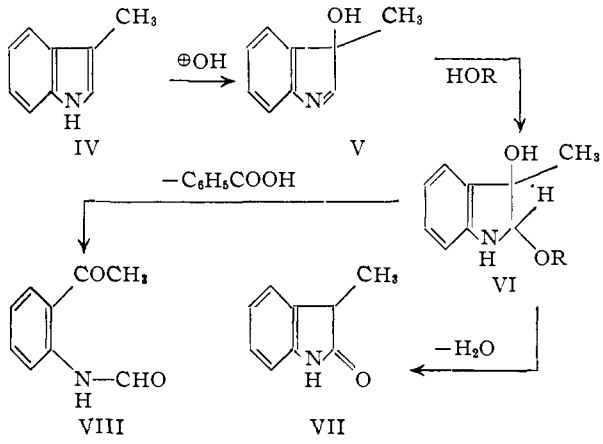


oxidation product of lysergic acid gave a product whose R_F-value was definitely different from the R_F of the presumable oxindole prepared by a more direct method. Such a distinction by paper chromatography was not possible for the analogous products from LSD.

(2) The attempted solvolysis of the commercially available bromination product of LSD, believed to be 2-bromo-LSD because of the negative Hopkins–Cole and Ehrlich reactions, was without success. Even heating with silver oxide for several hours failed to produce silver bromide.

(3) Finally, the reaction of LSD with disulfur dichloride (S_2Cl_2) was investigated. Pyrroles with free α and β-positions[12] and indoles with free α-position[13] are converted by this reagent to symmetrical disulfides. This procedure was applied to the trichloroacetate of LSD in order to prevent the basic tertiary nitrogen from reacting with the disulfur dichloride. The product obtained in this way had all the properties expected from a compound of the disulfide structure II. II is no longer physiologically active.[14] Whereas hydrolysis of the disulfide from tryptophan proceeds smoothly even with water alone, II had to be heated under fairly vigorous conditions with dilute acetic acid and zinc dust. Mineral acid led to resinification, and base could not be used without the danger of losing the amide group. The purification of the hydrolysis mixture by fractionation and countercurrent distribution finally yielded a pure compound which, though not obtained crystalline, was identical with regard to ultraviolet and fluorescence spectra, color reactions, distribution coefficients and R_F-values with the metabolite obtained by enzymatic oxidation of LSD. In addition to the negative Ehrlich and the positive Folin reactions the formation of a diazotizable amino group on treatment with base and the sharp absorption maximum at 259 mμ[15] support the oxindole structure III for this metabolite.

(12) H. Fischer and M. Herrmann, *Hoppe Seyler's Z. Physiol. Chem.*, **122**, 4 (1922).

(13) Th. Wieland, O. Weiberg, E. Fischer and G. Hörlein, *Ann.*, **587**, 146 (1954).

(14) E. V. Evarts, Proc. Symposium on Neurochemistry, Vol. 3, Paul B. Hoeber, Inc., New York, N. Y., in press, 1956.

(15) For a discussion of oxindole spectra, *cf.* R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta*, **34**, 1145 (1951).

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Quebrachamine. I

BY BERNHARD WITKOP

RECEIVED NOVEMBER 19, 1956

Dehydrogenation of quebrachamine, $C_{19}H_{26}N_2$ (II), furnished a mixture of homologous indoles, a mixture of 3-methyl-5-ethyl- and 3,5-diethylpyridine, a mixture of homologous carbazoles and a propyl derivative of α- or β-carboline. Two major oxidation products, the hydroxy base $C_{19}H_{26}N_2O$, m.p. 188° (V), and an N(a)-acetyldihydroindole base, $C_{21}H_{28}N_2O_2$, m.p. 213° (IV), were obtained on oxidation of II with ozone or hydrogen peroxide in acetic acid. The hydroperoxide VI, formed by catalytic oxygenation of II, on sublimation or warming in polar solvents disproportionated to V and oxygen. V, on catalytic hydrogenation, yielded the hexahydrohydroxy base $C_{19}H_{32}N_2O$, m.p. 177° (IX), which on dehydrogenation with palladium gave a base, $C_{11}H_{17}N$, isolated as the picrate, which also has been obtained from aspidospermine.

Quebrachamine has been isolated from the bark of *Aspidosperma quebracho blanco*,[1] together with aspidospermine and yohimbine or quebrachine, from *Aspidosperma chakensis*, together with spegazzinine,[2] and from the bark of *Gonioma kamassi*.[3,4] It belongs to the small group of crystalline oxygen-free plant bases. It contains an indole system, possibly unsubstituted at the α-position (positive Hopkins–Cole and Ehrlich reactions, red picrate),[5,6] and, judging from its resistance to mild catalytic hydrogenation, no other unsaturation. In addition to the indolic non-basic nitrogen N(a), there is a basic (*pK* 6.76, Table II) nitrogen N(b) which must be tertiary. The structure of a N-(3-indolylethyl)-1,2,3,4-tetrahydroisoquinoline (I, ring junction *cis* or *trans*)[7] is ruled out for, at least, two reasons: (i) the Hofmann degradation of compounds of type I, *e.g.*, of *chano*desoxyyohimbol[8] gives a volatile base, optically active N-methyl-*trans*-decahydroisoquinoline, in good yield. (ii) Catalytic dehydrogenation of I would lead to isoquinoline. Quebrachamine methiodide gives no easily volatile base on attempted Hofmann degradation, and the dehydrogenation of the free alkaloid does not lead to an isoquinoline.

(1) O. Hesse, *Ann.*, **211**, 249 (1882).

(2) O. O. Orazi, R. A. Corral, J. S. E. Holker and Carl Djerassi, *J. Org. Chem.*, **21**, 978 (1956).

(3) E. Schlittler and E. Gellért, *Helv. Chim. Acta*, **34**, 920 (1951).

(4) E. Gellért and B. Witkop, *ibid.*, **35**, 114 (1952).

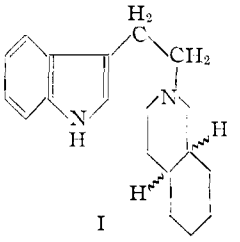
(5) A. J. Ewins, *J. Chem. Soc.*, **105**, 2738 (1914).

(6) E. Field, *ibid.*, **125**, 1444 (1924).

