3-Formyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (10). Procedure F.—A stirred mixture of Ac_2O (9.5 ml) and 98% formic acid (4.0 ml) was allowed to stand at 25° for 1 hr, cooled in an ice bath, and treated with 5.6 g (0.03 mole) of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole. As the amine went into solution, a second precipitate formed. Ether (25 ml) was added to this mixture which was left at room temperature under N_2 for 18 hr and poured into H_2O. The solid was collected, washed with H_2O, and dried *in vacuo* to give 6.3 g of crude product, mp 220–221.5°. Recrystallization of this material from MeOH–EtOAc yielded in three crops, 5.7 g (89%), of **10**. The infrared spectrum showed C=O, 1655, 1645 cm^{-1}.

3-Methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (9). Procedure G.—To a stirred suspension of $LiAlH_4$ (1.0 g) in ice-cold THF (100 ml) was added **10** (1.0 g, 0.005 mole), and the mixture was refluxed under N_2 for 18 hr, cooled in an ice bath, and treated successively with H_2O (1 ml), 15% NaOH solution (1 ml), and H_2O (3 ml). The resulting mixture was stirred for 1 hr and filtered. Concentration of the filtrate (reduced pressure) gave a solid which was recrystallized from EtOAc to yield 0.85 g (91.3%) of **9**, mp 162–166°.

Acknowledgment.—The authors are indebted to Dr. G. S. Fonken and his associates for generous supplies of starting material, to Dr. W. A. Struck and his associates for physical and analytical data, and to Mr. D. B. Hooker, Mr. J. R. Greene, Mr. H. J. Triezenberg, Mr. R. A. Zandt, Mr. A. P. Tazelaar, and Mr. R. Russell for laboratory assistance.

Bisquaternary Ammonium Indolines and Perhydroindoles in Ganglionic Blockade[1]

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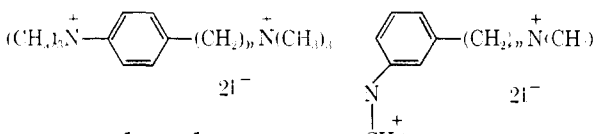
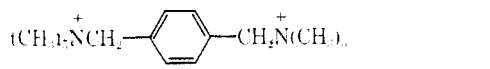
The indoline derivatives, 1-methyl-6-dimethylaminoindoline dimethiodide (**4**) and 1-methyl-5-dimethylaminoindoline dimethiodide (**5**), were synthesized by methylation of 6-aminoindoline and 5-aminoindoline. 1-Methyl-6-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (**7**) and 1-methyl-6-*anti*-dimethylamino-*cis*-octahydroindole dimethiodide (**6**) were obtained by reduction of 6-aminoindoline to the corresponding octahydro compounds followed by reductive methylation and quaternization. 1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (**8**) was synthesized in a similar manner from 5-aminoindoline. Preliminary biological results on the guinea pig ileum indicate that dimethiodide **7**, with only three carbons separating the onium heads, is as active as hexamethonium.

The discovery by Paton and co-workers[2] of potent ganglionic-blocking activity in the bisquaternary alkyls was followed rapidly by investigations into the nature of the blockade, in particular the effect of distance between the onium heads on activity. Compounds of the general structure **1** and **2** are reported to have considerable activity, particularly **1b** which is



1a, $n = 1$
b, $n = 2$
c, $n = 3$

2a, $n = 1$
b, $n = 2$
c, $n = 3$



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four times as active as hexamethonium on the isolated guinea pig ileum.[3,4] However, the isomeric bisquaternary *p*-xylylene **3** has been found to be inactive.[5] Reduction of the benzene ring of **1b** to the cyclohexyl analogs afforded the opportunity of examining the geometric isomers. One of the isomers was reported to be as active a ganglion-blocking agent as the corresponding phenyl analog **1b**, whereas the other isomer was only one-tenth as active; the author failed to assign the isomeric structure.[6]

The dependence of activity on chain length in the polymethylene bisoniums and in **1** and **2** was interpreted by assuming that the blocking agent made simultaneous contact with two anionic receptor groups and that the length of the most active compounds was a measure of the interreceptor distance.[6,7]

Gill[8] has calculated the interquaternary distance probability distributions for the polymethylene compounds (n = 4–8) and for **1a**–**c**. From these calculations for the most active members of each series (6–8 Å) it was assumed that the interreceptor distance would lie within these limits. The qualitative agreement between these calculated and observed activities of the individual members of the two series of compounds was taken as proof for the validity of the "two-point contact" hypothesis. Gill's[8] explanation for the inactivity of **1a** and **3** is that there is not a range of interquaternary distances in these compounds, but this

(1) This work was generously supported in part by the University of Kansas Graduate School and by Research Grant 1K3-CA 10739 of the National Institutes of Health, U. S. Public Health Service.

(2)(a) W. D. M. Paton and E. J. Zaimis, *Brit. J. Pharmacol.*, **4**, 381 (1949); **6**, 115 (1951); (b) W. D. M. Paton and W. L. M. Perry, *J. Physiol. (London)*, **119**, 43 (1953).

(3) J. N. Ashley and W. J. Leeds, *J. Chem. Soc.*, 2706 (1957).

(4) R. Wien and D. F. J. Mason, *Brit. J. Pharmacol.*, **8**, 306 (1953).

(5) F. R. Domer and F. W. Schueler, *Arch. Intern. Pharmacodyn.*, **114**, 217 (1958).

(6) R. Wien, *ibid.*, **97**, 395 (1954).

