alkyl groups of triethylamine, possessing a large degree of rotational freedom, diminish the availability of the electron pair and, consequently, the nucleophilicity of the nitrogen atom. The dependence of psychotogenic activity on the availability[8] of the electron pair can be demonstrated by

VIII IX X

comparing the activity of the other esters with the nucleophilicity of their amino groups. Although data on the relative rate of nucleophilic substitution are not available for the other cyclic amines under consideration, a meaningful estimate of their nucleophilicities may be obtained through the technique of conformational analysis.

The two most stable conformers of 1-methylpiperidine are the two "chair" forms in which the methyl group can be either equatorial (IX) or axial (X). Although the nonbonded electron pair on nitrogen usually has a steric requirement similar to a hydrogen atom, its steric requirement appears to be much larger in hydroxylic solvents by virtue of hydrogen bonding.[9]

Interaction of IX with an electrophilic center would be subjected to unfavorable 1,3-diaxial interference from the two axial hydrogen atoms located on C-3 and C-5 of the piperidine ring. Similar interaction of X would be free of such steric inhibition. This steric interference with the availability of the amino electron pair of IX would decrease its nucleophilicity compared to quinuclidine. However, inasmuch as the inversion of substituents on nitrogen is extremely rapid and since X is undoubtedly a much better nucleophile than IX, interaction with an electrophilic center may proceed almost completely by way of X.

This mixture of IX and X which constitutes 1-methylpiperidine may, therefore, be expected under similar environmental conditions to exhibit almost the same nucleophilic character as quinuclidine. In conformity with this assumption is the finding that the BDI (behavioral disturbance index) of the glycolate esters of 1-methyl-4-hydroxypiperidine (II) is almost identical with the BDI for the quinuclidyl esters.

The observation that the esters of 1-methyl-3-piperidinol (III) are generally less active than those of 1-methyl-4-piperidinol (II) can be explained by considering the greater ease with which the 3-isomer can undergo intramolecular, electronic interactions of the

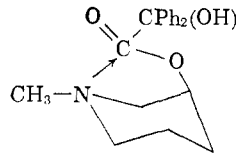
(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 207. At 25° the ratio of cyclohexane "chairs" to cyclohexane "boats" is approximately 1000:1.

(7) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 455 (1949).

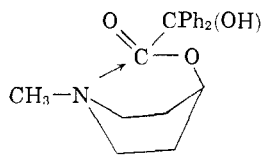
(8) Nucleophilicity generally connotes coordination of the attacking group with carbon. Since the mechanism of action of psychotogenics is not implied herein, the more general term, "availability of the electron pair," in employed.

(9) E. L. Eliel, personal communication.

type depicted by XI. Interaction of the carbonyl group of this ester with the nonbonded electron pair on nitrogen would not necessitate a "boat" form conformation (XII) as it would in the 4-isomer. Such intra-



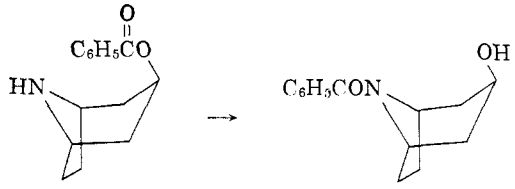
XI



XII

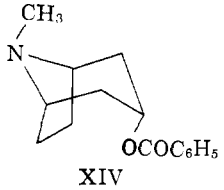
molecular electronic interactions could markedly decrease the possibility for intermolecular interaction of the electron pair on nitrogen with an electrophilic center. An illustration of this effect is the facile migration of the benzoyl group from oxygen to nitrogen in the benzoyl derivative of norpseudotropine (XIII).[10]

The glycolate esters of tropine (VI), 9-methyl-3-granatanol (V), and 1,2,2,6-tetramethyl-4-piperidinol (IV) show a large decrease of comparable magnitude in psychotogenic potency. The magnitude and direction of this change in potency correlate well with decreasing availability of the electron pair. Through an elegant

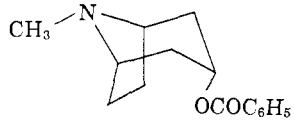


XIII

application of n.m.r. spectroscopy, Closs determined the equilibrium constants of the nitrogen inversion process for several tropane bases.[11] It was found that conformer XV predominates over conformer XIV by a ratio of 20:1 in atropine and benzoyltropine. Nevertheless, it has been reported by Fodor[12] that in nearly



XIV

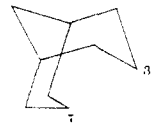


XV

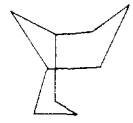
all cases tropane derivatives yield on quaternization exclusively that isomer in which the entering substituent is located on the same side of the piperidine ring as the ethylene bridge. Thus, it would seem that despite the predominance of conformer XV, its rate of reaction with an electrophilic center is negligible in comparison to conformer XIV. Presumably steric hindrance due to 1,3-diaxial interactions is involved, although the presence of a significant concentration of "boat" form cannot be precluded. The evidently more favorable approach by an electrophilic center to conformer XIV will, however, be offset by steric hindrance from the ethylene bridge hydrogens. This hindrance can lead to decreased availability of the electron pair on nitrogen.