(7) C. Scholz, Dissertation, "Eidgenössische Technische Hochschule," Zürich, 1934, p. 32.

(8) B. Witkop, THIS JOURNAL, **71**, 2559 (1949).

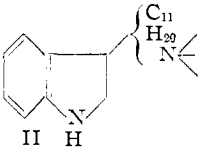
Dehydrogenation with zinc dust under the conditions applied to yohimbine,[9] C-dihydrotoxifer-



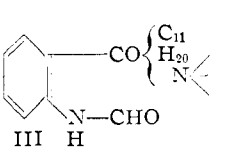
I

ine-I,[10] gelsemine[11] and aspidospermine[12] yielded four products: (i) The picrate of a base $C_9H_{13}N$. Its melting point (180–181°) was undepressed on admixture with 3,5-diethylpyridine picrate from aspidospermine (m.p. 180–182°).[12] The pyrolytic product apparently contains some 3-methyl-5-ethylpyridine whose picrate (m.p. 191–192°)[13] must be isomorphous with that of the homolog. It is present in an amount small enough not to alter significantly the analysis. The pyrolytic cracking of an ethyl to a methyl side chain is a frequent phenomenon observed also with the indolic degradation products. (ii) The steam-volatile indole fraction yielded a mixture of picrates which were exceedingly difficult to purify. One probably is dealing here with a similar mixture of β-alkylindole picrates as observed in the pyrolysis of yohimbine,[9] C-dihydrotoxiferine[10] and aspidospermine.[12] The non-volatile non-basic fraction formed needles, m.p. 218°, probably a mixture of carbazole and its 2-(or 3-)methyl homolog.[14] Dehydration of quebrachamine with palladium black gave ammonia and, in a yield of 1%, the picrate (m.p. 257°) of a base $C_{14}H_{16}N_2$ (m.p. 202°). Its ultraviolet spectrum (Table I) is suggestive of an α- or β-carboline system of which the dehydrogenation product may be a propyl derivative.

If quebrachamine contains an α-unsubstituted indole system, its formula can be resolved into II. Oxidation by ozone,[15] peracids[16] and oxygen[17] would be expected to lead to a substituted *o*-formaminophenone (III). Ozonization of quebrachamine in 60% acetic acid led, however, to two unexpected products (Chart I): an N(a)-acetyldihydro base IV, $C_{21}H_{28}N_2O_2$ (m.p. 213°), and a base V, $C_{19}H_{26}N_2O$ (m.p. 188°). Both bases are formed in very low yield probably by a secondary decomposition of ozone or ozonides to yield hydro-



II H



III H

gen peroxide in equilibrium with peracetic acid by interaction with the solvent. The ultraviolet spectra of both compounds ruled out a γ-quinolone system as is sometimes formed from 2,3-disubstituted indoles by intramolecular condensation of the ozonolysis product.[18] The products resulting from prolonged ozonolysis of quebrachamine could not be precipitated by base and were not obtained crystalline. The nature of base IV is disclosed by its spectral resemblance to N-acetylhexahydrocarbazole and by the loss of acetyl on acid hydrolysis to yield a dihydroindole base $C_{19}H_{26}N_2O$ (VII, m.p. 103°) isomeric with the hydroxy base V. The oxygen function in IV is lost on reduction with $LiAlH_4$ and an N(a)-substituted indole base (VIII) is obtained. The unusual N(a)-acetylation in the formation of IV is reminiscent of the acylating power of peracetic acid–sodium bisulfite mixtures[19] and may reflect on the role of quebrachamine as a biogenetic precursor of aspidospermine.

As expected, much higher yields of bases IV and V were observed in the oxidation of quebrachamine with peracetic acid, *i.e.*, mixtures of acetic acid and hydrogen peroxide. By careful control of time and temperature of the reaction (*cf.* Experimental) 90% of base V and 10% of base IV were obtained. With perbenzoic acid only base V was produced.

The infrared and ultraviolet spectra of the base $C_{19}H_{26}N_2O$ (V) suggest a dihydroindole derivative rather than a β-hydroxyindolenine (XII). The second tertiary nitrogen atom N(b) could possibly add to the β-hydroxyindolenine (XII) to form in aqueous or alcoholic solutions a quaternary eseroline type compound XIII. Base V in alcoholic solution does not obey Beer's law and in the determination of the *pK* value (inflection points at 11.9 and 5.65, Table II) which is higher than that of quebrachamine (6.76 in methyl Cellosolve) a marked hysteresis was observed on back-titration indicative of tautomerism (*e.g.*, XII ⇄ XIII). Lithium aluminum hydride reduces base V smoothly to quebrachamine, a type of reduction typical of β-hydroxyindolenines[20] or derivatives such as quinamine,[21] and catalytic reduction of V leads to a hexahydro base IX in which apparently full saturation has been achieved by hydrogenation of

TABLE I

ULTRAVIOLET SPECTRUM OF THE PRODUCT OF PALLADIUM DEHYDROGENATION OF QUEBRACHAMINE IN COMPARISON WITH α- AND β-CARBOLINE

Carboline, m.p. 202°, from quebrachamine	α-Carboline	β-Carboline
349 (3.70)	348 (3.72)[a]	342 (3.71)[a]
335 (3.70)	338 (3.70)	328 (3.70)
288 (4.24)	288 (4.23)	285 (4.2)
235 (4.57)	237 (4.61)	220–230 (4.6)

[a] L. Horner, *Ann.*, **540**, 77 (1939).

