acid, $C_6H_5CONHOCOAr$, and found a direct relationship between the ease of these Lossen rearrangements and the strengths of the analogous carboxylic acids, ArCOOH. The stronger sulfonic acids, therefore, should promote a still faster Lossen rearrangement, and such was the observation in the present work.

Experimental

Benzo-(phenylcarbamylhydroxamic) Acid. Using Toluenesulfonyl Chloride.—Benzohydroxamic acid was converted into its sodium salt. Then a solution of 4.2 g. of *p*-toluenesulfonyl chloride in 10 ml. of chloroform was added dropwise during 15 minutes to a stirred, cold (10°) suspension of 3.2 g. of the salt in 40 ml. of chloroform. The reaction was vigorous. The mixture was stirred for 15 more minutes, then the solid was collected on a filter, washed with chloroform, ligroin and finally with water to remove sodium salts. That there was some unused benzohydroxamic acid was evident since the wash water gave a strong ferric chloride color test. The yield of insoluble product was 2.45 g. It crystallized from ethanol in flat needles. The compound gave no coloration with ferric chloride and it dissolved readily in cold alkali. It decomposed at about 180°, then resolidified and melted to a clear meniscus at 232°. The second m.p. was that of *sym*-diphenylurea. A smaller yield (1.3 g.) was obtained by refluxing for one hour after the initial 15 minutes at 10°.

Anal. 180° product (by C. White, J. Sorensen). Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.72; N, 10.9. Found: C, 65.8; H, 4.85; N, 10.9.

Using Phenyl Isocyanate.—One ml. of phenyl isocyanate was added to an ice-cold suspension of 1.6 g. of sodium benzohydroxamate in 20 ml. of chloroform. The temperature immediately rose to 20°. After half an hour and recooling to 5°, 0.5 ml. more phenyl isocyanate was added. The mixture was processed 30 minutes later by adding 1 ml. of acetic acid and 20 ml. of petroleum hexane. The solid was collected, rinsed free of inorganic salts and crystallized from 95% ethanol (20 ml.); yield 1.2 g., and another 0.4 g. from the filtrate by precipitating it with an equal volume of water. The same decomposition and fusion behavior was shown as was described above.

Rearrangement.—A solution of 0.97 g. of this compound in water containing 0.14 g. of sodium hydroxide was heated to 100° for 30 minutes. *sym*-Diphenylurea separated promptly; yield 0.58 g., m.p. 232°. One recrystallization from ethanol brought the m.p. (and mixture m.p.) to 235°.

Hydrocinnamohydroxamic Acid and Its Benzoyl Derivative.—Hydrocinnamohydroxamic acid was prepared by reaction of equimolar portions of ethyl hydrocinnamate, hydroxylamine and sodium ethoxide, with ultimate acidification by carbon dioxide. Crystallization from benzene yielded lustrous plates, m.p. 82° (lit.,[6] 78°). The benzoyl derivative, prepared by Schotten–Baumann procedure and crystallized from benzene, melted at 131° which agrees with Bright and Hauser's value[5] of 132–133° but is noticeably higher than the 117° reported by Thiele and Pickard.[6] It underwent a satisfactory rearrangement into *sym*-diphenethylurea of m.p. 137° (lit.[6] 137°).

Hydrocinnamo-(phenethylcarbamylhydroxamic) Acid.—Sodium hydrocinnamohydroxamate (2.0 g.) was treated in chloroform suspension (20 ml.) at 5–10° with *p*-toluenesulfonyl chloride in the manner detailed above for the benzohydroxamic salt. After an hour of reaction time the mixture was diluted with an equal volume of petroleum hexane and filtered. The solid was washed with hexane and with water; yield 0.8 g. After crystallization from benzene it melted with gas evolution at 133–134°.

Anal. (by White and Sorensen). Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.45; N, 8.97. Found: C, 69.2; H, 6.53; N, 8.98.

Rearrangement.—The acid (1.06 g.), when dissolved in cold sodium hydroxide solution (0.13 g. in 3.5 ml. of water) and heated at 100° for half an hour, gave rise to 0.82 g. of *sym*-diphenethylurea which separated during this period. Crystallization from 2-propanol produced lustrous plates, m.p. 137°.

3-Benzenesulfonoxy-5,6-dihydrouracil.—To a rapidly stirred suspension of 2.4 g. of sodium succinohydroxamate in 25 ml. of chloroform at 25° was added dropwise during about half an hour a solution of benzenesulfonyl chloride in toluene (5.3 g. in 10 ml.). Addition at this rate kept the temperature nearly constant. After 45 minutes, the mixture was diluted with two volumes of hexane. The solid was collected, triturated with water containing 1% of acetic acid (15 ml.), and the mixture filtered; yield 0.9 g., after one crystallization from 2-propanol, m.p. 158–160°. Lustrous plates were obtained after recrystallization from 2-propanol or water.

The substance was soluble in hot water or ethanol and insoluble in chloroform. It dissolved in warm alkali. It gave no coloration with ferric chloride solution. It depressed the m.p. of N,N'-ethylenedibenzenesulfonamide (m.p. 168°).

Anal. (by White and Sorensen for C, H, N and Micro-Tech Lab. for S). Calcd. for $C_{10}H_{10}N_2O_5S$: C, 44.42; H, 3.73; N, 10.36; S, 11.86. Found: C, 44.75; H, 3.63; N, 9.93; S, 12.25.

(6) J. Thiele and R. H. Pickard, *Ann.*, **309**, 197 (1899).