(10) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).
(11) G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959).
(12) G. Fodor, *Tetrahedron*, **1**, 87 (1957); *Acta Chim. Acad. Sci. Hung.*, **5**, 379 (1955); *Experientia*, **11**, 129 (1955).

The two geometrical isomers of 9-methyl-3-granatanol each exist in primarily two conformations. The argument for this is that there is an intolerable transannular nonbonded interaction between the axial hydrogens at C-3 and C-7 (which would be about 1 Å. apart) in a "chair–chair" form of bicyclo[3.3.1]nonane (XVI).[13] The molecule must therefore exist in a "chair–boat" form (XVII). Since the 9-methyl-3-granatanol ring system is analogous to bicyclo[3.3.1]-

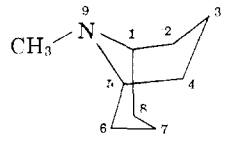


XVI



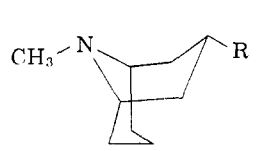
XVII

nonane, it also should exist preferentially in a "chair–boat" form. In addition the N-methyl group will be preferentially equatorial with respect to the "boat" form (XVIII) in order to avoid a further unfavorable, nonbonded interaction with hydrogens or substituents on C-3 or C-7. The foregoing conditions are met by conformers XIX and XX of the *endo* isomer and con-

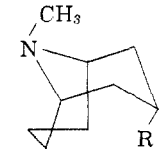


XVIII

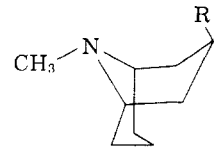
formers XXI and XXII of the *exo* isomer. Approach of an electrophilic center to the amino group electron



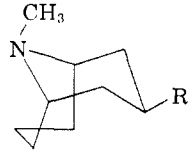
XIX



XX



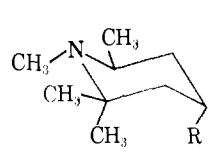
XXI



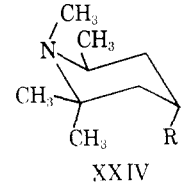
XXII

pair of these conformers would be highly hindered by 1,4-diaxial "bowsprit–flagpole" interactions. This hindrance evinces itself in the aforementioned diminished psychotogenic potency of the 9-methyl-3-granatanol esters (V).

The diminished efficacy of the ester of 1,2,2,6-tetramethyl-4-piperidinol (IV) also correlates well with decreased availability of the electron pair on nitrogen. The methyl group on C-6 should be equatorial in the predominant conformers (XXIII and XXIV).[14] It is apparent that there are associated with



XXIII

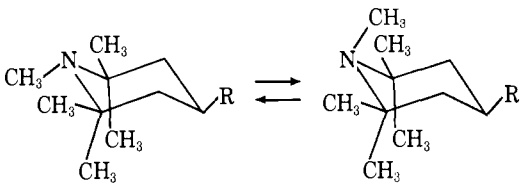


XXIV

(13) E. L. Eliel, ref. 6, p. 296.
(14) Only one of the geometrical isomers is shown.

the electron pair of conformer XXIII four 1,3-diaxial nonbonded interactions due to the hydrogens on C-3 and C-5 and the methyl substituents in the 2- and 6-positions. Since there are only three such interactions which are due to the methyl groups for XXIV, interaction with an electrophilic center may occur primarily in this somewhat less hindered conformational form.

Finally, the glycolate esters of 1,2,2,6,6-pentamethyl-4-piperidinol (VII), which are virtually devoid of psychotogenic activity, can be seen to have a highly hindered amino nitrogen. An approaching electrophilic center would be subjected to four 1,3-diaxial nonbonded interactions in each of the two possible



XXV XXVI

conformers (XXV and XXVI). As corroboration for the inaccessibility of the amino group of VII, it should be noted that 2,2,6,6-tetramethylpiperidine is alkylated in a very low yield even after prolonged heating with an excess of ethyl *p*-toluenesulfonate.[15] Quaternization can be expected to be even more difficult.