(9) B. Witkop, *Ann.*, **554**, 122 (1943); **556**, 111 (1944).
(10) H. Wieland, B. Witkop and K. Bähr, *ibid.*, **558**, 153 (1947).
(11) B. Witkop, THIS JOURNAL, **70**, 1424 (1948).
(12) B. Witkop, *ibid.*, **70**, 3712 (1948).
(13) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Compt. rend.*, **237**, 1718 (1953).
(14) *Cf.* 1-methylcarbazole, m.p. 120°, has been obtained from C-curarine by H. Schmid, A. Ebnöther and P. Karrer, *Helv. Chim. Acta*, **33**, 1486 (1950); 2-methylcarbazole melts at 259°; 3-methylcarbazole (m.p. 207°) has been identified in the mixture of products from the soda-lime distillation of strychnine acetic acid by K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947).
(15) B. Witkop, *Ann.*, **556**, 103 (1944).
(16) B. Witkop and H. Fiedler, *ibid.*, **558**, 91 (1947).
(17) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2196 (1951).
(18) B. Witkop and S. Goodwin, *ibid.*, **75**, 3371 (1953).
(19) A. H. Soloway and S. L. Friess, *ibid.*, **73**, 5000 (1951).
(20) B. Witkop, *ibid.*, **72**, 2311 (1950).
(21) R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

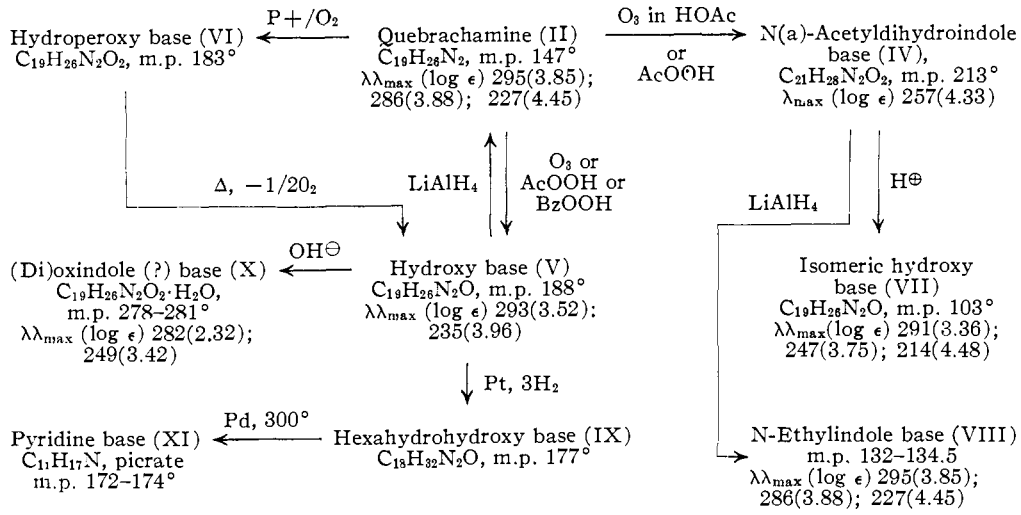
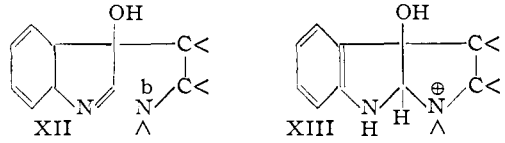


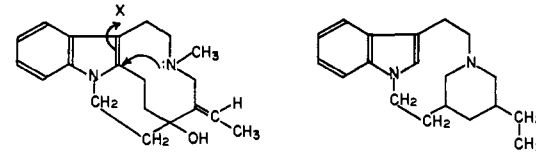
Chart I.—Products obtained in the oxidation of quebrachamine with ozone oxygen and peracids.

the benzene ring (*cf.* infrared spectra, Fig. 1) but with no loss of the hydroxyl group located initially



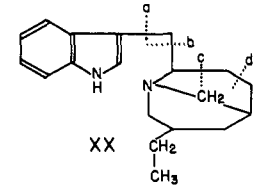
probably at a benzyl position. This retention of a hydroxyl group would indicate that the reduction of the aromatic ring is faster than the hydrogenolysis of a substituted benzyl alcohol. Base V is also formed from the hydroperoxide VI, obtained by catalytic oxygenation of quebrachamine, by thermal disproportionation: 2R–OOH → 2R–OH + O_2.[22] The most likely position for the initial attack of oxygen is again the β-indole carbon rather than a methylene group adjacent to the indole system or to N(b). Further evidence for the β-hydroxyindoline nature of V comes from the action of alkali which leads to two fractions, one having oxindole or dioxindole properties, the other displaying the spectral characteristics of indoxyl compounds. The formation of indoxyls under much less vigorous conditions has been observed in the autoxidation and rearrangement of the indole alkaloids (nor)mavacurine to (nor)fluorocurine[23] and of ibogaine to iboluteine.[24]

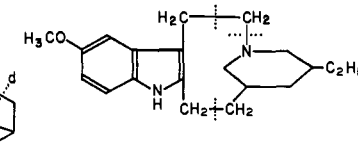
The interaction of N(b) with the double bond of the indole system as the result of a transannular or proximity effect is observed in ϵ_2-dihydromavacurine XVIII which adds a proton (X = H^+) or



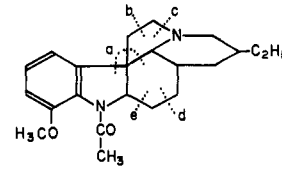
XVIII

XIX





XXI



XXII

methyl iodide (X = CH_3^+) as indicated by the arrows.[23] A related system XIX would be capable of similar effects. However, the isomeric quebrachamine has a strong narrow NH band in the infrared spectrum (Fig. 1), characteristic of an indole imino group, and its methiodide has an N-methyl and no additional C-methyl group.[25] The expression XX for quebrachamine offers no explanation

TABLE II

RELATIVE *p*H AND *pK* VALUES OF QUEBRACHAMINE AND SOME OXIDATION PRODUCTS

Compound	Relative basicity 0.01 *M* soln. *p*H, 20°	*pK'* and apparent *pK'* (inflections)	Solvent system
Quebrachamine (II)	8.53	6.76	80% methyl Cellosolve
Hydroxy base V	11.36	(7.43) (10.57)	Water
$C_{19}N_{26}N_2O$, m.p. 188°	12.62	(5.65) (11.9)	80% methyl Cellosolve
Hydroperoxy base VI	12.30	(9.65) (12.13)	50% water–ethanol
$C_{19}H_{26}N_2O_2$, m.p. 183°	12.28	(5.5) (11.0)	80% methyl Cellosolve
N(a)-Acetyl base IV			
$C_{21}H_{28}N_2O_2$, m.p. 213°	9.1	7.85	40% water–ethanol

(22) The acid-catalyzed rearrangement of the hydroperoxide VI in chloroform (ref. 17) led to traces only of ketonic material.

(23) H. Bickel, H. Schmid and P. Karrer, *Helv., Chim. Acta*, **38**, 649 (1955); P. Karrer and H. Schmid, *Angew. Chem.*, **67**, 361 (1955).