(7) F. W. Schueler, *ibid.*, **93**, 417 (1953); **95**, 376 (1953).

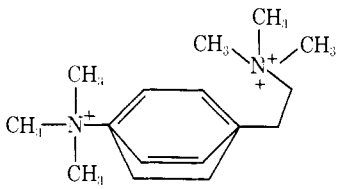
(8)(a) E. W. Gill, *Proc. Roy. Soc. (London)*, **B150**, 381 (1959); (b) J. Fakstorp, J. C. A. Pedersen, R. Poulsen, and M. Schilling, *Acta. Pharmacol. Toxicol.*, **13**, 52 (1957).

distance is fixed at the single value of 6.4 A for **1a** and 6.82 and 7.35 A for **3**.

The two-point contact hypothesis, however, fails to account for the activity of the unsymmetric, bisquaternary ammonium compounds.[9] Cavallito and Gray[10] proposed that in addition to the bisquaternary, ion–receptor site complex in the two-point contact hypothesis, an ion–site complex in which both onium heads of a bisquaternary ammonium are attracted to the same negative site is also possible. Furthermore, there will be a definite preference for two-point contact only when the geometry of the bisquaternary ammonium ion and the site provide a uniquely favorable situation.

The failure of Gill's two-point hypothesis to account for the inactivity of the benzyl compound, **1a**, the xylylene compound, **3**, and other examples, combined with flexibility and hence uncertainty of the "shape" of hexamethonium and similar analogs at the receptor, prompted examination of another possible conformation for the "active" structure, bisonium compounds. Furthermore, when the high activity exhibited in the unsymmetrical short-chain compounds is considered, some modification of both the two-point and one-point theories on the nature of ganglionic blockade is desirable.

It is proposed that ganglionic blocking activity of **1b** is exerted in the conformation where the trimethylammonium group of the side chain is over the flat surface of the phenyl ring. Energy to maintain such a



1b, active conformation

conformation can be derived from the attraction between the π electrons of the phenyl ring and the positively charged nitrogen of the side chain. This assumption is strengthened by the fact that **3**, which has nearly the same extended-form, interquaternary distance (~7 A) as **1b**, but cannot assume the proposed folded conformation (~6 A), is inactive (Table I).

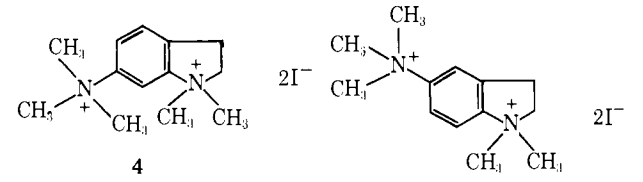
Evidence in support of such a conformation for **1b** is provided by the work of Oki and Iwamura[11] and others[12] on the intramolecular interaction between the hydroxyl group and π electrons in phenylalkanols as determined from the fundamental O–H stretching absorption bands. The molecular structures of benzyl alcohol and 2-phenylethanol are formulated as the internally interacting OH···π-bonded structure. Similar conclusions were reached by Goldman and Crisler[13] after examining the O–H stretching absorption of 2-phenylethanol.

TABLE I

Compd	n	Interquaternary distance, A: Extended form	Folded form
1a	2	7.6	6.0
b	3	8.6	4.8
2a	2	6.8	5.8
b	3	7.4	4.8
3		6.8, 7.3	6.8, 7.3

The lower ganglionic blocking activity of **2b** (about half that of **1b**) could be due to lesser probability of a folded conformation. Such a conformation in **2b** would bring two cations much nearer than in **1b** causing repulsion. The reason for very low ganglionic blocking activity of **2c** could be the same as that for the very small interaction between the hydroxyl group and the π electrons in 3-phenylpropanol.[11] If this were not the reason for low activity of **2c** and if interquaternary distance and flexibility of the molecule were the only requirements for high activity, then the *meta* compound **2c** and the *para* compound **1b** should have about the same activity, as both have nearly the same interquaternary distance and are flexible.

To investigate further the possibility that **1b** exists at the receptor in the folded conformation in which the flexible quaternary group is attracted to and folded over the ring and, further, that the optimum distance between the onium heads for highest ganglionic blocking activity does not necessarily correspond to the distances in the extended form, compounds **4**–**8** were synthesized.



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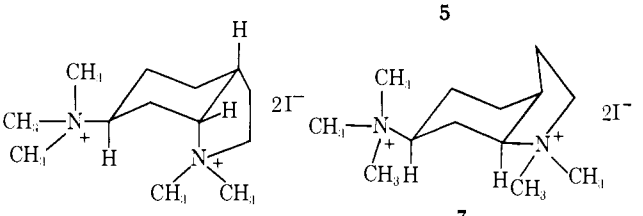

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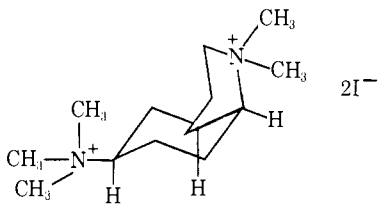

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The synthesis of the indolines **4** and **5** was accomplished by selective nitration of indoline according to Terent'ev and co-workers,[14] reduction of the resulting nitro compounds to 6-aminoindoline (**9**) and 5-aminoindoline (**13**), treatment with dimethyl sulfate, and conversion to the respective dimethiodides **4** and **5**.