Although further refinements could be made regarding the nucleophilicities of these drugs, they would be unwarranted in view of the semiquantitative nature of the pharmacological assays. As an addendum, however, substituent groups on nitrogen larger than methyl will decrease nucleophilicity and should, therefore, decrease potency, as has been verified.[1] Replacement of the N-methyl group by hydrogen will promote rapid destruction of the drug *via* transfer of the acyl group to nitrogen to form an amide. It must be emphasized that although the drugs were differentiated by their degree of nucleophilicity, it remains to be demonstrated whether an alkylation step is essential for their pharmacological action.

(15) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5444 (1957).

Compounds Affecting the Central Nervous System. I. 4-Piperidones and Related Compounds

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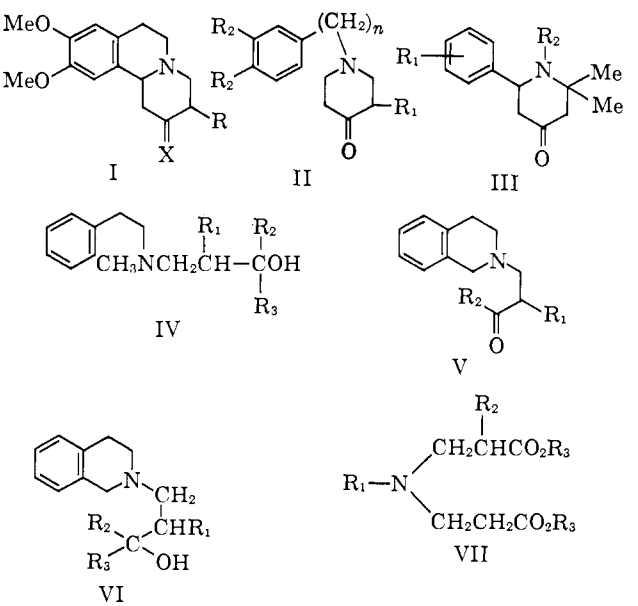
Received February 23, 1965

1-Arylalkyl-3-alkyl-4-piperidones, the corresponding secondary alcohols and their esters, and 2,2-dimethyl-6-aryl-4-piperidones (III) were prepared as modifications of 9,10-dimethoxy-3-isobutyl-2-oxo-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine for pharmacological testing. Other related structures, IV–VI, were also synthesized. None of these compounds possessed reserpine-like activity, but structures III and IV had a combination of stimulant and depressant effects on the central nervous system.

Reserpine possesses therapeutically useful sedative and antihypertensive properties,[1] but major modifications of the pentacyclic nucleus of the alkaloid destroys this biological activity.[2] Kralt, *et al.*,[3] suggested that the pharmacological properties of reserpine are determined by three chemical groups in the molecule: (1) the β-indolylethylamine group, (2) the tertiary nitrogen atom, and (3) the alcohol group esterified by trimethoxybenzoic acid. Other investigators have shown that activity does not reside specifically in the trimethoxybenzoyl ester group and that trimethoxybenzoic acid may be replaced by other acids[4] or even by alkyl.[5] Brossi, *et al.*,[6,7] during synthetic studies in the emetine field, discovered reserpine-like activity in the benzoquinolizines I (X = =O, or H and OH), thus indicating that the β-indolylethylamine



I II III

IV V

VI VII

residue can be replaced by arylethylamine. The noteworthy features common to both structures appear to be an oxygen-containing function, a basic tertiary nitrogen atom which is sterically shielded, and an aromatic ring system. Tetrabenazine® (I, R =

(1) R. E. Woodson, Jr., H. W. Yangken, E. Schittler, and J. A. Schneider, "*Rauwolfia:* Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, Mass., 1957.

(2) M. A. Karim, *Pakistan J. Sci.*, **12**, 119 (1960).

(3) T. Kralt, W. J. Asma, H. H. Haeck, and D. H. Moed, *Rec. trav. chim.*, **80**, 313 (1961).

(4) R. A. Lucas, M. E. Kuehne, M. J. Ceglowksi, R. L. Dziemian, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959).

(5) M. M. Robison, R. A. Lucas, H. B. MacPhillamy, W. Barrett, and A. J. Plummer, *Experientia*, **17**, 14 (1961).

(6) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958).

(7) A. Brossi, L. H. Chopard-dit-Jean, and O. Schnider, *ibid.*, **41**, 1793 (1958).