The ultraviolet spectrum of the substance (solvent ethanol) exhibited only one broad maximum at 238–244 mμ (log ε 3.95) instead of the two maxima shown by 3,4-dihydrothieno(3,2-c)pyridines. The band was considerably stronger and broader than a similarly located band of 2-methoxythiophene.[24] In the infrared it absorbed strongly at 1695 cm.$^{-1}$, but there was no hydroxyl band and the peaks at 1212 and 1155 cm.$^{-1}$ characteristic of arylalkyl ethers[23] were missing (*cf.* the spectrum of 2-thienol[24] which has these bands and an intense band at 1670 cm.$^{-1}$, presumably due to a thiolactone band). Consideration of the spectra and the chemical evidence cited earlier suggest that the base exists in form VI.[26]

Cyclization of N-Acetyl-2-(5-methoxy-2-thienyl)-ethylamine.—A mixture of 3.2 g. of the acetyl derivative, 1 g. of phosphorus pentoxide and 30 ml. of phosphorus oxychloride in 230 ml. of dry toluene was refluxed, with stirring, under a nitrogen atmosphere. The solvent and excess oxychloride was removed at reduced pressure and the resinous residue was taken up in ice-cold dilute hydrochloric acid, washed with ether, filtered through Hyflo-supercel, cautiously made basic with ammonium hydroxide under cooling and thoroughly extracted with ether. The dried ether extracts were concentrated at reduced pressure. The residue was distilled *in vacuo* at a bath temperature of 80–90°. The light yellow oil, wt. 0.1 g., was converted to a picrate, m.p. 171.2–171.6° (cor.) after three recrystallizations from ethanol.

Anal. Calcd. for $C_{14}H_{12}O_8N_4S$: C, 42.42; H, 3.05. Found: C, 42.79; H, 3.10.

The ultraviolet spectrum of the base in 95% ethanol exhibited a maximum at 224–228 mμ (log ε 3.5) superimposed on a broad band whose maximum could not be determined but which appears as a shoulder near 260 mμ (log ε approximately 3).

2-(5-Methoxy-2-thienyl)-ethanol.—2-Methoxythiophene (16.5 g., 0.145 mole) was added with stirring to a solution of phenyllithium prepared from 1.92 g. of lithium and 14.5 ml. of bromobenzene in 100 ml. of anhydrous ether under a nitrogen atmosphere. After an hour, the flask was cooled in an ice–salt-bath and the nitrogen inlet was replaced by a tube leading to a flask containing 11.0 g. of ethylene oxide. The oxide was slowly vaporized and introduced under the surface of the mixture with stirring and cooling. Stirring was continued at room temperature for eight hours and the mixture was worked up in the usual way. Two fractions were obtained: a low-boiling fraction, b.p. 64–69°, $n^{24}D$ 1.5309, wt. 11.7 g., whose ultraviolet and infrared spectrum indicated that it contained about 50% of unchanged methoxythiophene, and a higher-boiling material, b.p. 95–105° (0.4 mm.), wt. 10 g. 87–89° (0.3 mm.), $n^{23}D$ 1.5384.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.14; H, 6.37. Found: C, 53.00; H, 5.80.

The infrared spectrum (film and CCl_4 solution) exhibited bands at 3690 and 3520 cm.$^{-1}$ (free and bonded OH); the characteristic C–O band of primary alcohols[28] was at 1050 cm.$^{-1}$.

The naphthylurethan was recrystallized from ligroin (b.p. 65–110°), m.p. 107.8–108° (cor.).

Anal. Calcd. for $C_{18}H_{17}O_3NS$: N, 4.28. Found: N, 4.23.

(26) The carbonyl absorption of α,β-butenolides (1750 cm.$^{-1}$) is approximately the same as that of an acyclic ester (1735–1755 cm.$^{-1}$). This is explained by assuming that the hypsochromic shift on passing from an acyclic to a cyclic system is compensated by a bathochromic shift due to the conjugative effect of α,β-unsaturation. Similarly one expects the carbonyl absorption of an α,β-unsaturated thiobutenolide to be approximately the same as that of an acyclic thioester (1680 cm.$^{-1}$).[27] Hence the 1695 cm.$^{-1}$ band in the spectrum of the base may be due to the α,β-thiobutenolide structure VI.