EVANSTON, ILLINOIS

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

Bis Ammonium Salts. Derivatives of Some Carboline and Related Heterocyclic Bases[1]

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

RECEIVED DECEMBER 28, 1953

A group of bis salt derivatives of some relatively large heterocyclic bases, twinned by an alkylene chain (4 to 10 carbons) attached to nitrogen, has been prepared. The bases involved include substituted β-carbolines, α-carboline, yohimbine and tetrahydroberberine. Several methods have been employed for the preparation of the β-carboline derivatives. Many of the salts produced transitory hypotensive effects; a few exhibited strong curare-like activity.

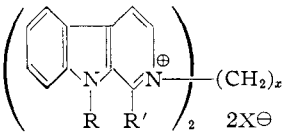
As a part of an extensive examination of the effects of variations in structure of bis ammonium salts on biological properties,[2] a group of derivatives of some carbolines, yohimbine and tetrahydroberberine, in which these large, relatively flat structures are twinned by alkylene bridges through a ring nitrogen, has been prepared. Variations in size, flatness, electrostatic charge distribution, steric hindrance about bonding functions, and distance between such functions have been introduced.[3a,b]

(1) Presented in part before the Division of Medicinal Chemistry at the 124th National Meeting of the American Chemical Society, Chicago, Illinois, September 6–11, 1953.

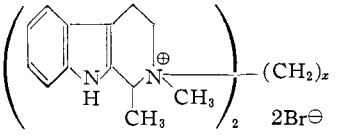
(2) Preceding paper, C. J. Cavallito A. P. Gray and E. E. Spinner, THIS JOURNAL, **76**, 1862 (1954).

(3) (a) The effects of variations of biological activity with distances between ionic groups have been reported by a number of investigators. *Cf.* R. B. Barlow and H. R. Ing, *Nature*, **161**, 718 (1948); *Brit. J. Pharmacol.*, **3**, 298 (1948); W. D. M. Paton and E. J. Zaimis, *Nature*, **161**, 718 (1948); H. O. J. Collier, *Brit. J. Pharmacol.*, **7**, 392 (1952); D. Bovet, *Ann. N. Y. Acad. Sci.*, **54**, 407 (1951). See also H. King, E. M. Lourie and W. Yorke, *Ann. Trop. Med.*, **31**, 435 (1937); *ibid.*, **33**, 289 (1939). (b) The effect of flatness and van der Waals bonding on antimicrobial action has been elegantly demonstrated; *cf.* A. Albert, S. D. Rubbo and M. I. Burvill, *Brit. J. Exptl. Path.*, **30**, 159 (1949).

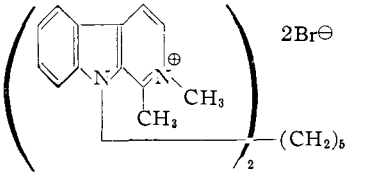
Although the heterocyclic bases required for the preparation of these bis salts were for the most part known compounds synthesized by conventional methods, some comments are warranted. The β-carbolines were prepared from tryptophan by modifications of the elegant method devised by Kermack, Perkin and Robinson.[4] An intriguing step in this synthesis, the simultaneous decarboxylation and dehydrogenation which is effected by dichromate (and other oxidizing agents), has never had adequate explanation. The original suggestion,[4] that the carboxyl group was first replaced by a hydroxyl and that the hydroxycarboline was then dehydrated, does not seem in accord with present knowledge. A significant point is that tetrahydrocarbolines which do not have a carboxyl group apparently yield no isolable carboline on treatment with aqueous dichromate.[5] A formulation of the reaction, which is compatible with the known facts and with general ideas of oxidation, may be extrapolated from the work of Swain and Hedberg,[6] and from the fact that open chain α-amino acids may be oxidatively decarboxylated to aldehydes.[7,8]



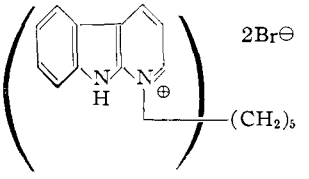
	R	R′	x
XI	H	CH_3	4
XII	H	CH_3	5
XIII	H	CH_3	6
XIV	H	H	5
XV	H	n-C_3H_7	5
XVII	CH_3	CH_3	5
XVIII	CH_3	CH_3	6