(9)(a) A. J. Plumer, J. H. Trapold, J. A. Schneider, R. A. Maxwell, and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955); (b) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner, and C. J. Cavillito, *J. Am. Chem. Soc.*, **77**, 3536 (1955); (c) T. B. O'Dell, C. Luna, and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **114**, 317 (1955); (d) A. P. Gray, E. E. Spinner, D. C. Schlieper, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 3533 (1955); (e) W. L. Archer, C. J. Cavallito, and A. P. Gray, *ibid.*, **78**, 1227 (1956); (f) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *ibid.*, **79**, 3805 (1957); (g) T. B. O'Dell and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **120**, 438 (1957).

(10) C. J. Cavallito and A. P. Gray, *Progr. Drug Res.*, **2**, 186 (1960).

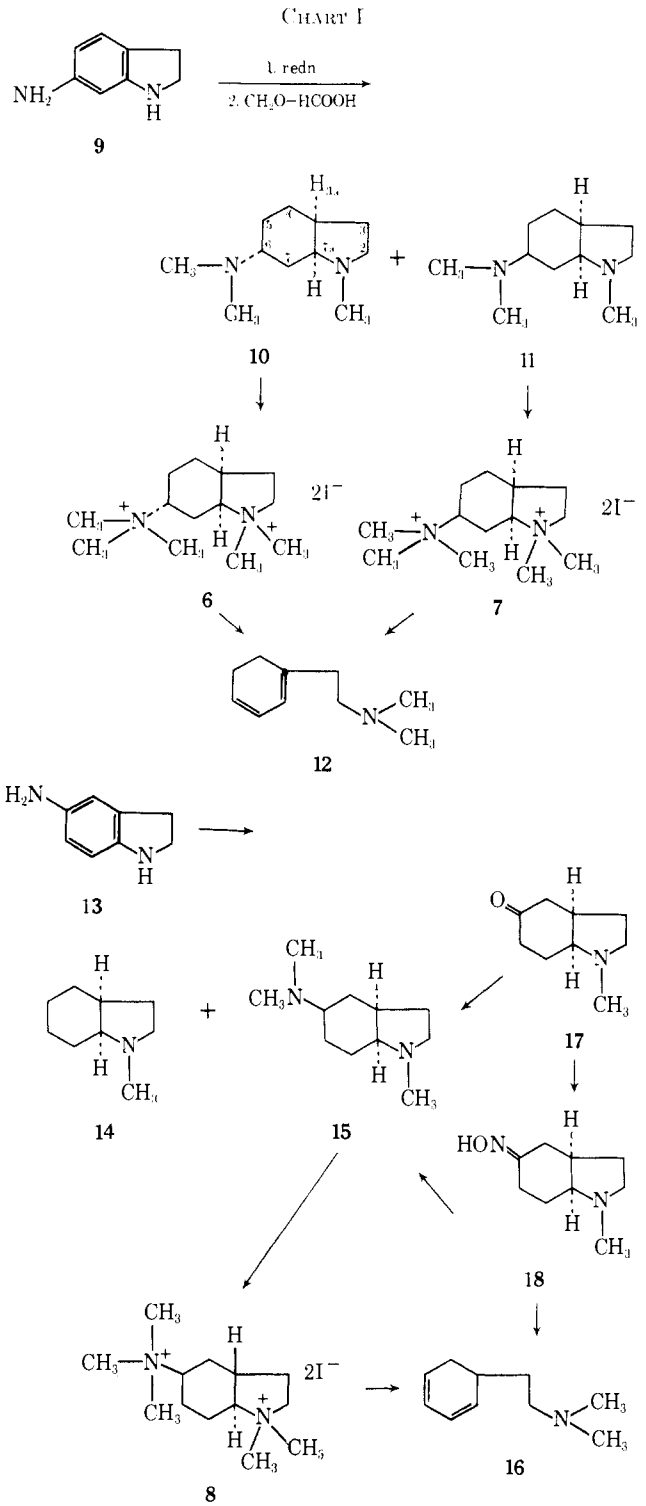
(11) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, **32**, 950, 1135 (1959).

(12) See M. Tichy, *Adran. Org. Chem.* **5**, 157 (1965).

(13) I. M. Goldman and J. L. Crisler, *J. Org. Chem.*, **23**, 751 (1958).

(14) A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *J. Gen. Chem. USSR*, **29**, 2504 (1959).

CHART I



Since attempts to synthesize the corresponding trimethylaminoindolines were unsuccessful the perhydroindoles were prepared by catalytic reduction of the aminoindolines. High-pressure reduction of 6-aminoindoline (**9**) gave an unstable oil that was reductively methylated to give a mixture containing two major components (Chart I). One compound was assigned the *anti*-amino-*cis*-ring structure (**10**, 1-methyl-6-*anti*-dimethylamino-*cis*-octahydroindole), the other component the *syn*-amino-*cis*-ring structure (**11**, 1-methyl-6-*syn*-dimethylamino-*cis*-octahydroindole).[15]

(15) The stereochemistry of octahydroindole may be compared to that of hydrindane, since the normal angle of carbon–nitrogen–carbon valencies is known to be virtually identical with that of the carbon bonds in the unstrained cyclopentane ring. Furthermore, *trans*-hydrindane is strained, the torsional angle of 72° of the *trans*-1,2 bonds in the five-membered ring being larger than the normal torsional angle of 60° in a six-membered ring [K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959)]. In *cis*-hydrindane the strain is much less, since the torsional angle of the *cis* bonds (48°) can be readily accommodated in the six-membered ring by a slight flattening [E. L. Eliel and C. Pillar, *ibid.*, **77**, 3600 (1955); R. Granger, P. F. G. Nau, J. Nau, and C. Francois, *Bull. Soc. Chim. France*, 196 (1962)]. Accordingly, on this analogy it is to be expected that the *cis* form would be strainless and readily formed and that the *trans* form, a strained configuration, would be produced in relatively small amounts during complete hydrogenation in indoline.