(27) H. T. Clark, J. R. Johnson and R. Robinson (ed.), "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 382–415.

(28) H. H. Zeiss and M. Tsutsui, THIS JOURNAL, **75**, 897 (1953).

TALLAHASSEE, FLORIDA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

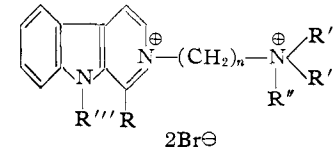
Bis-ammonium Salts. Unsymmetrical Derivatives of Some β-Carbolines[1]

BY ALLAN P. GRAY, ERNEST E. SPINNER, DOROTHY C. SCHLIEPER AND CHESTER J. CAVALLITO

RECEIVED JANUARY 31, 1955

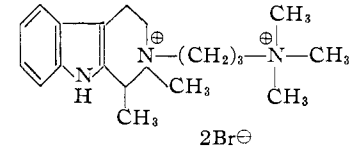
A series of unsymmetrical bisammonium salts has been prepared in which a small cationic head is attached through an alkyl chain to either the Py–N or Ind–N of a β-carboline. Included in this series are derivatives of norharman, harman, Ind-N-methylharman, Py–N-methyltetrahydroharman, and, for comparison, α-carboline. The derivatives in which the chain is linked at the Ind-N were synthesized by alkylation with the appropriate dialkylaminoalkyl chlorides in the presence of sodamide. A number of the Py-N-substituted β-carboline bis salts, in particular those in which the charged groups are separated by a three carbon chain, display intense hypotensive activity, not necessarily associated with strong ganglionic blocking properties. Structure–activity relationships are discussed.

A program concerned with the synthesis and biological examination of a variety of bis-ammonium salts has, for some time, been in progress in these laboratories. In the course of these investigations some symmetrical bis-carboline salts[2] were observed to be hypotensive agents of relatively short duration in comparison with the more potent ganglion blocking "methoniums." It thus became of interest to examine the pharmacological properties of compounds having a large, charged carboline structure and a small cationic (*i.e.* "methonium" type) head attached at either end of a carbon chain. The first compound prepared (VI) showed markedly greater hypotensive activity than could be ascribed to ganglionic blockade, and this prompted the synthesis of a large number of related unsymmetrical bis-ammonium salts. The present paper deals with the preparation of carboline derivatives, *viz.*



2Br⊖

I–XI, XIII

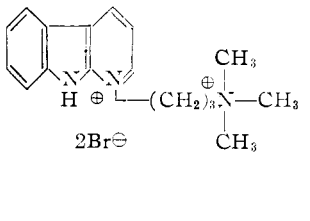


2Br⊖

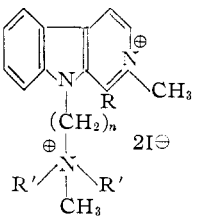
XII

(1) Presented in part before the Division of Medicinal Chemistry at the 127th National Meeting of The American Chemical Society, March 29–April 7, 1955.

(2) A. P. Gray, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **76**, 2792 (1954).



XIV



XVI, XIX, XXIII, XXVIII

Requirements for activity in regard to size of the small cationic head and length of the chain have been examined.

The bis salts I–XIV[3] all were obtained by condensation of the required carboline with the appropriate bromoalkyl quaternary ammonium bromide.[4] Earlier comments[2] relating to the ease of quaternization of the various carbolines apply equally well to the formation of the unsymmetrical derivatives.

The Ind-N alkylated bases listed in Table II were obtained by reaction of the β-carboline with a dialkylaminoalkyl chloride in the presence of sodamide. The method was similar to that previously employed for the synthesis of Ind-N substituted harman derivatives.[2,5] Although sodamide reacted relatively rapidly with norharman in toluene at steam-bath temperature, reaction with harman was sluggish and prolonged refluxing in xylene was required in order to effect complete evolution of ammonia. This difference in reactivity would appear to be related to the greater solubility of norharman rather than to a difference in acidity or accessibility of the indole N. Yields of the Ind-N-(dialkylaminoalkyl)-carbolines averaged approximately 50%. Some of these bases were not obtained quite pure, apparently being contaminated with small amounts of the starting carboline.