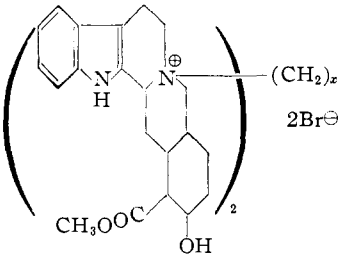
XIX, $x = 4$
XX, $x = 6$



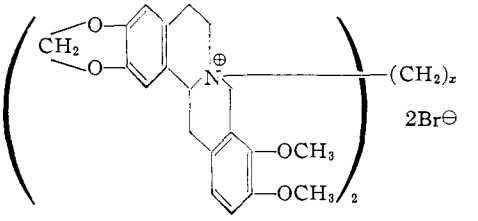
XVI



XXI

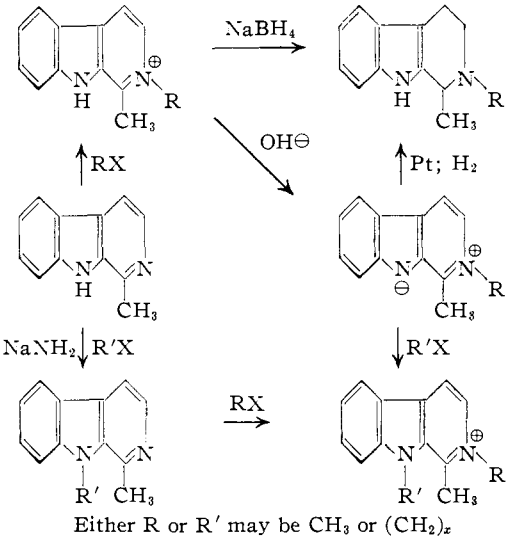


XXII, $x = 4$; XXIV, $x = 6$
XXIII, $x = 5$; XXV, $x = 10$



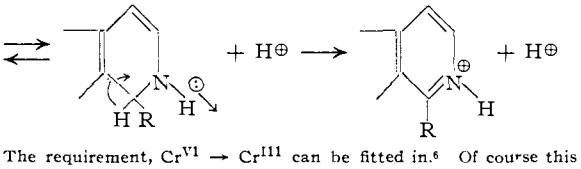
XXVI, $x = 4$; XXVIII, $x = 6$
XXVII, $x = 5$; XXIX, $x = 10$

The indole N-substituted β-carboline salts were obtained in two different ways. The first, and somewhat less satisfactory, method involved the alkylation of Py-N-alkyl (or alkylenebis) carboline bases.[9]

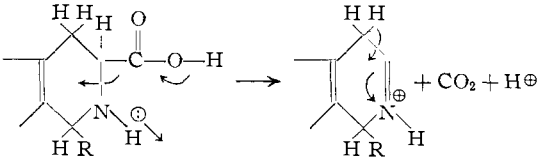


Either R or R′ may be CH_3 or $(CH_2)_x$

III, XVI and XVII were synthesized in this manner. Quaternization of the anhydronium bases does not go in spectacular yield, particularly with larger alkyl halides, and is accompanied by side



The requirement, $Cr^{VI} \rightarrow Cr^{III}$ can be fitted in.[6] Of course this is merely a skeletal representation, implying nothing concerning the intimate details of the reaction.



(4) W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(5) E. Spaeth and E. Lederer, *Ber.*, **63B**, 2102 (1930); (J. N. Ashley and R. Robinson, *J. Chem. Soc.*, 1376 (1928), however, report a "poor yield" of norharman from the oxidation of tetrahydronorharman).

(6) C. G. Swain and K. Hedberg, THIS JOURNAL, **72**, 3373 (1950), showed convincingly that a hydroxy derivative was not an intermediate in the oxidation of leuco malachite green.

(7) See for example, A. Schönberg, R. Moubasher and M. Z. Barakat, *J. Chem. Soc.*, 2504 (1951).

(8) A possible picture of carboline formation might involve abstraction of a pair of electrons from a center of high electron density by a chromate complex, with aromatization being the driving force for reaction, *i.e.*

(9) (a) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **115**, 933 (1919); W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *ibid.*, **121**, 1872 (1922); (b) for a recent discussion *cf.*, H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

reactions such as reversion to salt of the starting material. In the alternative method, used for XVI and also for XVIII, the Ind-N-substituted base was first prepared by alkylation of the sodium salt of harman (from sodamide in toluene or xylene[10]) and the product was then quaternized. Although the β-carboline anion reacts predominantly to give Ind-N-alkylation, reaction on the other nitrogen occurs to some extent (as evidenced by the development of strong green fluorescence); however, it was not found possible to isolate any pure side products. Further exploitation of this convenient means of substitution on the β-carboline nucleus is in progress and will be reported on at a later date.

XIX and XX were most conveniently synthesized from Py-N-methyltetrahydroharman, obtained either by the catalytic hydrogenation of Py-N-methylharman,[11] or, better, by sodium borohydride reduction of harman methobromide.[12] In either instance the melting point of the methyltetrahydroharman agreed with the literature[13] and the product exhibited the characteristic indole ultraviolet absorption spectrum. The sodium borohydride technique provides an eminently satisfactory route to Py-N-alkyltetrahydro-β-carbolines.

For the most part, the bis salts were prepared by heating an excess of the heterocyclic base with the appropriate alkylene dibromide (x = 4–10) in a suitable polar solvent. Acetonitrile was found to be an excellent reaction medium for the β-carbolines, but sterically hindered and readily oxidized bases such as yohimbine and tetrahydroberberine were much more satisfactorily quaternized in an alcohol-containing solvent. A variety of conditions was explored and the most useful methods are described in detail in the Experimental. Probably as a result of lower basicity, α-carboline was much less reactive than the β-carbolines. Steric hindrance was undoubtedly the principal factor in the poor yields of bis yohimbine and tetrahydroberberine quaternary salts. No attempt was made to separate stereoisomers, presumably present in all of the tetrahydro-bis salts.

Biological Properties.[14]—The mono-salts listed in Table I are not unusually active pharmacodynamic agents[15]; yohimbine has been known to possess adrenergic blocking action. The mono quaternary salts administered intravenously in anesthetized dogs produce a slight (10% ±) transitory (5 min. ±) reduction in blood pressure at doses of about 2 mg. per kg.