King and co-workers and others[16] reported that catalytic hydrogenation of indole gave only *cis*-octahydroindole; the ring junction was shown to be *cis* and the disposition of the nitrogen to be axial by Hofmann degradation. Thus, it was assumed that the reduction gave a mixture of *anti*-amino and *syn*-amino compounds with the *cis* ring junction.

Conversion to the dimethiodides **6** and **7** followed by Hofmann elimination in both compounds afforded the dielimination product **12**, which was characterized by nmr data and by reduction to 2-dimethylaminoethylcyclohexane. In accord with the findings of King and co-workers[16] on the Hofmann degradation, the ring fusion was assigned *cis*. Attempts to isolate the product of monoelimination in the Hofmann degradation of **6** or **7** were unsuccessful even when the reaction was incomplete.

Nmr spectroscopy was used to distinguish between the two *cis*-ring forms, **10a** and **11a** (Chart II). The nmr spectrum of **10a** (*anti*) shows a sextet for one proton about 3.16 ppm. Comparable, low-field absorption was absent in the nmr spectrum of **11a** (*syn*). As a general rule, it has been established for a wide variety of six-membered ring systems that axial, ring protons absorb at higher field than do their epimeric equatorial counterparts.[17] From these considerations it would be expected that the axial, angular hydrogen at C-7a in **11a** would absorb at higher field than the corresponding equatorial angular proton in **10a**. The assignment of the *anti* structure (**10a**) to the compound with the signal at 3.16 ppm is, therefore, consistent with the above considerations. According to the Karplus equation the coupling constants for protons on adjacent sp^3 carbons is estimated to be between 1.8 and 2.5 cps, although the observed range is 1–7 cps.[18] Dreiding models of the *anti-cis* compound **10a**, in analogy to *cis*-hydrindane, show the six-membered ring to be distorted to the half-chair form. The dihedral angles of the C-7a equatorial proton with the C-3a axial proton is estimated from models to be $\simeq 40°$, with the C-7 axial proton $\phi \simeq 45°$, and with the C-7 equatorial proton $\phi \simeq 75°$. The respective coupling constants would then be about 6 and 1 cps. In the nmr spectrum, the C-7a equatorial angular proton in **10a** couples with the fields of axial protons at C-3a and C-7 with apparent coupling constants of 8 cps and of the equatorial

(16) (a) F. F. King, D. Povey, K. Mason, and R. L. Whitehead, *J. Chem. Soc.*, 250 (1953); (b) F. F. King, J. A. Barltrop, and R. J. Wally, *ibid.*, 277 (1945); (c) A. Bertho and J. F. Schmidt, *Ber.*, **97**, 3284 (1964); (d) M. A. Volodina, G. V. Kiryushkina, and A. P. Terent'ev, *Dokl. Akad. Nauk SSSR*, **162**, 90 (1965); *Chem. Abstr.*, **63**, 5583*f* (1966).

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy," The Macmillan Co., New York, N. Y., 1959, p 115.

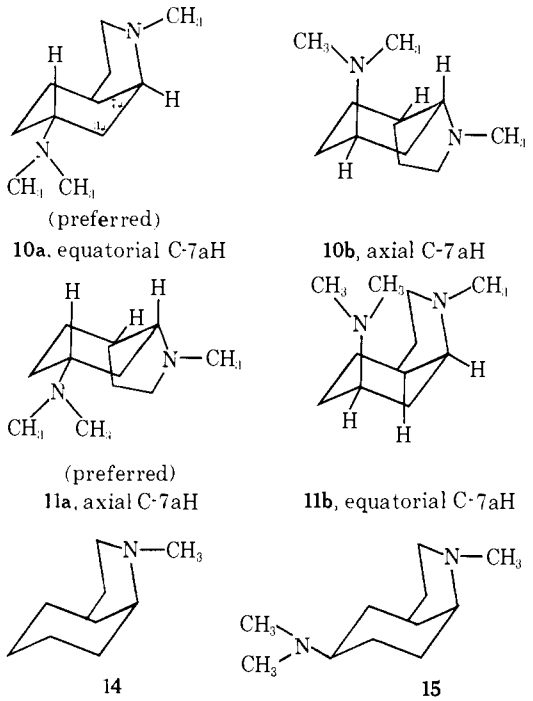
(18) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); (c) M. Karplus, *ibid.*, **85**, 2870 (1963); (d) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 50.

proton at C-7 with an apparent coupling constant of 2.5 cps.

After catalytic reduction of 5-aminoindoline (**13**) and subsequent reductive methylation, two major components were isolated; 1-methyl-*cis*-octahydroindole (**14**) and the desired 1-methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (**15**). The former compound, the result of reductive deamination,[19] was characterized as the previously reported[16] 1-methyl-*cis*-octahydroindole. From the nmr spectrum, similar to **10a**, structure **14** was assigned the axial nitrogen conformation, since a low-field multiplet at 3.13 ppm with a peak half-width of 18 cps is consistent with coupling of the equatorial C-7a proton in a distorted half-chair form.

The nmr spectrum of **15**, examined at both 60 and 100 Mc, again showed a 3.16-ppm sextet for the equatorial C-7a proton with coupling constants of 8 and 2.5 cps. The preferred conformation for **15** is shown in Chart II. Treatment of **15** with methyl iodide gave 1-

CHART II



methyl-5-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (**8**). Hoffman degradation of **8** afforded the diene **16**, characterized by nmr and reduction.