(24) M. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *ibid.*, **39**, 742 (1956).

(25) A. A. Patchett, unpublished observation.

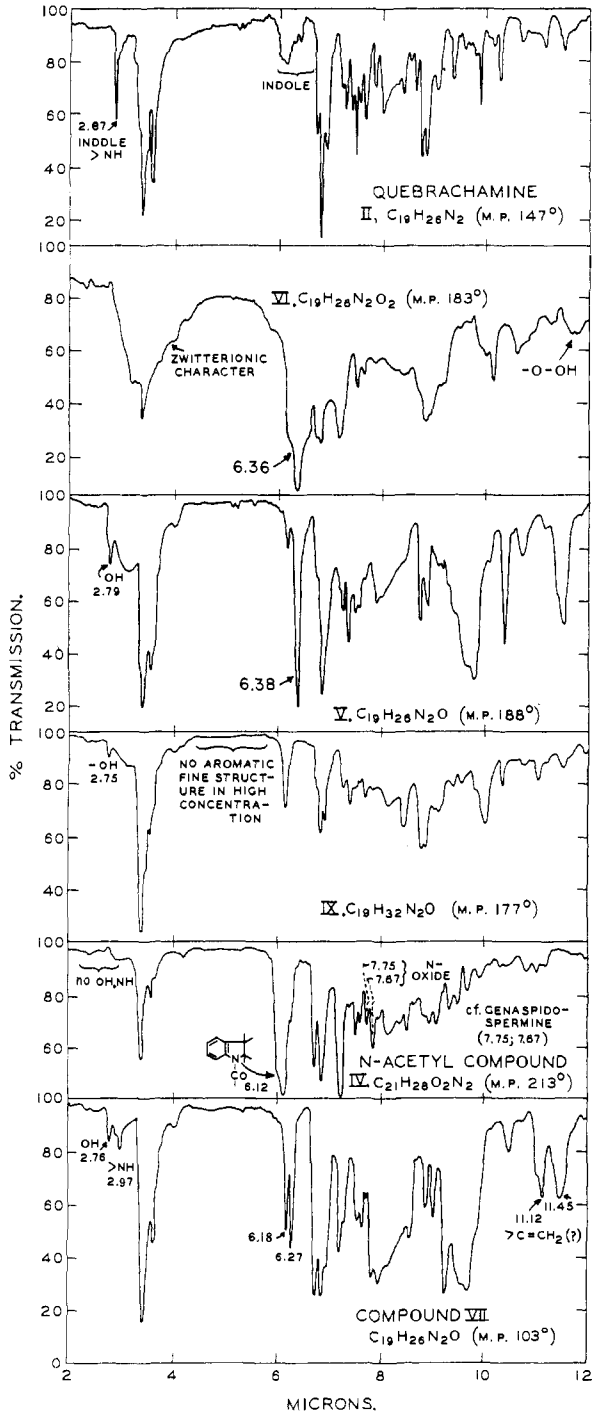


Fig. 1.—Infrared spectra of quebrachamine (II), bases VI, V, IX, IV and VII in chloroform.

for the reactions in chart I but serves as a model to illustrate formally the types of fission observed on dehydrogenation: b → skatol, c → 3-ethylindole + 3,5-diethylpyridine, d → 3-methyl-5-ethylpyridine. Rupture at a would yield indole and 3-ethyl-5 *n*-butylpyridine. The picrate (m.p. 172–174°) of a base of this composition was obtained when the hexahydrohydroxy base, m.p. 177° (IX), was dehydrogenated with palladium. No evolution of ammonia was observed in this dehydrogenation in contrast to all dehydrogenation reactions carried out with quebrachamine. The picrate of the pyridine base XI had the same m.p. and m.m.p. as a basic by-product from the zinc dust distillation of aspidospermine[12] (possible structure XXII, cleavage at a and c; other pyrolytic fissions at b, d and e.[26] Quebrachamine belongs to the family of (dihydro)indole alkaloids which on pyrolysis yield 3,5-disubstituted pyridine bases. Ibogaine (dihydro form possibly XXI)[27] retains only one methyl group of the second pyridine side chain. Whether complete loss of the second side chain occurs from position 4 or 5 of the 3-ethylpyridine obtained in the dehydrogenation of C-curarine[14] and the C-toxiferines[10] has not yet been ascertained.

NOTE ADDED IN PROOF.—Since the submission of this manuscript studies on the deuterium exchange (with K. Freter) and the nuclear magnetic resonance spectra of quebrachamine have adduced new evidence bearing on the α-substitution and on the presence of a N-methyl group. In coöperation with D. H. Conroy, to whom I am most indebted for discussions, NMR spectra and the communication of his results with aspidospermine [H. Conroy, P. N. Brook, K. Rout and N. Silverman, THIS JOURNAL, **79**, in press (1957)], formulas for quebrachamine and its transformation products have been postulated which will be discussed in a forthcoming joint publication.

Experimental[28]

Dehydrogenations. Zinc Dust Distillation of Quebrachamine.—Preliminary experiments showed that a ratio of 25 parts of reagent grade zinc dust to one part of free base was insufficient, since a considerable part of unchanged quebrachamine was found in the volatile fraction. For every distillation 50 mg. of quebrachamine was intimately mixed with 7 g. of zinc dust. Fifty such distillations were carried out using the same conditions and equipment as used previously for the dehydrogenations of yohimbine,[9] C-dihydrotoxiferine-I,[10] gelsemine[11] and aspidospermine.[12]

Basic Fraction.—The combined ethereal solutions of the volatile degradation products were concentrated to 50 cc. and extracted with dilute hydrochloric acid. The free bases were liberated from the solution of their hydrochlorides with base and taken up into ether. The more volatile bases were separated from the dark colored residue by steam distillation. The volatile bases were obtained from the steam distillate by salting out with ammonium chloride and extraction with ether. After evaporation of the ether there remained a few drops of a colorless oil with a strong collidine-like odor. The base was dissolved in 2 cc. of dilute hydrochloric acid, and excess aqueous picric acid solution was added. After 1 hr. the supernatant was clear and the flocculent picrate was collected and washed with water. The dry picrate crystallized on trituration with 0.5 cc. of cold acetone. The acetone washing was separated from the residue which on recrystallization from 1 cc. of acetone appeared in fine glistening needles, m.p. 179°. One more recrystallization raised the m.p. to 180–181°, undepressed on admixture with the 3,5-diethylpyridine picrate from aspidospermine.[12]

Anal. Calcd. for $C_9H_{13}N \cdot C_6H_3N_3O_7$: C, 49.45; H, 4.39; N, 15.38. Found: C, 49.23; H, 4.15; N, 15.21.