TABLE I

Cpd.	Base	Salt	Cor. m.p., °C.[a]	Halogen, % Calcd.	Halogen, % Found[b]
I	Harman	HCl	292–295		
II	Harman	CH_3I[c]	300		
III	Py-N-Methylharman	CH_3I[d]	>270		
IV	Norharman	CH_3I[e]	235–238	40.92	40.82
V	Py-N-Methyltetrahydroharman	CH_3I (ref. 13)	226–228		
VI	α-Carboline	CH_3I[f]	218–220	40.92	40.99
VII	Yohimbine	HCl[g]	287–293	9.07	8.90
VIII	Yohimbine	CH_3I[h]	231–250	25.57	25.70
IX	Tetrahydroberberine	HCl	230–232	9.43	9.27
X	Tetrahydroberberine	CH_3I[i]	245–247	26.37	26.05

[a] Most of the salts melt with decomposition. [b] The halogen analyses reported are from volumetric ionic halogen determinations unless the result is marked with an asterisk, in which case it represents a microanalysis for total halogen. [c] *Anal.* Calcd. for $C_{13}H_{13}IN_2$: C, 48.16; H, 4.04. Found: C, 48.16; H, 4.14. J. Keufer, *Bull. soc. chim. France*, 109, (1950), reported m.p. 275°. [d] *Anal.* Calcd. for $C_{14}H_{15}IN_2$: C, 49.72; H, 4.47. Found: C, 49.23; H, 4.44. [e] R. Speitel and E. Schlittler, *Helv. Chim. Acta*, **32**, 860 (1949), reported m.p. 238–240°. [f] *Anal.* Calcd. for $C_{12}H_{11}IN_2$: C, 46.47; H, 3.58. Found: C, 46.84; H, 3.75. [g] *Cf.*, T. A. Henry, "The Plant Alkaloids," Blakiston, 4th Edition, Philadelphia, Pa., 1949, p. 502; m.p. 302–303°. [h] G. Barger and E. Field, *J. Chem. Soc.*, **107**, 1025 (1915), reported this compound, indefinite m.p. about 250°, as a hydrate, but analysis indicated the material, dried in the oven at 80°, to be anhydrous. [i] No attempt was made to separate isomers. *Cf.*, F. L. Pyman, *J. Chem. Soc.*, **103**, 825 (1913).

The bis-β-carboline derivatives, XI–XIV, are more potent hypotensive agents of short duration than the corresponding mono salts; one mg. per kg. intravenously in dogs lowers blood pressure 10 to 40% for 5 to 20 minutes. The tetrahydro derivatives are slightly more active. No curarimimetic effects are evident at this dosage. The α-carboline, XXI, shows no effects at this level and is less toxic than the β-derivatives (mouse, I.V. LD_{50} for XXI is 28, for XIV is 4 mg. per kg.). The β-carbolines substituted on the indole nitrogen, such as XVI, XVII and XVIII are quite toxic, markedly lower blood pressure for short periods at 0.1 mg. per kg. and XVII is curarimimetic in dogs at 0.5 mg. per kg. I.V. The order of biological activity and toxicity is also the order of ionization of these compounds. A marked difference was observed in the order of magnitude of pK_a values of Py-N-substituted β-carboline salts (10–10.7)[9b] as compared with α-carboline methiodide (7.4). Of course, the indole N-substituted derivatives are ionized completely.

There are interesting differences between the bis-yohimbines and bis-tetrahydroberberines, each being fused five-ring systems. The C_6 and C_{10} alkylene bis-tetrahydroberberines completely block (curare-like) the dog nerve–muscle preparation at 0.5 and 0.3 mg. per kg., respectively; the C_4 compound shows no block at 5 mg. per kg. These large bis quaternaries differ from the hexa- to decamethonium type in that the C_6 and C_{10} homologs are nearly equally active. The bis-yohimbines, in

(10) Ind-N-methylharman has been similarly prepared with the aid of potassamide in liquid ammonia. *Cf.*, A. M. Stephen and R. Robinson, *Nature*, **162**, 167 (1948); D. Mukherji, R. Robinson and E. Schlittler, *Experientia*, **5**, 215 (1949).

(11) The successful application of this hydrogenation, which occurs only with the anhydronium base—not with its salts or with the unalkylated carboline—to a simple carboline derivative serves to substantiate conclusions drawn from the behavior of more complex substances. *Cf.* T. M. Sharp, *J. Chem. Soc.*, 1353 (1938); R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, **16**, 506 (1951); H. Schwarz and E. Schlittler, ref. 9b.

(12) *Cf.*, B. Witkop, THIS JOURNAL, **75**, 3361 (1953); B. Witkop and J. B. Patrick, *ibid.*, **75**, 4474 (1953). These authors report the formation of an unidentified product from a similar reduction of harmaline methochloride. In the present work the reduction went smoothly and in good yield to the tetrahydroharman derivative.

(13) G. Barger, A. Jacob and J. Madinaveitia, *Rec. trav. chim.*, **57**, 548 (1938), have prepared the compound from N-methyltryptamine.

(14) The pharmacological data obtained by Doctors Frank Macri and T. B. O'Dell of these laboratories; details of pharmacology to be described elsewhere.

(15) Low curare-like activity has been reported for some similar mono quaternary compounds. *Cf.* P. Waser, *Helv. Physiol. Pharmacol. Acta*, **7**, 493 (1949); V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2132 (1950).