In an attempt to prepare the 5-*anti* isomer and to confirm the structure of the 5-*syn* isomers **8** and **15**, an alternate route of synthesis was followed. Reduction of 5-hydroxyindole under conditions used by King and co-workers[16] followed by chromium trioxide oxidation gave 1-methyl-5-oxo-*cis*-octahydroindole (**17**). The nmr spectrum of **17** had an unresolved triplet at 3.05 ppm assigned to the equatorial C-7a proton with a band half-width of 15 cps. Formation of the oxime **18**, reduction, and reductive methylation gave the *syn* compound **15** (equatorial 5-dimethylamino). Compound **15** was also the product of the Leuckart reaction on the ketone **17**. As catalytic reduction of oximes is reported to yield the axial isomer in aminocholestanes,[20] this procedure was attempted for the synthesis of the 5-*anti* compound. Reduction of **18** followed by reductive methylation gave only the 5-*syn* compound **15**; none of the 5-*anti* compound could be detected.

Biological Results.—The ganglionic blocking activity of **4**–**8** was compared to reference compounds **1b** and **2b**[21] on the isolated guinea pig ileum.[22] All of the compounds, including **1b** and **2b**, inhibited contractions produced by the specific ganglionic stimulant, nicotine, leaving mostly unaltered the effects of acetylcholine and histamine. The preparation readily differentiated twofold increases in the dose, and doses of 25–100 μg caused partial to complete inhibition of the reflex. The recovery of the preparation was slow with compounds **1b**, **2b**, **6**, and **7** but quick with **8**. Compounds **1b**, **2b**, **4**, **5**, and **6** appeared to have cumulative action.

Table II shows the ganglionic blocking activity of these compounds expressed as equipotent, molar ratio relative to **1b**.

TABLE II
GANGLIONIC BLOCKING ACTIVITY

Compd	Intraquaternary distance, A: Extended	Folded	Equipotent molar ratio relative to **1b**
1b	7.6	5.4	1
2b	6.8	4.6	2
4	4.8	...	100
5	5.5	...	65
6	4.3	...	32
7	5.0	...	4
8	5.1	...	75

The most active compound **7**, the equipotent molar ratio of which is 4, is as active as hexamethonium; it is reported that the equipotent molar ratio of hexamethonium relative to **1b** is 3.3. Compounds **4** and **5** are relatively inactive.

On the basis of either a two-point or one-point site of attachment, it is reasonable to assume that **4** and **5**, having the ammonium heads in the same plane, would have little or no activity. Structures **6**–**8** represent three of the possible folded forms proposed for **1b** and **2b** wherein the onium heads are at approximately the same minimum distance. Compound **6**, having an intraquaternary distance of about 4.3 A, has relatively low activity. The intraquaternary distances in **7** and **8** are approximately the same (~5 A), yet **7**, equipotent with hexamethonium while separated by only three carbons, is 20 times more active than **8**. Examination of Dreiding models suggests that the approach of **8** to the receptor from the side or top is more sterically hindered than the approach of **7**.

From these results it is suggested that for potent ganglionic blockade the optimum distance between the quaternary heads is not the maximum or statistically probable distance but rather some value in the range of 4.5–5.5 A. Steric factors may play a dominant role in drug–receptor action at the ganglionic receptor.

(19) (a) F. Balas and P. Sevcenco, *Collection Czech. Chem. Commun.*, **3**, 171 (1931); *Chem. Abstr.*, **25**, 2990 (1931); (b) A. E. Barkdoll, D. C. England, H. W. Gray, W. Kirk, and G. M. Whitman, *J. Am. Chem. Soc.*, **75**, 1156 (1953).

(20) (a) C. W. Shoppee, D. E. Evans, H. Richards, and G. Summers, *J. Chem. Soc.*, 1649 (1956); (b) C. W. Shoppee, R. Cremlyn, D. Evans, and G. Summers, *ibid.*, 4364 (1957).

(21) Synthesized in these laboratories according to ref 3 and 4.

(22) R. Wien and D. F. J. Mason, *Brit. J. Pharmacol.*, **6**, 611 (1951).

Experimental Section

Melting points, obtained on a Thomas–Hoover Unimelt apparatus, are corrected. Infrared spectra were recorded on Beckman IR 5, 8, and 10 spectrophotometers, nmr spectra on Varian Associates Model A-60 and HA 100 spectrometers. Ultraviolet spectra were recorded on a Beckman DB spectrophotometer. Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England; Midwest Microlab, Indianapolis, Indiana; and Alfred Bernhard, Mühlheim, Germany. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

1-Methyl-6-dimethylaminoindoline Dimethosulfate and Dimethiodide (4).—A mixture of 0.8 g (0.006 mole) of **9**,[6] 2.5 g (0.03 mole) of $NaHCO_3$, 3.1 g (0.024 mole) of Me_2SO_4, and 10 ml of H_2O was stirred for 2 hr at 10° under N_2. The bath was removed, and the solution was stirred at room temperature for 3 hr, then gradually heated to 50° (stirring) until the evolution of CO_2 stopped. After cooling, the solution was made strongly alkaline with NaOH solution and extracted four times with 20-ml portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and evaporated to dryness giving 0.4 g of thick oil which crystallized on treatment with dry Et_2O. Recrystallization from Me_2CO–Et_2O gave the dimethosulfate as white needles, mp 158–159°. *Anal.* ($C_{13}H_{22}N_2O_4S$) C, H, N.