Biological Properties.—The pharmacodynamics of I, VI, VII and VIII have been discussed elsewhere[6a] and details of the pharmacology of compounds in Table I will be published.[6b] It is of particular interest that the intense and prolonged hypotensive activity of some of these compounds is unrelated to the degree of sympathetic ganglionic blockade which they produce. With simple, symmetric bisquaternary-substituted alkanes of the "methonium" type, a six-carbon chain between quaternary nitrogen atoms provides maximum hypotensive and ganglionic blocking activity. As the substituents on the nitrogen atoms become larger, optimum activity is associated with shorter linking chain derivatives.[6a] Compounds I–IV furnish evidence that, among the bis salts of this series, greater duration of action is associated with the C_3 linking chain. Bisquaternary derivatives in which the chain is attached through the indole nitrogen (Table II) are much weaker hypotensive agents than are corresponding derivatives in which the side chain is attached to the pyridine-nitrogen (Table I). This may very well be related to the greater than optimum distances between "onium" centers in the indole-nitrogen-substituted derivatives. In addition to length of the alkylene bridge, another critical factor in governing hypotensive activity of the compounds in Table I is the size of the small cationic group. A group smaller than triethylammonium apparently is necessary as a sharp break in activity occurs in going from active diethylmethylammonium (VI) to much weaker triethylammonium (VII) and benzyldimethylammonium (V) derivatives. In this series, the N-methylpyrrolidinium group provides more active derivatives than does the trimethylammonium group (VIII and XI *vs.* I and X). A progressive increase in hypotensive activity is evident with these bis salt derivatives in the order of increasing degree of ionization of the Py-substituted carboline moiety,[2] *i.e.*, α-carboline (XIV), β-carboline (I, VIII, XIII), Ind-N-methylcarboline (X, XI), N-methyltetrahydrocarboline (XII). The derivatives of the last two types are, of course, completely ionized bisquaternary salts. These are approximately equally active in lowering blood pressure although XII produces much more intense ganglionic blockade.

That steric factors, ionization (*i.e.* of the carboline portion) and electron field distribution about the charged nitrogen atoms influence activity is not unexpected since these factors could affect not only the ease of approach to and electrostatic bonding energy at a receptor site but also the ease of displacement of the compound by other ions after adsorption. The influence of some additional structural modifications on biological activity will become evident in the subsequent publication describing related studies.

Experimental[7]

Preparation of Intermediates.—Harman, norharman, Ind-N-methylharman, Py-N-methyltetrahydroharman and α-carboline were synthesized as described earlier.[2] The preparation of the ω-bromoalkyl quaternary ammonium bromides is reported in an accompanying paper.[4]

3-Dimethylaminopropyl chloride was prepared essentially as described by Marxer[8] who obtained the compound in low yield. With some slight modification, particularly of the isolation procedure, the method has afforded consistently good yields. Into a solution of 78.8 g. (0.5 mole) of 1-bromo-3-chloropropane in 300 ml. of benzene was bubbled 45 g. (1 mole) of anhydrous dimethylamine. After 16 hours at room temperature, the reaction mixture was filtered from the precipitate of dimethylamine hydrobromide. The benzene filtrate was acidified with ethereal hydrogen chloride and the solvent decanted from the oily precipitate which was treated with 20% sodium hydroxide and extracted with ether. Drying and removal of the ether left an oil which was distilled to yield 39.2 g. (70%) of product, b.p. 51–53° (50 mm.). For storing, the base was converted to the hydrochloride salt; yield 46.9 g., m.p. 141–143°.

(3) A word on nomenclature might be in order. There have been several recent discussions on the need for a prefix which would signify "ammonium." J. F. Bunnett, *et al.*, THIS JOURNAL, **75**, 642 (1953); *Chem. Revs.*, **49**, 291 (1951), suggest use of the term "ammonio" in phrases such as "ammonio" group. In naming the compounds described in the present paper it is extremely difficult to avoid the use of some prefix for "ammonium" and the term "ammonio" provides a partial solution. Thus compound 1 might be designated, 1-(1-methyl 9-pyrid-3,4b-indolio)-3-(trimethylammonio)-propane dibromide.