TABLE II

BIS CARBOLINE SALTS OF GENERAL FORMULA: $R-\overset{\oplus}{(CH_2)_x}-\overset{\oplus}{R}\ 2X^{\ominus}$

Cpd.	Carboline (R)	x	X	Method	Cor. m.p., °C.[a]	Mol. formula	Analyses, % Calcd. C	Calcd. H	Calcd. X	Found C	Found H	Found X[b]
XI	Harman	4	Br	A	333–336	$C_{28}H_{28}Br_2N_4$	57.94	4.86	27.54	57.36	5.08	27.44
XII	Harman	5	Br	A	291–293	$C_{29}H_{30}Br_2N_4$	58.60	5.09	26.89	58.95	5.28	26.22
XIII	Harman	6	Br	A	>310	$C_{30}H_{32}Br_2N_4$	59.22	5.30	26.27	59.56	5.43	25.78
XIV	Norharman	5	Br	A	241–242	$C_{27}H_{26}Br_2N_4$	57.26	4.63	28.22	57.18	4.98	27.85
XV	1-Propyl-9-pyrid-3,4b-indole	5	Br	A	261–262	$C_{33}H_{38}Br_2N_4$	60.93	5.89	24.57	60.73	6.17	24.22
										60.95	5.87	23.74*
XVI	Py-N-Methylharman	5	Br	B	288–290	$C_{31}H_{34}Br_2N_4$	59.81	5.52	25.68	59.90	5.69	25.11
				B-1								25.22
XVII	Ind-N-Methylharman	5	I	C	265–267	$C_{31}H_{34}I_2N_4$	51.97	4.78	35.43	51.96	4.82	34.94
												34.99
XVIII	Ind-N-Methylharman	6	Br	A	270–271	$C_{32}H_{36}Br_2N_4$	60.38	5.70	25.11	60.16	5.62	25.26
XIX	Py-N-methyltetrahydroharman	4	Br	D	[c]	$C_{30}H_{40}Br_2N_4$	58.44	6.54		58.43	6.61	
										58.39	7.12	
XX	Py-N-Methyltetrahydroharman	6	Br	D	190–230	$C_{32}H_{44}Br_2N_4$	59.63	6.88	24.80	59.60	7.12	24.56
XXI	α-Carboline	5	Br	E	242–243	$C_{27}H_{26}Br_2N_4$	57.26	4.63	28.22	57.31	4.90	27.80*

[a] Most of the salts melt with decomposition. [b] See footnote (*b*) of Table I. [c] Evolved gas at 110°; softened gradually after this but was not completely melted at 250°.

TABLE III

BIS POLYCYCLIC SALTS OF GENERAL FORMULA: $-\overset{\oplus}{N}-(CH_2)_x-\overset{\oplus}{N}-\ 2Br^{\ominus}$

Cpd.	Base	x	Method	Cor. m.p., °C.[a]	Mol. formula	Analyses (%) Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br[b]
XXII	Yohimbine	4	F	267–274	$C_{46}H_{60}Br_2N_4O_6$	59.74	6.54	17.28	59.64	6.69	16.98*
XXIII	Yohimbine	5	F	249–250	$C_{47}H_{62}Br_2N_4O_6$	60.12	6.66	17.02	59.78	6.72	16.60*
XXIV	Yohimbine	6	F	269–276	$C_{48}H_{64}Br_2N_4O_6$	60.50	6.77	16.77	59.94	7.07	16.90
						N, 5.88; O–CH_3, 6.51			N, 6.03; O–CH_3, 6.44		
XXV	Yohimbine	10	F	230–232	$C_{52}H_{72}Br_2N_4O_6$	61.90	7.19	15.84	61.66	6.95	15.37
XXVI	Tetrahydroberberine	4	G	205	$C_{44}H_{50}Br_2N_2O_8$	59.06	5.63	17.86	58.68	5.60	17.46*
XXVII	Tetrahydroberberine	5	G	187–189	$C_{45}H_{52}Br_2N_2O_8$	59.50	5.77	17.60	59.45	6.07	17.87
XXVIII	Tetrahydroberberine	6	G	220–226	$C_{46}H_{54}Br_2N_2O_8$	59.87	5.90	17.32	60.29	6.12	17.39*
									59.72	6.11	17.27*
XXIX	Tetrahydroberberine	10	G	192	$C_{50}H_{62}Br_2N_2O_8$	61.35	6.38	16.33	61.13	6.46	15.86*

[a] The salts melt with decomposition. [b] See footnote (*b*), Table I.

contrast, show no curare-like activity at 1 mg. per kg. in dogs at the C_4 to C_{10} chain length. All of the bis-tetrahydroberberines produce a marked reduction in blood pressure in dogs, the bis-yohimbines are less active. The mouse intravenous LD_{50} values of the bis-yohimbines range from 0.5 to 2.5 mg. per kg.; in sharp contrast subcutaneous LD_{50} values are greater than 40 mg. per kg. Similar results were observed with the bis-tetrahydroberberines. These large molecules apparently are poorly or slowly absorbed from subcutaneous areas in mice.

Anticoagulant properties have been observed with a number of these compounds and bis-quaternaries are more active than monoquaternary derivatives. The compounds listed in the tables are relatively ineffective germicides.

Experimental[16]

Preparation of Bases. 1-Substituted-9-pyrid-3,4b-indoles.—Harman, m.p. 238–239°, after recrystallization from acetone, and norharman, m.p. 201–202°, from benzene, were prepared according to modifications of Robinson's procedure.[4,17] It was found, however, that the total volume of solutions and the quantity of potassium dichromate employed in the oxidation step (as described in ref. 17b) could be halved, with the result of greatly facilitating operations at no sacrifice in yield, provided that the reaction mixture was refluxed for 30 minutes after all of the oxidizing agent had been added. The use of strong sodium hydroxide solution in place of sodium carbonate markedly reduced emulsion difficulties encountered in the extraction of the product.