The dimethosulfate was dissolved in H_2O, taken to pH 5 (HCl), and treated with excess saturated KI. Cooling afforded 0.42 g of lemon yellow solid. Treatment of the filtrate with concentrated NaOH yielded an additional 0.8 g (total yield of **4**, 44%). Recrystallization from EtOH afforded colorless needles, mp 224–225° dec. *Anal.* ($C_{13}H_{22}I_2N_2$) C, H, N; I: calcd, 55.16; found, 54.69.

1-Methyl-5-dimethylaminoindoline Dimethiodide (5).—To a suspension of 0.4 g (0.003 mole) of 5-aminoindoline[14] and 1.76 g (0.02 mole) of $NaHCO_3$ in 5 ml of H_2O was added 2.3 g (0.02 mole) of Me_2SO_4 in small portions with vigorous stirring (ice-bath temperature, N_2 atmosphere). The mixture was stirred at room temperature for 30 min and at 45° for 30 min. The mixture was filtered, and the filtrate was acidified to pH 5 with HCl. Treatment of the solution with excess saturated KI and cooling afforded 0.55 g of light white solid. Treatment of the filtrate from above with concentrated NaOH yielded 0.31 g, 63%. Recrystallization from EtOH yielded a white, amorphous solid, mp 259.5–261.5°. *Anal.* ($C_{13}H_{22}I_2N_2$) C, H, I, N.

1-Methyl-6-*syn*-dimethylamino-*cis*-octahydroindole (11) and 1-Methyl-6-*anti*-dimethylamino-*cis*-octahydroindole (10).—6-Aminoindoline[14] (**9**) (8 g, 0.06 mole) was dissolved in 75 ml of purified dioxane. The solution was hydrogenated at 45.7 kg/cm² and 90–100° for 24 hr using 0.35 g of RuO_2 (Engelhard Industries Inc.). The cooled suspension was filtered through a layer of Celite and evaporated (vacuum) to give a dark brown liquid. Distillation at 80–128° (10 mm) under N_2 afforded 5.5 g (66%) of a mixture as a colorless liquid.

With vigorous stirring, 5.6 g (0.04 mole) of this mixture was added dropwise to 15.7 g (0.3 mole) of 88% HCO_2H at 5° followed by 14.6 g (0.18 mole) of 37% CH_2O at 5–10°. The mixture was heated until evolution of CO_2 became vigorous, whereupon heating was discontinued. When the exothermic reaction was completed, the mixture was heated for 6 hr at 100–110° and cooled to 50°; 75 ml of 4 *N* HCl was added. Evaporation of the solution (vacuum) removed excess HCO_2H and CH_2O affording a thick brown residue. Treatment of the residue with 40 ml of 18 *N* NaOH afforded a golden yellow oil which was extracted with Et_2O. The Et_2O was dried ($MgSO_4$) and evaporated to give 8 g (73%) of a mixture of **10** and **11** as a colorless, mobile liquid. Tlc of the liquid on alumina using 10% MeOH in 1:1 Et_2O–Skelly B indicated two major components which were separated on a neutral, alumina column (Woelm, activity grade I, 500 g) prepared in Skelly B. The eluent used was 0.5% MeOH in 1:1 Et_2O–Skelly B; 50-ml fractions were collected. The column chromatography was followed by tlc.

The fractions containing **10** were mixed and evaporated to yield 1.9 g. Distillation afforded a colorless liquid, bp 105–106° (17 mm), $n^{20}D$ 1.4844. *Anal.* ($C_{11}H_{22}N_2$) C, H, N.

The fractions containing **11** were combined and found by tlc to be contaminated with **10**. The impure oil (1.8 g) was distilled twice to give the product **11**, bp 116° (15 mm), $n^{20}D$ 1.4836. The nmr spectrum of **10** had a sextet centered at 3.16 ppm for the equatorial C-7a proton (band half-width 18 cps), that of **11** had complex signals at a higher field.

1-Methyl-6-*anti*-dimethylamino-*cis*-octahydroindole Dimethiodide (6).—A solution of 0.4 g of **10** in 10 ml of dry Me_2CO was refluxed with excess MeI for 3 hr. Filtration gave 0.25 g (quantitative) of **6**. Recrystallization from absolute EtOH afforded white needles, mp 209.5–211°. *Anal.* ($C_{13}H_{28}I_2N_2$) C, H, N; I: calcd, 54.44; found, 55.0.

1-Methyl-6-*syn*-dimethylamino-*cis*-octahydroindole dimethiodide (7) was prepared according to the method used for **6** and crystallized from Me_2CO–EtOH–Et_2O as small white flakes, mp 247–250° dec. *Anal.* ($C_{13}H_{28}I_2N_2$) C, H, I, N.

Hofmann Degradation of 6 and 7 to Give 1-(2-Dimethylaminoethyl)-1,2,3,4-cyclohexadiene (12).—A solution of 2.4 g (0.014 mole) of $AgNO_3$ in 20 ml of H_2O was heated to 85° and treated with an equally warm solution of 0.56 g (0.014 mole) of NaOH in 20 ml of H_2O. The precipitated Ag_2O was washed by decantation with five portions of hot H_2O. A solution of 2.6 g (0.0054 mole) of **6** in 10 ml of H_2O was added to the Ag_2O and stirred for 5 min. After filtering, the solid material was washed with 10 ml of H_2O, and the filtrate was evaporated at 40–50° (vacuum, N_2). The residue was decomposed at 110°, and the distillate was extracted with Et_2O, dried ($MgSO_4$), and filtered, and the solvent was removed to give 0.55 g (66%) of **12** as a colorless liquid, bp 87° (13 mm), $n^{20}D$ 1.4846, $\lambda_{max}^{95\%EtOH}$ 263 mμ (ε 5000). The nmr spectrum of **12** had a broad multiplet centered at 5.75 ppm for the three vinyl protons. *Anal.* ($C_{11}H_{17}N$) C, H, N.