(4) A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955).

(5) Since completion of this work, reports have appeared concerning similar alkylations of α-carboline, R. Burtner, U. S. Patent 2,688,022 (1954); and of Py-N-methyltetrahydroharman, U. Hörlein, *Chem. Ber.*, **87**, 463 (1954).

(6) (a) C. J. Cavallito, A. P. Gray and T. B. O'Dell, *Arch. intern. pharmacodynamie*, **101**, 38 (1955); (b) T. B. O'Dell, Cris Luna and Martha Napoli, *J. Pharmacol. Exptl. Therap.*, in press.

(7) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. Melting points are corrected for stem exposure.

(8) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

TABLE I

PY-N-SUBSTITUTED CARBOLINE SALTS

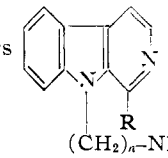
$RN^{\oplus}—(CH_2)_nN^{\oplus}R_2'R''2Br^{\ominus}$

	Carboline (RN)	n	NR_2	R″	M.p., °C.[a]	Formula	Analyses, % Calculated C	H	Br	Found C	H	Br[b]	Hypotensive activity % fall/durn. hr.,[f] 0.5 mg. per kg.	Ganglionic blockade,[g] 1 mg. per kg.
I	Harman	3	$N(CH_3)_2$	CH_3	271–274	$C_{18}H_{28}Br_2N_2$	48.77	5.70	36.06	49.04	5.76	35.86	35/1	4+
II	Harman	5	$N(CH_3)_2$	CH_3	268	$C_{20}H_{32}Br_2N_2$	50.96	6.21	33.91	50.64	6.44	33.87	40/0.2	
III	Harman	6	$N(CH_3)_2$	CH_3	264–265	$C_{21}H_{34}Br_2N_2$	51.96	6.45	32.93	52.08	6.66	32.36	40/0.5	
IV	Harman	10	$N(CH_3)_2$	CH_3	162–164	$C_{25}H_{44}Br_2N_2$	55.45	7.27	29.52	55.26	7.63	28.75	85/0.75	
V	Harman	3	$N(CH_3)_2$	$C_6H_5CH_2$	230–240	$C_{34}H_{38}Br_2N_2$	55.50	5.64	30.78	55.20	5.77	30.12	30/0.1	
VI	Harman	3	$N(C_2H_5)_2$	CH_3	252–254	$C_{20}H_{32}Br_2N_2$	50.97	6.20	33.92	51.51	6.22	33.56	40/2	3+
VII	Harman	3	$N(C_2H_5)_2$	C_2H_5	250–252	$C_{21}H_{34}Br_2N_2$	51.96	6.45	32.93	52.25	6.39	33.03	0	+
VIII	Harman	3	NC_4H_8[c]	CH_3	281	$C_{20}H_{30}Br_2N_2$	51.18	5.81	34.06	51.09	6.06	33.46	(0.25) 40/3	2+
IX	Harman	3	NC_5H_{10}[d]	CH_3	274–275	$C_{21}H_{32}Br_2N_2$	52.18	6.06	33.07	51.88	6.15	33.28	50/3	2+
X	Ind-N-methyl-harman	3	$N(CH_3)_2$	CH_3	254	$C_{19}H_{27}Br_2N_3$	49.94	5.93	34.95	49.89	6.04	34.95[e]	50/>3	+
XI		3	NC_4H_8[c]	CH_3	254–257	$C_{21}H_{30}Br_2N_2$	52.18	6.06	33.07	51.91	6.12	32.40	(0.25) 40/>3	4+
XII	Py-N-methyl-tetrahydroharman	3	$N(CH_3)_2$	CH_3	220–222	$C_{19}H_{31}Br_2N_3$	49.45	6.78	34.65	48.95 49.69	6.52 7.18	34.29 34.09[e]	40/>4	4+
XIII	Norharman	3	$N(CH_3)_2$	CH_3	269	$C_{17}H_{23}Br_2N_3$	47.57	5.41	37.24	47.63	5.35	36.69	40/1	±
XIV	α-Carboline	3	$N(CH_3)_2$	CH_3	226–230	$C_{17}H_{23}Br_2N_3$	47.57	5.41	37.24	47.82	5.21	36.53	0	