1-Propyl-9-pyrid-3,4b-indole.—This compound was prepared essentially by the method used for harman[17b] from tryptophan and a 0.1 mole excess of butyraldehyde heated on the steam-bath for 8 hours in aqueous acid solution. Excess aldehyde was extracted with ether, and dissolved ether boiled out, prior to the oxidation of the unisolated initial condensation product. Recrystallization from aqueous alcohol afforded a 34% yield of the propyl derivative, m.p. 216–218°.[18]

1,2-Dimethyl-2-pyrid-3,4b-indole (Py-N-Methylharman).—The procedure used was similar to that described for N-ethylnorharman.[19] Harman methiodide (II), m.p. 300° dec. and harman methobromide, m.p. 298–300° dec., were prepared in acetone. Dissolution of either salt in water followed by treatment with 20% sodium hydroxide precipitated the yellow base. The appearance and properties of the product depended markedly on the method of purification and on the degree of hydration (*cf.* Schwarz and Schlittler[9]). Recrystallization from water and from aque-

(16) The microanalyses reported in the tables were performed by the Clark Microanalytical Laboratories, Urbana, Illinois.

(17) (a) D. G. Harvey, E. J. Miller and W. Robson, *J. Chem. Soc.*, 153 (1941); (b) H. R. Snyder, S. M. Parmerter and L. Katz, THIS JOURNAL, **70**, 222 (1948).

(18) E. Spaeth and E. Lederer[6] prepared this compound by a Bischler–Napieralski reaction from tryptamine and give m.p. 211–212°.

(19) N. J. Leonard and R. C. Elderfield, *J. Org. Chem.*, **7**, 556 (1942).

ous alcohol gave bright yellow needles. Solutions were yellow with green fluorescence. On vacuum drying over P_2O_5 at room temperature followed by oven drying at 80° the material turned a deep green and its solutions were red with a much stronger green fluorescence. Recrystallization of the oven dried product from benzene afforded orange-brown needles, melting with decomposition at about 180° after preliminary darkening.[20]

1,2-Dimethyl-1,2,3,4-tetrahydro-9-pyrid-3,4b-indole (Py-N-Methyltetrahydroharman). A. By Platinum Hydrogenation.—This was most successful when the dry, purified methyl base was used.[11] A solution of 7.5 g. of dry methylharman in 150 ml. of methanol was hydrogenated at 40 p.s.i. with 0.6 g. of Adams platinum oxide. After 15 hours the catalyst was filtered off, the solution diluted with a liter of water and extracted with ether. The ether extract was dried and concentrated to an oily residue which was treated with water and again taken into ether. After removal of the solvent the oil was crystallized by trituration with low boiling petroleum ether and recrystallized from benzene and petroleum ether. A yield of 5.9 g. (79%) of pale yellow pellets, m.p. 108–110°, was obtained.[13]

Attempts to hydrogenate harman itself in acetic acid or harman methobromide in aqueous methanol over platinum oxide were not successful.

B. By Sodium Borohydride Reduction.—Slow, dropwise addition of 10.5 g. (0.276 mole) of sodium borohydride dissolved in 75 ml. of methanol to a suspension of 9.95 g. (0.036 mole) of harman methobromide in 175 ml. of methanol was accompanied by vigorous evolution of heat and hydrogen, and gradual dissolution of the harman salt. Addition was kept at a rate sufficient to maintain gentle refluxing. After all of the reagent had been added, the solution was refluxed for two hours. The solvent was removed, the residue taken up in water and the product extracted into ether. Purification as in A afforded a total of 5.7 g. (79%) of material which did not depress the melting point of the methyltetrahydroharman prepared by catalytic hydrogenation.

The compound obtained in either way exhibited an ultraviolet spectrum (measured in 95% ethanol with a Beckman DU quartz spectrophotometer) superimposable on that of tetrahydroharman, λ_{max} 280 mμ (log ε 3.86); λ_{max} 227 mμ (log ε 4.25).

Tetrahydroharman.—A solution of 15.0 g. (0.0825 mole) of harman in 750 ml. of anhydrous *n*-butyl alcohol was heated to boiling. Heating was discontinued and 60 g. of sodium was added as rapidly as possible to the hot, vigorously stirred solution. When the last of the sodium had dissolved, the hot colorless liquid was poured without delay (darkening occurred on standing) into a beaker containing 2 kg. of ice and 300 ml. of concentrated hydrochloric acid. After removal of the butanol by steam distillation *in vacuo* the remaining aqueous solution was made alkaline and extracted with ether. The ether extract was thoroughly dried with anhydrous potassium carbonate. Ethereal hydrochloric acid was added to the dry ether solution and the precipitated salt was charcoaled in water. Addition of aqueous ammonia yielded 11.8 g. (77%) of white crystalline precipitate, m.p. 179–181°.[21]

1,9-Dimethyl-9-pyrid-3,4b-indole (Ind-N-Methylharman).—To a slurry of 14.56 g. (0.08 mole) of harman in 400 ml. of dry toluene was added 3.2 g. (0.081 mole) of sodamide. The mixture was stirred and refluxed (oil-bath) for a total of 14 hours until evolution of ammonia had essentially ceased. The reaction mixture was transferred to a steam-bath, stirring was continued, and a solution of 10.08 g. (0.08 mole) of dimethyl sulfate in 25 ml. of dry benzene was added dropwise. The mixture was heated for four hours after all of the methyl sulfate had been added (development of strong green fluorescence). Water was added cautiously to the cooled mixture to decompose any excess sodamide, and, after washing with water, the organic layer was extracted with 3% sulfuric acid. The acid extract was charcoaled, brought to *p*H 8 ± with sodium carbonate and the product taken into ether. After drying and removal of the ether, the residue was recrystallized twice from benzene and Skellysolve B to yield 3.7 g. (23%) of Ind-N-methylharman, m.p. 100–102° (*cf.* ref. 10, also Spaeth and Lederer, ref. 5).