The **methiodide**, recrystallized from Me_2CO–Et_2O, afforded white needles, mp 175–176°. *Anal.* ($C_{12}H_{20}IN$) C, H, I, N.

Dimethiodide 7 (2.6 g, 0.0054 mole) afforded 0.5 g of **12** on Hofmann degradation by the same procedure.

2-Dimethylaminoethylcyclohexane.—Compound **12** (0.4 g), 10 ml of HOAc, and 0.05 g of PtO_2 were hydrogenated at 2.1 kg/cm² and filtered and most of the HOAc was removed *in vacuo*. The residue was made strongly basic with NaOH solution and extracted with Et_2O. The extract was dried ($MgSO_4$), filtered, and evaporated to give 0.08 g of 2-dimethylaminoethylcyclohexane. The infrared spectrum showed no unsaturation. The methiodide, a white solid, was recrystallized from Me_2CO–EtOH to give white needles, mp 223° (lit.[16] mp 224°).

1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (15) and 1-Methyl-*cis*-octahydroindole (14).—A solution of 8 g of 5-aminoindoline (0.006 mole) in 75 ml of purified dioxane was hydrogenated at 49.21 kg/cm² and 90–100° in the presence of 0.3 g of RuO_2 for 24 hr. The bomb was cooled to room temperature, the contents were filtered, and the solvent was removed under vacuum to afford a brown liquid which on distillation at 80–110° (9 mm) gave 4.9 g of colorless, mobile liquid.

To 13.8 g (0.02 mole) of 88% HCO_2H at 5° was added dropwise 4.9 g (0.035 mole) of the reduced indoles **14** and **15** followed by the addition of 12.3 g (0.16 mole) of 37% CH_2O, maintaining the temperature at 5–10°. The mixture was stirred and heated until the evolution of CO_2 became vigorous whereupon heating was discontinued. When the exothermic reaction was complete, the mixture was heated for 4 hr at 100° and cooled to 50°; 70 ml of 4 *N* HCl was added. The mixture was extracted with Et_2O which was dried ($MgSO_4$), filtered, and distilled to give 4.95 g of a colorless, mobile liquid. Tlc of the liquid on alumina using 5% MeOH in 8:2 Skelly B–ether indicated two major components which were separated by column chromatography on neutral alumina (Woelm, activity grade I, 300 g). The substances were eluted with 0.5% MeOH in 8:2 Skelly B–ether; 100-ml fractions were collected. The first fraction contained 0.55 g (7%) of 1-methyl-*cis*-octahydroindole (**14**), bp 57° (9 mm) (lit.[16] 178–179° at 757 mm). The 3.13-ppm multiplet (band half-width, 18 cps) was assigned to the C-7a equatorial proton. The **methiodide** of **14** recrystallized from Me_2CO–Et_2O as needles, mp 209° (lit.[16] 208°). *Anal.* ($C_9H_{20}IN$) C, H, I, N.

The second fraction contained 4.1 g (40%) of the desired product, **15**. Distillation afforded a colorless liquid, bp 110 (9 mm). The nmr spectrum at both 60 and 100 Mc showed a 3.16-ppm sextet (band half-width 18 cps) for the C-7a equatorial proton. *Anal.* ($C_{11}H_{22}N_2$) C, H, N.

1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole Dimethiodide (8).—A solution of 0.2 g of **15** in 20 ml of dry Me_2CO was refluxed with excess MeI and the white solid (0.5 g, 100%) recrystallized from absolute EtOH–Et_2O to give **8** as white needles, mp 264.5–265.5°. *Anal.* ($C_{13}H_{28}I_2N_2$) C, H, I, N.

According to the method used in the preparation of **12**, **8** yielded 0.61 g (74%) of **16** as a colorless liquid, bp 91° (20 mm),

$n^{24}D$ 1.4800, $\lambda_{max}^{95\%EtOH}$ 260 mμ (ε 4300). A multiplet centered at 5.8 ppm was assigned to the four vinyl protons in the nmr spectrum of **16**. *Anal.* ($C_{10}H_{15}N$) C, H, N.

Its methiodide crystallized from Me_2CO–Et_2O as white needles, mp 179–180°. *Anal.* ($C_{11}H_{20}IN$) C, H, I, N.

Compound **16** was reduced as described for **12** to give 2-dimethylaminoethylcyclohexane. The methiodide of the reduced product was recrystallized from Me_2CO–Et_2O to furnish white needles, mp 223° (lit.[16] mp 224°).

1-Methyl-5-oxo-*cis*-octahydroindole (17).—A solution of 5-hydroxyindole (1 g) in 20 ml of MeOH was hydrogenated at 120–125° (initial pressure, 119.4 kg/cm²) with 3 g of Raney nickel for 1 hr. The cooled contents were filtered and evaporated to afford 1.0 g of a colorless syrup. CrO_3 (0.3 g, 0.0033 mole equiv) in 0.2 ml of H_2O and 2 ml of HOAc was added dropwise to a solution of 0.51 g (0.0033 mole) of the reduced indole in 10 ml of HOAc at 60–65°. The mixture was stirred at 60–65° until the solution was completely green. Most of the HOAc was removed, and the residue was made strongly basic with NaOH solution and extracted with three 20-ml portions of Et_2O. The Et_2O extracts were combined, dried ($MgSO_4$), and filtered. Removal of solvent at reduced pressure afforded a colorless liquid. Tlc of the liquid on neutral alumina using 1:1 EtOH–Skelly B showed spots for starting material and product **17**. The mixture was chromatographed on an alumina column made in Skelly B (Woelm, activity grade III, 40 g) using 5% EtOAc in Skelly B_1 and 20-ml fractions were collected. The ketone **17** (0.15 g, 30%) had an unresolved triplet at 3.05 ppm (band half-width 15 cps) assigned to the equatorial C-7a proton.