[a] Most of the salts melt with decomposition. [b] Ionic halogen determinations. [c] Pyrrolidino. [d] Piperidino. [e] This value was obtained by microanalysis for total bromine. [f] In anesthetized dogs; dose 0.5 mg. per kg. intravenously excepting VIII and XI which are 0.25 mg.; values are: % maximum fall in blood pressure/duration in hours before return to pre-drug level. [g] Superior cervical ganglion in cat; dose 1 mg. per kg. intravenously; block from 0 (zero) to 4+ (complete) for from 30 to 120 minutes.

TABLE II

IND-N-SUBSTITUTED CARBOLINES AND SALTS



$(CH_2)_n–NR'_2$

	R	R′	n	Di-salt	M.p. or b.p. (mm.), °C.[a,b]	Formula	Analyses, % Calcd. C	H	Halogen	N[c]	Found C	H	Halogen[d]	N[c]
XV	CH_3	CH_3	2	...	184–187 (0.6) 74–76[g]	$C_{16}H_{19}N_3$	75.85	7.56		16.59[f]	76.15	7.44		16.76[f]
XVI	CH_3	CH_3	2	CH_3I	289–291	$C_{18}H_{26}I_2N_3$	40.24	4.69	47.25		40.10	4.95	47.56	
XVII	H	C_2H_5	2	...	167–174 (0.7)[i]	$C_{17}H_{21}N_3$				10.48				9.73
XVIII	H	C_2H_5	2	HCl	239–241	$C_{17}H_{23}Cl_2N_3$	60.00	6.81	20.84		59.73	7.09	20.19[e]	
XIX	H	C_2H_5	2	CH_3I	256	$C_{19}H_{27}I_2N_3$	41.39	4.94	46.05		40.52	5.27	45.61	
XX	CH_3	C_2H_5	2	...	155–157 (0.5)									
XXI	CH_3	C_2H_5	2	HCl	267–270	$C_{18}H_{25}Cl_2N_3$	61.01	7.11	20.01		61.32	6.77	19.73	
XXII	H	CH_3	3	...	169–172 (0.5)[k]	$C_{16}H_{19}N_3$	75.85	7.56		11.02	76.24	7.52		10.45
XXIII	H	CH_3	3	CH_3I	270–273	$C_{18}H_{26}I_2N_3$	40.24	4.69	47.25		39.46	5.15	46.91	
XXIV	CH_3	CH_3	3	...	168–170 (0.2)[k]	$C_{17}H_{21}N_3$				10.48				9.70
XXV	CH_3	CH_3	3	HCl	258–260	$C_{17}H_{23}Cl_2N_3$	60.00	6.81	20.84		60.65	6.98	20.58	
XXVI	CH_3	C_2H_5	3	...	178–181 (0.3)[i]	$C_{19}H_{25}N_3$	77.24	8.53		9.49 14.23[f]	77.14	8.75		9.07 13.92[f]
XXVII	CH_3	C_2H_5	3	HCl	291	$C_{19}H_{27}Cl_2N_3$	61.95	7.39	19.25		61.58	7.04	18.50	
XXVIII	CH_3	C_2H_5	3	CH_3I	254	$C_{21}H_{31}I_2N_3$	43.54	5.39			43.62	5.66		

[a] Most of the salts melt with decomposition. [b] Boiling points are listed for the free bases. [c] These values are for basic nitrogen. [d] Ionic halogen determination. [e] Microanalysis for total halogen. [f] This value is for total nitrogen by microanalysis. [g] This compound solidified on standing and was recrystallized from Skellysolve B. [h] Partially solidified on standing. [i] Thick oil. [j] $n^{24}D$ 1.6098. [k] $n^{25}D$ 1.6323.

Ind-N-(Dialkylaminoalkyl)-carbolines.—The two following examples illustrate the general method (*cf.* ref. 2) employed. Yields averaged 40–60%. As might be expected, the lowest yield was obtained when dimethylaminoethyl chloride was the alkylating agent.