The remaining aqueous solution was made strongly basic and extracted to give a strongly green fluorescent ether layer. Only small amounts of unpurifiable material could be obtained from this extract.

9,9′-Pentamethylenebis-(1-methyl-9-pyrid-3,4b-indole).—A slurry of 10.92 g. (0.06 mole) of harman and 2.36 g. (0.0606 mole) of sodamide in 300 ml. of dry xylene was stirred and refluxed for 13 hours. The reaction mixture was transferred to a steam-bath, and, after the dropwise addition of 6.44 g. (0.028 mole) of 1,5-dibromopentane in 30 ml. of dry xylene, was stirred and heated for a total of 21 hours. Water was added, and a solid which precipitated was collected, washed with benzene and recrystallized from acetone to give 4.5 g. of recovered harman.

The combined benzene–xylene solution was extracted with 3% sulfuric acid, the acid layer made alkaline and the product taken into chloroform. After drying and removal of the solvent, the dark residue was recrystallized twice from alcohol and water and then twice from benzene and Skellysolve B to yield 2.25 g. (19%) of product, m.p. 203–205°.

Anal. Calcd. for $C_{29}H_{28}N_4$: C, 80.52; H, 6.53; N (basic), 6.48. Found: C, 80.62; H, 6.51; N (basic), 6.23.

The dihydrochloride, after recrystallization from methanol, melted above 280°.

Anal. Calcd. for $C_{29}H_{30}Cl_2N_4$: Cl, 14.03. Found: Cl (ionic), 13.62.

As before, only negligible amounts of strongly green fluorescent materials were obtained from the remaining alkaline layer.

9-Pyrid-2,3b-indole (α-Carboline).—This base, m.p. 211.5–212°, was synthesized according to Lawson, Perkin and Robinson[22] except that the cyclization was effected with 85% phosphoric acid[23] rather than zinc chloride. **The methiodide** (VI), prepared in benzene, melted at 218–220° after recrystallization from alcohol, pK_a (water) 7.4.

Tetrahydroberberine.—Zinc and acid reduction[24] of berberine sulfate yielded the tetrahydro base, m.p. 170–172°.

Representative Procedures for Preparation of Salts.—The methiodides and hydrochlorides described in Table I were prepared by the usual methods. In the preparation of the bis derivatives a 3 to 1 ratio of base to alkylene dibromide was found most generally satisfactory. A number of variations in solvent, conditions, etc., were tried in efforts to eliminate impurities (*e.g.*, mono quaternary material) and to improve yields. In the following, examples of some of the more successful procedures are presented.

1,2-Dimethyl-2-pyrid-3,4b-indole Methiodide (Py-N-Methylharman Methiodide) (III).—This salt was prepared in benzene essentially as described by Leonard and Elderfield[13] for the preparation of the ethiodide from 2-ethyl-2-pyrid-3,4b-indole. Methylharman showed a strong tendency to revert to unsubstituted salt when treated with various alkyl halides and for satisfactory alkylation it was necessary that the base be thoroughly dry. Nevertheless, the crude product from reaction with methyl iodide was found to be a mixture of recovered base, harman methiodide and III. The harman methiodide must have resulted from the presence of some water in the reaction mixture. Recrystallization of the crude material from ethanol gave a 52% yield of light yellow crystals, not melted by 270°. An aqueous solution did not yield a yellow precipitate or yellow-green solution on treatment with alkali, indicating that the indole N had been alkylated.

A. Reaction of Harman with 1,5-Dibromopentane. Compound XII.—A solution of 5.46 g. (0.03 mole) of harman and 2.3 g. (0.01 mole) of 1,5-dibromopentane in 150 ml. of acetonitrile was refluxed for 48 hours. The precipitate of 5.06 g. was filtered hot and washed with hot acetonitrile. After several recrystallizations from ethanol and water mixtures, the white powder melted at 291–293° with decomposition. The yield was 3.76 g. (64% on the basis

(20) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **113**, 759 (1936), reported m.p. 180° for this substance prepared by another method.

(21) G. Hahn and H. Ludwig, *Ber.*, **67**, 2031 (1934), give m.p. 179–180° for tetrahydroharman prepared from tryptamine.

(22) W. Lawson, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **125**, 626 (1924).

(23) R. Robinson and S. Thornley, *ibid.*, **125**, 2169 (1924).

(24) J. W. McDavid, W. H. Perkin, Jr., and R. Robinson, *ibid.*, **101**, 1220 (1912).

of the alkyl halide used). A total of 1.85 g. of harman was recovered from the filtrates.

Salts of harman and related materials (particularly the bis salts), although not obviously hygroscopic, retained water tenaciously. For analysis it was found desirable to dry these compounds at 100° *in vacuo* over P_2O_5. Compounds of type XII were prepared in a variety of ways. Absolute ethanol was a fairly satisfactory solvent for the reaction, but the product obtained with acetonitrile was more readily purifiable. In many experiments the precipitate was filtered off at intervals in order to ascertain the optimum reaction time.