The basic residue from the steam distillation was taken up into ether. On slow evaporation, or on rubbing the residue with methanol, unchanged quebrachamine (m.p. 144°) was obtained.

Non-basic Fraction.—The ethereal solution from which the bases had been extracted with hydrochloric acid was evaporated and separated into a steam-volatile and non-volatile part. The volatile part had a strong indolic odor and was purified further by distillation *in vacuo*. This purified fraction was dissolved in petroleum ether and con-

(26) J. B. Patrick and B. Witkop, THIS JOURNAL, **76**, 5604 (1954).

(27) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 119.

(28) All melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and his associates of the Institutes' Analytical Service Laboratory.

verted into the picrate free of excess picric acid by cautious addition of a warm solution of anhydrous picric acid in petroleum ether (b.p. 60°). Not until after three recrystallizations from benzene–petroleum ether had the picrate lost its stickiness. Four more recrystallizations from benzene raised the m.p. as follows: 104°, 128°, 132°. From the last fraction which was just sufficient for C and H analysis, there was obtained after one more recrystallization a small sample, m.p. 143°, mixed m.p. with the isomorphous mixture of β-methyl- and β-ethylindole picrates (m.p. 154°) from yohimbine, 135–140°. The analysis was done on the picrate, m.p. 132°, and points to the presence of higher homologs of ethylindole.[29]

Anal. Calcd. for $C_{11}H_{13}N \cdot C_6H_3N_3O_7$: C, 52.58; H, 4.15. Found: C, 52.48; H, 4.15.

The analysis of a picrate from mother liquor, m.p. 128°, gave: C, 53.63; H, 4.31. From 3.64 mg. of this picrate there was obtained 0.713 mg. of AgI under the conditions of the Zeisel determination (2.57% "OCH_3") but no AgI under the conditions of the Herzig–Meyer determination.[8] This excludes methylation of the indole imino group in the course of dehydrogenation.[30]

The dark residue of the steam distillation of the volatile indoles was distilled at 140° (0.01 mm.). The colorless crystalline distillate on recrystallization from benzene appeared as sheaves of fine needles, m.p. 218°. The compound has all the properties of the product from the zinc distillation of C-dihydrotoxiferine-I[10] and is probably a mixture of carbazole and some homolog.[14] The Hopkins–Cole reaction is negative, the Ehrlich reaction gives a light-red color in the cold, dark-red on warming, fading on cooling, changing to dark blue-violet on addition of a trace of potassium nitrite.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.07; N, 7.73. Found: C, 85.86; H, 5.86; N, 7.51.

Dehydrogenation of Quebrachamine with Palladium Black.—A mixture of 0.5 g. of quebrachamine and 0.5 g. of freshly prepared palladium black was heated in a metal-bath to 320° for 4 hr. At 220° the odor and alkaline reaction (litmus paper) of ammonia was distinctly noticeable and persisted for about 3 hr. The crude dehydrogenation product was taken up in ether and separated from the palladium. The bases were extracted with dilute hydrochloric acid, liberated with alkali and again extracted into ether. After evaporation of the ether the brown semi-solid residue was freed of pyridines at 100° (1 mm.). Subsequent distillation at 180° (0.01 mm.) gave a droplet of a light-yellow oil, solidifying in the cold, which was dissolved in 1.0 *N* HCl and converted into the picrate. The dry picrate was triturated with 0.2 cc. of glacial acetic acid which dissolved dark-colored impurities. The yellow residue was freed of acetic acid with ether. The purified picrate was recrystallized from acetone, in which it is moderately soluble, yielding clusters of needles, m.p. 257° dec. On slow crystallization from more dilute solutions in acetone the picrate appeared in short prisms with the same m.p.

Anal. Calcd. for $C_{14}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 54.67; H, 3.87. Found: C, 54.83; H, 3.73.

By comparison the picrate of β-carboline (norharman) showed a similar dimorphism: from acetone it crystallized in light-yellow fine needles or yellow-red prisms, m.p. 265°, crystalline transformation at 220°, mixed m.p. with picrate from quebrachamine 240°.

Hydrochloride.—The solution of the picrate in acetone was acidified with 4 *N* hydrochloric acid and the picric acid extracted into ether. The solution of the base in hydrochloric acid shows in great dilution the same blue fluorescence as harman or norharman. The dry hydrochloride was recrystallized from ethanol–ether in sheaves of colorless needles, m.p. 210°.

Free Base.—The free base was liberated from the aqueous solution of its hydrochloride by the addition of alkali and extracted into ether. It crystallized from ether in colorless needles, m.p. 202°, mixed m.p. with norharman (m.p. 200°) 186°. For the ultraviolet spectrum *cf.* Table I.

(29) Isomorphous melting point curves (ref. 9) so far have not been recorded for 3-propylindole picrate (m. p. 113–114°).

(30) *Cf.* Cornanthine → N(a)-methylyobyrine (J. Le Men, *Compt. rend.*, **234**, 1559 (1952)); ibogaine → 1,2-dimethyl-3-ethyl-5-hydroxyindole (E. Schlittler, C. A. Burckhardt and E. Gellért, *Helv. Chim. Acta*, **36**, 1337 (1953)).

Dehydrogenations of quebrachamine with selenium at 300° led to the evolution of ammonia and yielded, besides volatile products, a neutral compound whose solution in benzene after filtration through alumina showed a strong green fluorescence. The dehydrogenation with sulfur led to the evolution of ammonia and H_2S beginning at 150°. In both cases the amorphous reaction products seemed to contain selenium or sulfur.