A. 9-(3-Dimethylaminopropyl)-9-pyrid-3,4b-indole (XXII).—To a slurry of 8.4 g. (0.05 mole) of norharman in 100 ml. of dry toluene was added 2.0 g. (0.051 mole) of sodamide. The mixture was stirred and heated at 90° for 2 hours, in the course of which time 65% of the calculated amount of ammonia (collected in a trap containing excess standard acid) was evolved. A solution of 6.0 g. (0.049 mole) of dimethylaminopropyl chloride in 20 ml. of dry toluene then was added dropwise, stirring was continued and the mixture was heated on the steam-bath for an additional 5 hours. The reaction mixture was cooled to room temperature, water added cautiously to decompose any excess sodamide and the toluene layer was separated, washed with water and extracted with dilute sulfuric acid. The acid extract was made alkaline and the product taken into ether. Drying and removal of the ether left an oil which was distilled to yield 5.6 g. (45%) of the product, b.p. 169–172° (0.5 mm.), $n^{25}D$ 1.6323.

B. 9-(3-Diethylaminopropyl)-1-methyl-9-pyrid-3,4b-indole (XXVI).—A slurry of 7.3 g. (0.04 mole) of harman and 1.6 g. (0.0405 mole) of sodamide in 200 ml. of dry xylene was stirred and refluxed (oil-bath) for 13 hours. The oil-bath then was replaced by a steam-bath and 6.0 g. (0.04 mole) of diethylaminopropyl chloride[9] in 10 ml. of dry xylene was added dropwise. Stirring was continued and the

(9) H. Gilman and D. A. Shirley, THIS JOURNAL, **66**, 888 (1944).

reaction mixture heated on the steam-bath for an additional 3 hours. The cold mixture was treated cautiously with water, the xylene layer separated and extracted with dilute sulfuric acid. The aqueous layer was brought to a *p*H of about 8 with potassium carbonate and extracted with ether. The ether solution was water-washed, dried over sodium sulfate, evaporated, and the residue distilled to yield 7.0 g. (60%) of the product as a thick oil, b.p. 167–170° (0.1 mm.).

On making the remaining alkaline layer strongly basic with 20% sodium hydroxide, a small amount of dark, green fluorescent oil was obtained. This could not be purified.

The dihydrochlorides and dimethiodides of the Ind-*N*-(dialkylaminoalkyl)-carbolines were prepared by the usual procedures. The dihydrochlorides generally were recrystallized from ethanol or propanol, and the dimethiodides from methanol.

Py-N-substituted Carboline Salts.—The examples that follow will serve to illustrate the methods used for the preparation of the salts listed in Table I. Yields ranged from a low of 20% for the α-carboline derivative up to about 70%. The β-carboline salts were as a rule obtained in yields of 50–70%.

A. Reaction of 1-Methyl-9-pyrid-3,4b-indole with 3-Bromopropylmethyldiethylammonium Bromide. Compound VI.—A solution of 12.0 g. (0.037 mole) of crude (90% pure) 3-bromopropylmethyldiethylammonium bromide and 3.6 g. (0.02 mole) of harman in 75 ml. of acetonitrile was refluxed on the steam-bath for 15 hours. The precipitate was collected and recrystallized from ethanol to yield 6.4 g. (69%) of VI, m.p. 252–254° dec.

B. Reaction of 1,9-Dimethyl-9-pyrid-3,4b-indole with 3-Bromopropylmethylpyrrolidinium Bromide. Compound XI.—Refluxing a solution of 2.7 g. (0.014 mole) of Ind-*N*-methylharman and 5.7 g. (0.021 mole) of 3-bromopropylmethylpyrrolidinium bromide in 30 ml. of acetonitrile for 18 hours afforded 5.1 g. of crystalline precipitate, m.p. 250–253°. After two recrystallizations from ethanol, there was obtained 3.5 g. (52% yield) of XI, m.p. 254–257° with gas evolution.

C. Reaction of 1,2-Dimethyl-1,2,3,4-tetrahydro-9-pyrid-3,4b-indole with 3-Bromopropyltrimethylammonium Bromide. Compound XII.—A solution of 2.8 g. (0.015 mole) of Py-*N*-methyltetrahydroharman and 3.9 g. (0.015 mole) of bromopropyltrimethylammonium bromide in 50 ml. of isopropyl alcohol was refluxed on the steam-bath for 24 hr. On refrigeration a crystalline precipitate formed. Two recrystallizations from *n*-propyl alcohol and ethyl acetate yielded 2.0 g. (29%) of XII, m.p. 220–222°.