B. **Reaction of 1,2-Dimethyl-2-pyrid-3,4b-indole with 1,5-Dibromopentane. Compound XVI.**—To 5.9 g. (0.03 mole) of the oven dried base in *t*-butyl alcohol was added 2.3 g. (0.01 mole) of 1,5-dibromopentane. The green-fluorescing solution was refluxed for 45 hours. The resultant precipitate was collected and recrystallized several times from methanol. A yield of 1.1 g. (18% on the basis of the dihalide) of light yellow powder, m.p. 288–290°, was obtained. Treatment with alkali indicated the substitution of the indole nitrogen.

B-1. **Preparation of XVI from 9,9′-Pentamethylenebis-(1-methyl-9-pyrid-3,4b-indole).**—Excess methyl bromide was bubbled into a solution of 2 g. of the bis base in 100 ml. of a 50–50 mixture of dioxane and ethanol, and the solution heated in a pressure bottle for 18 hours at 70°. The precipitate was collected and recrystallized from methanol to yield 2.25 g. (78%) of XVI.

C. **Reaction of Compound XII with Methyl Iodide. Compound XVII.**—A solution of 3.5 g. of XII in about 800 ml. of hot water was made alkaline with 10 ml. of 20% sodium hydroxide. After 15 minutes on the steam-bath the mixture was cooled and the yellow crystalline precipitate (2.26 g.) collected. Recrystallization from ethanol–water afforded 1.89 g., m.p. 242–250° dec. After drying in the oven at 80° the base was dissolved in 200 ml. of acetonitrile and refluxed 8.5 hours with 15 ml. of methyl iodide. The precipitate was recrystallized from aqueous ethanol to give 2.83 g. (67% over-all yield from XII) of yellow powder, m.p. 265–267° dec. An aqueous solution neither changed color nor was precipitated by alkali.

D. **Reaction of 1,2-Dimethyl-1,2,3,4-tetrahydro-9-pyrid-3,4b-indole with 1,6-Dibromohexane. Compound XX.**—Five grams (0.025 mole) of the base, dissolved in 60 ml. of absolute ethanol, was refluxed 20 hours with 2.0 g. (0.008 mole) of dibromohexane. Addition of ether to the cooled solution caused the precipitation of an extremely hygroscopic solid which was reprecipitated several times from propanol with anhydrous ether. A yield of 2.3 g. (45% on the basis of alkyl halide) of hygroscopic white powder, melting gradually from 190–230°, was obtained. No attempt was made to separate diastereoisomers.

E. **Reaction of 9-Pyrid-2,3b-indole (α-Carboline) with 1,5-Dibromopentane. Compound XXI.**—Attempted reaction in acetonitrile, as described for the preparation of the bis-harman derivatives, resulted largely in the recovery of starting material. A solution of 2.6 g. (0.0155 mole) of α-carboline with 1.2 g. (0.0052 mole) of dibromopentane in a mixture of 20 ml. of dioxane and 25 ml. of ethanol was refluxed on the steam-bath for 100 hours. The cooled solution was precipitated with ether. Recrystallization from propanol afforded 0.6 g. (20%) of white crystals, m.p. 242–243° dec.

F. **Reaction of Yohimbine with Dibromopentane. Compound XXIII.**—No doubt primarily as a result of steric hindrance, yohimbine gave notably poor yields of quaternary products with the higher alkyl halides. Side reactions involving formation of hydrohalide salts and apparent dehydrogenation of the tetrahydrocarboline nucleus (fluorescence) were prevalent. A variety of solvents (ethanol, *t*-butyl alcohol, propanol and dioxane) and solvent mixtures was explored. Higher temperatures (150°) appeared only to increase the proportions of by-products. The presence of some alcohol seemed to inhibit oxidation. As an example, a solution of 10 g. (0.028 mole) of yohimbine and 2.2 g. (0.0093 mole) of dibromopentane in a mixture of 100 ml. of dioxane and 50 ml. of propanol was heated on the steam-bath for 15 hours. The precipitate that formed on the addition of ether was reprecipitated twice from ethanol with ether and finally recrystallized from propanol to give 1.2 g. (13%) of white powder, m.p. 249–250° dec. About 0.5 g. of hydrobromide salt (not melted by 270°, precipitated from aqueous solution by alkali) was obtained from the purification mother liquors. Concentration and work up of combined mother liquors afforded 5 g. of unreacted yohimbine.

G. **Reaction of Tetrahydroberberine with 1,6-Dibromohexane. Compound XXVIII.**—Tetrahydroberberine was found to be much more refractory than yohimbine and was largely recovered unreacted when subjected to similar conditions. Therefore, 12.0 g. (0.035 mole) of tetrahydroberberine was dissolved in a mixture of 125 ml. of *t*-butyl alcohol and 125 ml. of toluene and refluxed for 160 hours with 2.8 g. (0.0115 mole) of dibromohexane. The resinous precipitate which formed on cooling was dissolved in cold ethanol and precipitated with ether. Two repetitions of the process gave 1.2 g. (11% yield on the basis of alkyl halide used) of hygroscopic yellow solid, softening 193–196° and melting with decomposition 220–226°. Addition of ether to the original mother liquor precipitated a solid. Recrystallization from ethanol afforded 5.2 g. (43%) of recovered tetrahydroberberine in the form of yellow prisms.

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