Base $C_{21}H_{28}N_2O_2$ (IV), M.p. 213°. A. By Ozonization of Quebrachamine in Acetic Acid.—One gram of quebrachamine was dissolved in 10 cc. of 60% acetic acid and a stream of oxygen containing 2.5% ozone was passed through the cooled solution for 2 hr. The reaction mixture was made alkaline to *p*H 8 and the base which precipitated collected. One obtained 0.4 g. of a light-brown powder, which showed a negative Hopkins–Cole reaction and did not react with dinitrophenylhydrazine. This material was placed in a filter thimble and continuously extracted with ether. On slow evaporation of the ether solution prisms appeared which were recrystallized from acetone in colorless needles, m.p. 213°. The viscous mother liquors on micro-sublimation in the vacuum of a mercury diffusion pump gave a second crop of the same compound. Whereas, on treatment with hot acid or base the pure compound showed no diazotizable aromatic amino group, the same test was positive with the crude ozonization product.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.2; H, 8.29; N, 8.23. Found: C, 74.74; H, 8.37; N, 7.68.

B. By Oxidation with Peracetic Acid.—A solution of 0.5 g. of quebrachamine in a mixture of 3 cc. of glacial acetic acid and 3 cc. of 30% hydrogen peroxide (Superoxol) was left for 40 hr. at 20°. The slightly pink solution was cooled and brought to a *p*H of 7.5–8.0 with alkali.

The precipitated base, after collecting, washing and drying, 45 mg. of a pink powder, was easily soluble in ether, methanol, acetone, etc. The solution in acetone on slow concentration deposited long glistening needles which were washed with little ice-cold acetone; m.p. 213°. The substance sublimed in high vacuum at 180–200° (bath). The reactions according to Ehrlich and Hopkins–Cole were negative. The azo test for aromatic NH_2 was ambiguous: By the short action of 2 *N* mineral acid on the steam-bath, a diazotizable amine seemed to be formed whereas longer action of 4 *N* hydrochloric acid led to the new base $C_{19}H_{26}N_2O$, m.p. 103° (see below). When analytically pure, negative diazo tests were given regardless of short or prolonged action of acid or alcoholic alkali.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.2; H, 8.29; N, 8.23; N–$COCH_3$, 12.64; mol. wt., 340.4. Found: C, 74.98, 74.84; H, 8.40, 8.26; N, 8.08; N–CO–CH_3,[31] 11.4; mol. wt., 351, 357 (Rast), 358 (Signer[32]).

Infrared Spectrum ($CHCl_3$).—No band in the OH, NH region; strong and broad band at 6.12 μ (*cf.* aspidospermine 6.13 μ, but N-acetyltetrahydrocarbazole, 5.91 μ); shoulders at 6.20, 6.26; 6.72s; 6.85s; 6.93sh; 7.22s; 7.51w; 7.60w; 7.75w; 7.87m; 8.15w; 8.37vw; 8.50w; 8.95w; 9.08w; 9.33w; 9.49w; 9.68w; 9.92w; 10.29vw; 10.83vw; 11.0w.

Ultraviolet Spectrum (95% EtOH).—λ_{max} (log ε) 257 mμ (4.33); 220 (4.52) end absorption; $\lambda_{min.}$ (log ε) 235 (3.94); *cf.* N-acetylhexahydrocarbazole, λ_{max} (log. ε) 254 (4.21).[33]

Microtitration (Table II, Fig. 2).[34]—The basicity of a $^1/_{250}$ *M* solution of the base in 60% ethanol–water was 9.1 *p*H units at 20°. The microtitration with glass electrode according to Ingold[35] carried out under nitrogen gave *pK* 7.85.[36]

Base VIII, M.p. 132–134.5°, by Reduction of IV with $LiAlH_4$.—When a solution of 80 mg. of base IV in ether was treated with excess $LiAlH_4$ there was a distinct reaction. After the usual work-up an oily reduction product was obtained which crystallized on rubbing with methanol. A still somewhat sticky sample of these crystals showed m.p.

(31) There was no O–$COCH_3$ according to the micro method of J. F. Alicino, *Anal. Chem.*, **20**, 590 (1948).

(32) R. Signer, *Ann.*, **478**, 246 (1930); *cf.* E. P. Clark, "Semimicro Quantitative Analysis," Academic Press, Inc., New York, N. Y., 1943, p. 78.

(33) H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948).

(34) Carried out by A. Peisker-Ritter, Brugg, Switzerland.

(35) W. Ingold, *Helv. Chim. Acta*, **29**, 1929 (1946).

(36) I am greatly indebted to Dr. Henry M. Kissman for carrying out the titrations in methyl Cellosolve.

132–134.5°. The infrared spectrum of the crude material has no bands in the OH–NH region, 6.22m; 6.72vs; 6.83–6.86s; 7.24–7.26m. The ultraviolet spectrum ($\lambda\lambda_{max}$ (log ϵ) 294 (3.83); 288 (3.85); 231 (4.55)] was almost identical with that of quebrachamine [$\lambda\lambda_{max}$ (log ϵ) 295 mμ (3.85); 286 (3.88); 227 (4.45)]. An analysis of the best crystalline fraction obtained (Found: C, 80.03; H, 12.34) gave a surprisingly high value for hydrogen (Calcd. for $C_{21}H_{36}N_2$: C, 79.68; H, 11.46). The hydrochloride was precipitated from ethereal solution with gaseous HCl as a hygroscopic powder, unsharp m.p. 155–165°; Hopkins–Cole and Ehrlich reactions essentially negative. By carrying out the Ehrlich directions according to Dutcher[37] with material from mother liquors, no color was observed until nitrite was added which produced a dark purple color.

Base VII, $C_{19}H_{26}N_2O$, M.p. 103°, by Acid Hydrolysis of IV.—A solution of 50 mg. of base IV in 4 cc. of 4 *N* HCl was left on the steam-bath for 3 hr. and then taken to dryness in a desiccator at room temperature. The colorless residue was easily soluble in water. From this solution alkali precipitated the flocculent base. The dry base, after two recrystallizations from ether, formed fine colorless needles, m.p. 103°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.58; H, 8.61; N, 9.14.

Infrared Spectrum ($CHCl_3$).—2.76, 2.96 (NH and OH); 6.18s; 6.27s; 6.73vs; 6.85vs; 6.93sh; 7.21m; 7.27sh; 7.53m; 9.67s; 10.48m; 11.12m; 11.45m.

Ultraviolet Spectrum (95% ethanol).—$\lambda\lambda_{max}$ (log ϵ) 291 (3.36); 247 (3.75); 214 (4.48); $\lambda\lambda_{min}$ (log ϵ) 271 (3.12); 234 (3.65); 222 (4.09). A comparable dihydroindole, *e.g.*, deacetylaspidospermine, shows $\lambda\lambda_{max}$ (log ϵ) 291 3.48); 245 (3.77); 215 (4.42).