1-Methyl-5-oximino-*cis*-octahydroindole (18).—The ketone **17** (0.18 g, 0.0012 mole) was heated on a steam bath for 3 hr with a solution of 0.4 g of $NH_2OH \cdot HCl$ in 5 ml of H_2O. The solution was neutralized with Na_2CO_3 solution and heated on a steam bath for 30 min. Cooling of the solution did not precipitate the oxime. It was evaporated to dryness by codistillation with two 100-ml portions of absolute EtOH, and the dry residue was extracted with two 10-ml portions of boiling EtOAc. The extracts were concentrated to a small volume. The solution, on cooling, afforded 0.14 g (70%) of **18** as white crystals (EtOAc–Skelly B), mp 154.5–156.5°. *Anal.* ($C_9H_{16}N_2O$) C, H, N.

1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (15). A. From 18.—A solution of 0.50 g (0.003 mole) of **18** in 8 ml of absolute EtOH was heated to boiling; the heating was discontinued, and temperature was maintained by introducing pieces of Na (1 g) through the condenser. After the solution was refluxed for 30 min and cooled, it was diluted with an equal volume of H_2O, acidified with HCl, and evaporated. The residue was made strongly alkaline with NaOH solution and extracted with $CHCl_3$. The extraxts were dried and filtered. Solvent was removed under reduced pressure to give 0.17 g (37%) of a thick colorless liquid. To this was added 0.25 g of 37% CH_2O and 0.26 g of 88% HCOOH, and the mixture was heated on the steam bath for 2 hr. The solution was treated with 5 ml of dilute HCl and excess CH_2O and HCO_2H were removed by evaporation to dryness. The residue was made alkaline with NaOH solution and extracted with Et_2O. The solvent was evaporated to give 0.16 g of a liquid which was identical with **1**-methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (**15**) by infrared and tlc.

The amino ketone **17** (0.23 g, 0.0015 mole) was heated at 160–170° for 3 hr with 0.44 g (0.006 mole) of DMF and 0.41 g (0.008 mole) of 88% HCO_2H. The cooled solution was treated with 5 ml of **4** *N* HCl and evaporated to dryness. The residue was made alkaline with NaOH solution and extracted with Et_2O. The extract was dried ($MgSO_4$) and evaporated to afford 0.21 g of a yellowish liquid which was identical with **15** by infrared and tlc.

Catalytic Reduction of 1-Methyl-5-oximino-*cis*-octahydroindole (18).—A solution of 0.25 g of **18** in 10 ml of HOAc was hydrogenated overnight at 2.1 kg/cm² (room temperature) with 75 mg of PtO_2. After filtering, the solution was evaporated to remove most of the HOAc. The residue was made alkaline with NaOH solution and extracted with Et_2O to give (after drying and evaporation) 0.19 g of a thick liquid. The liquid was heated on the steam bath for 3 hr with 0.26 g of 37% H_2CO and 0.28 g of 88% HCOOH, treated with 5 ml of 4 *N* HCl, and evaporated to dryness. The residue was made strongly alkaline with NaOH solution, extracted with Et_2O, and dried ($MgSO_4$), and the solvent was removed to afford 0.18 g of a colorless liquid which was identical with **15** by ir and tlc.

Biological Testing.—The contractions of the isolated ileum were obtained by treatment with ganglionic stimulants, and the percentage reduction in the size of these contractions brought about by the antagonists was used as a measure of their effect. Each compound was examined three times on fresh ileum preparations.

The normal control contractions of the guinea pig ileum were obtained by the addition of 2-, 10 , and 20-μg doses of nicotine, acetylcholine, and histamine, respectively, in the bath in which the ileum was suspended. Then, the contractions were obtained with the same drugs after the previous addition (90 sec before) of the antagonist to the bath. The doses of the antagonists used were 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μg.

Preparation and Antiinflammatory Properties of Some 5-(2-Anilinophenyl)tetrazoles[1]

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Tetrazole analogs of a series of known N-phenylanthranilic acid antiinflammatory agents were prepared. Some of these 5-(2-anilinophenyl)tetrazoles showed antiinflammatory activity comparable to the corresponding carboxylic acids when tested orally in rats.

The knowledge that 5-substituted tetrazoles and their carboxylic acid analogs have comparable acidic dissociation constants[2,3] has led a number of chemists to replace the carboxyl group in biologically active compounds with the 5-tetrazolyl group (–CN_4H). Hopes of maintaining or improving upon biological activity have been realized in some cases.

Tetrazole analogs of plant growth regulators such as 3-indolylacetic acid and 2,4-dichlorophenoxyacetic acid retained some activity.[4,5] Two out of three tetrazole analogs of glutamic acid acted as substrates for beef liver L-glutamic dehydrogenase,[6] whereas 5-(4-aminophenyl)tetrazole, an analog of *p*-aminobenzoic acid, was found to be inactive against *Staphylococcus aureus*

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