D. Reaction of 9-Pyrid-2,3b-indole with 3-Bromopropyltrimethylammonium Bromide. Compound XIV.—A solution of 3.4 g. (0.02 mole) of α-carboline and 10.4 g. (0.04 mole) of bromopropyltrimethylammonium bromide in 100 ml. of a 1-to-1 mixture of dioxane and isopropyl alcohol was refluxed (oil-bath) for 50 hours. Addition of ether to the cooled solution precipitated the crude product which was recrystallized several times from ethanol and ethyl acetate and finally from absolute ethanol to yield 1.8 g. (21%) of XIV, m.p. 226–230°.

Acknowledgment.—The authors wish to express their appreciation to Mr. Donald L. Miller for performing the ionic halogen and basic nitrogen determinations.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER AND CO.]

Bis-ammonium Salts. Unsymmetrical Derivatives of Some Isoquinolines and Related Heterocyclic Bases[1]

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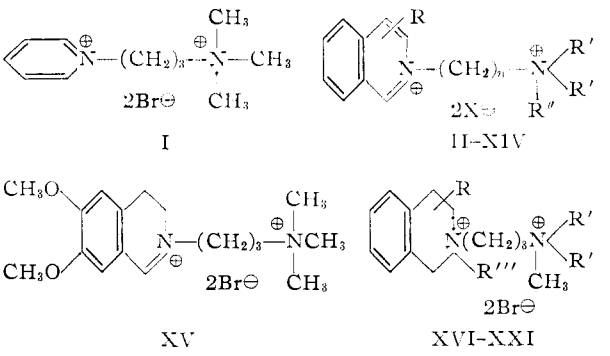
Investigations of unsymmetrical bis ammonium salts have been extended to include derivatives of isoquinoline, tetrahydroisoquinoline and various substituted relatives, 2,3-dihydro-1-benz[de]isoquinoline, some substituted quinolines, benzo[f]quinoline and phenanthridine. As in the carboline series, each of these salts comprises a small cationic head attached through an alkyl chain to the ring nitrogen of a heterocyclic base. Many of these salts possess potent hypotensive activity not necessarily associated with strong ganglionic blockade. Structure–activity relationships are discussed.

Some carboline unsymmetrical bis-ammonium salts with high hypotensive activity were described in the preceding paper.[2] On the basis of that investigation, requirements for pharmacological activity in regard to size of the small cationic head and distance between the two charged nitrogens were fairly well delineated, and tentative conclusions were drawn concerning the effects of changes in charge distribution and degree of ionization. These studies have been continued in order to probe further the problem of the relationship of chemical to biological properties and, in particular, to ascertain the structural and size limitations imposed on the large, charged heterocyclic nucleus.

That the β-carboline ring system was not unique in imparting activity soon became evident as a wide variety of heterocyclic bases has afforded potent unsymmetrical bis salt derivatives.[3] The present series comprises derivatives of pyridine, isoquinoline, tetrahydroisoquinoline, 2,3-dihydro-1-benz[de]isoquinoline, quinoline, benzo[f]quinoline and phenanthridine, *viz.*



(1) Presented in part before the Division of Medicinal Chemistry at the 127th National Meeting of the American Chemical Society, Cincinnati, Ohio, March 29–April 7, 1955.

(2) A. P. Gray, E. E. Spinner, D. C. Schlieper and C. J. Cavallito, THIS JOURNAL, **77**, 3533 (1955).

(3) Subsequent to the initation of this work, L. M. Rice, C. H. Grogan and E. E. Reid (*ibid.*, **75**, 4911 (1953)), reported on the marked hypotensive activity of various isoindoline bisquaternary derivatives. These were considered by the authors to be structurally related to the Ergot alkaloids. One of these isoindole derivatives, obtained through the courtesy of Dr. Rice, showed intense ganglionic blocking activity. It remains to be determined whether the isoindoles also have a central component of action (see Biological section).