Base $C_{19}H_{26}N_2O$ (V), M.p. 188°. A. By Ozonization of Quebrachamine.—The solution from the ozonization of 1 g. of quebrachamine from which the base m.p. 213° had been precipitated at *p*H 8 was made very strongly alkaline with excess 50% NaOH and extracted with ether. On slow evaporation of the ether extract colorless clear prisms were obtained, m.p. 188°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.82; H, 9.01; N, 9.49.

The ozonization of quebrachamine, even with less than the calculated amount of ozone, invariably led to water-soluble or acidic compounds which were no longer precipitated with base of any strength. When 1 g. of quebrachamine in 15 cc. of methanol was treated with excess 3% ozone under ice cooling, on evaporation 1.3 g. of a light-brown powder was obtained, insoluble in ether, easily soluble in alkali, which did not blue potassium iodide–starch paper. The reaction product with dinitrophenylhydrazone could not be crystallized.

B. By the Action of Perbenzoic Acid on Quebrachamine.—The solution of 184 mg. of quebrachamine in chloroform was left for 24 hr. with 140 mg. of perbenzoic acid in chloroform. The red solution was extracted with dilute alkali to remove the benzoic acid. After evaporation of the solvent the residue was taken up in 2 *N* HCl, brought to *p*H 8, and a small amount of basic material (starting material) removed by extraction with ether. On addition of strong alkali and extraction with ether, 110 mg. of the base $C_{19}H_{26}N_2O$, m.p. 186–188°, was obtained on recrystallization from ether.

C. By the Action of Peracetic Acid on Quebrachamine.—From the filtrate, *p*H 8, of the preparation of the base m.p. 213°, strong alkali precipitated more of a colorless base which on dilution with water went into solution again but which could be extracted with ether. The residue of the dried ether extract weighed 450 mg. Table III lists the yields of the two bases from quebrachamine as function of the time the peracetic acid is allowed to react.

Two recrystallizations from ether furnished large glass-clear prisms, m.p. 188°. After reaction with excess acetic anhydride at room temperature for 24 hr. unchanged starting material was recovered.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.75; H, 8.86; N, 9.68.

On slow recrystallization from acetone clusters of needles were obtained, m.p. 115°. The material gave an insoluble dinitrophenylhydrazone which indicates an acetone adduct.

(37) J. D. Dutcher and A. Kjaer, THIS JOURNAL, **73**, 4140 (1951).

The compound was dried for two days at 100° *in vacuo* and then melted at 178–180°. The analysis was performed on material dried at 20°.

TABLE III

YIELDS OF THE TWO BASES V (M.P. 188°) AND IV (213°) IN THE REACTION OF 500 MG. OF QUEBRACHAMINE WITH A MIXTURE OF 3 CC. OF GLACIAL ACETIC ACID AND 3 CC. OF 30% HYDROGEN PEROXIDE FOR VARIOUS LENGTHS OF TIME AT 20°

Time of reacn., 20° hours	Recovd. quebrachamine, mg.	Base (V) $C_{19}H_{26}N_2O$ m.p. 188°, mg.	Base (IV) $C_{21}H_{28}N_2O_2$ m.p. 213°, mg.	Acidic products not pptd. by base, %
14	200	290	..	...
24	..	470	35	...
40	..	450	45	Little
100	..	..	..	>90

Anal. Calcd. for $C_{19}H_{26}N_2O \cdot CH_3COCH_3$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.52; H, 8.53; N, 8.26.

Rapid recrystallization from acetone led to pure base, m.p. 186–188°, which was used for rotation: $[\alpha]^{20}D$ −504° (*c* 1.0 in 50% aqueous EtOH).

Color Reactions.—Quebrachamine gives a lasting strong purple color in the Hopkins–Cole test; the base m.p. 188° gives a red color (fading to blue-green after 20 hr.) similar to that shown by quebrachamine in high dilution. The Ehrlich reaction gives a pink color in the cold, which becomes red on warming. Samples recrystallized from acetone showed weak or no color in these tests.

Infrared Spectrum ($CHCl_3$).—Distinct sharp band at 2.78, broad and flat band at 3.15, characteristic C–H doublet at 3.42 and 3.57; slight but distinct dip at 4.04 (zwitterionic ammonium structure), very weak aromatic band at 6.20; 6.38vs; 6.86vs; 7.26m; 7.40s; 7.54w; 7.80m; 8.76s; 8.90m; 9.80vs; 10.39s; 10.71m; 11.17vw; 11.54s.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 293 mμ (3.52); 235 (3.96) at a molar concentration of 1.57×10^{-5}; 294 (3.48) at *c* 1.57×10^{-4}; at *c* 1.57×10^{-3} only linear absorption is observed which at 340 mμ has log ϵ 2.90 and at 360 mμ, 2.0; Beer's law is *not* obeyed.

Microtitration.—The basicity of a 0.01 *M* solution in water was 11.36 *p*H units at 20°. On titration with 0.01 *N* HCl two points of inflection were found: *pK* 10.57 and 7.43. On back-titration with 0.01 *N* NaOH a marked hysteresis was observed indicating rearrangement during titration.[21] In 80% methyl Cellosolve the *p*H of comparable solutions at the starting point was: quebrachamine 8.53; base V, 12.62. While quebrachamine gave a distinct *pK* of 6.76, only inflection points at 11.9 and 5.65 were observed for base V. The observed neutralization equivalent was within 3% of the calculated value. The maximum change in *p*H was observed after the addition of the amount of 0.01 *N* HCl in 80% methyl Cellosolve corresponding to 60% of the neutralization equivalent.

Hydrochloride.—The hydrochloride was prepared from ethereal solution with gaseous HCl. It formed a crystalline powder which appeared from chloroform solution on slow concentration in colorless clear prisms, m.p. 285–287° (sublimation 200–240°). Found: C, 65.44; H, 8.54; N, 8.12; Cl, 10.85. Calcd. for $C_{19}H_{26}N_2O \cdot HCl \cdot {}^3/_4H_2O$: C, 65.52; H, 8.25; N, 8.04; Cl, 10.3.

Infrared Spectrum ($CHCl_3$).—2.73vw; 3.14 (broad and strong band); 4.07 (saturated ammonium); 4.27vw, 4.93vw; 6.19m (phenyl or protonated azomethine?), 6.37sh; 6.80vs; 7.25m.

Picrate.—From the solution of the hydrochloride, aqueous picric acid precipitated the amorphous picrate which after collecting, washing and drying crystallized from aqueous acetone in glistening yellow scales, m.p. 173° (clear yellow melt).

Anal. Calcd. for $C_{19}H_{26}N_2O \cdot C_6H_3N_3O_7$: C, 56.92; H, 5.54; N, 13.28. Found: C, 56.49; H, 5.86; N, 13.04.

Hydriodide.—The addition of excess methyl iodide to an ethereal solution of base V led after a few minutes to the precipitation of a crystalline powder which was recrystallized from methanol–ether as needles, m.p. 280° (dec., darkening at 260°, sintering 275°). The reduction of the hydriodide

with lithium aluminum hydride or sodium borohydride yielded quebrachamine in good yield.[38]

Anal. Calcd. for $C_{19}H_{26}N_2O\cdot HI$: C, 53.52; H, 6.38; N, 6.58. Found: C, 53.62; H, 6.91; N, 6.88.

The picrate from this hydriodide melted at 172°, the free base, after recrystallization from hexane, melted at 186°, undepressed on admixture with the starting material.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 291 (3.50); 285 (3.51); 220 (4.38). The solutions obeyed Beer's law.

Reduction of Base V to Quebrachamine with $LiAlH_4$.—To a solution of 200 mg. of base V in ether was added excess $LiAlH_4$. After the reaction had subsided the mixture was left for 1 hr. at room temperature. After the usual work-up the ether-soluble fraction was dissolved in 0.1 *N* HCl and brought to *p*H 7.5. The precipitated base was recrystallized from methanol as colorless prisms, m.p. 145–147°, undepressed on admixture with quebrachamine. The comparison was confirmed by infrared analysis and by conversion to the picrate, red prisms from methanol, m.p. 194°, undepressed on admixture with authentic quebrachamine picrate. A by-product of this reduction was isolated when the aqueous solution was brought from *p*H 8 to 11. In addition to about 60 mg. of an oily ether-soluble base (picrate yellow prisms from MeOH, m.p. 170–172°) 10 mg. of a flocculent ether-insoluble product separated at the interface between water and ether; it formed short prisms from chloroform, m.p. 183–186° (yellow melt). The analysis (C, 66.79; H, 8.57) is reminiscent of the hydrochloride of base V. There was insufficient material for investigation. The infrared spectrum was that of an indole and very similar to, though not identical with, that of quebrachamine. Quebrachamine itself was recovered unchanged after refluxing for 1 hr. with excess $LiAlH_4$ in tetrahydrofuran.

Catalytic Hydrogenation of Base V.—A solution of 0.3 g. of base V in 4 cc. of glacial acetic acid was allowed to take up to 2 equivalents of hydrogen in the presence of 100 mg. of PtO_2. The uptake of hydrogen was slow (10, decreasing to 4 cc./hour). The reduction mixture after separation from the catalyst was brought to *p*H 8. A flocculent base (about 40 mg.) separated which formed beautiful prisms from acetone, m.p. 165°, after two recrystallizations 177°. The mixed m.p. with the starting base was 135–155°. The compound gave negative Hopkins–Cole and Ehrlich tests. Its solution in 95% ethanol had only end absorption in the ultraviolet. A highly concentrated saturated solution in chloroform showed no aromatic fine structure, a narrow band at 2.80 μ, 2.86sh; 3.05sh; 3.12sh; 3.17 (broad band), 6.16m; 6.84s; 6.92sh; 7.27w; 7.41m; 7.70w; 8.85m; 10.05m; 10.37w; 11.05.

Anal. Calcd. for $C_{19}H_{32}N_2O$: C, 74.95; H, 10.59; N, 9.20. Found: C, 74.78; H, 10.47; N, 8.91.

Further addition of 50% alkali to the aqueous reaction mixture precipitated two additional basic fractions at *p*H 12 and 14, which were taken up in ether separately. Slow crystallization of the latter fraction from acetone overnight at 0° yielded cushions of colorless needles, m.p. 136–138°. The Ehrlich reaction gave a wine-red color.

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 75.95; H, 9.39; N, 9.33. Found: C, 76.38; H, 9.48; N, 9.15.

The ultraviolet and infrared spectra of this "dihydro base" were practically identical with those of the starting material.

Further hydrogenation of the "dihydro base" m.p. 138° gave in the usual work-up at *p*H 8 some hexahydro base (m.p. 175°; C, 74.29, H, 10.45) and at *p*H 14 crystals from acetone, m.p. 141–145° (loss of acetone), resolidification at 165°, second m.p. 175°, mixed m.p. with starting base (m.p. 188°) 135–170°. Found: C, 74.11; H, 9.48; N, 8.05. Calcd. for $C_{19}H_{28}N_2O\cdot CH_3COCH_3$: C, 73.70; H, 9.56; N, 7.81.

Palladium Dehydrogenation of Hexahydrohydroxy Base IX.—In a preliminary experiment *no odor of ammonia* was noticeable when equal parts of base V and palladium black were heated to 300°. The same absence of ammonia was noticed when 500 mg. of the hexahydro base IX and 300 mg. of palladium black were heated in a Späth tube to 300–320° (metal-bath). During the course of 2 hr. 120 cc. of hydrogen was evolved. The dehydrogenation mixture was extracted with ether and the oily bases (104 mg.), after distillation at 150° (14 mm.), extracted into 0.1 *N* HCl. The picrate was made in aqueous solution and recrystallized from methanol; yellow needles were obtained, m.p. 168–170°, recrystallized from acetone, m.p. 172–174°, undepressed on admixture with "picrate A," m.p. 168–172° from aspidospermine.

Anal. Calcd. for $C_{11}H_{17}N\cdot C_6H_3N_3O_7$: C, 52.04; H, 5.14; N, 14.28. Found: C, 51.64; H, 5.43; N, 13.88.

Action of Potassium Hydroxide in Refluxing Amyl Alcohol on V.—A solution of 0.3 g. of the base V and of 1 g. of KOH in 5 cc. of amyl alcohol was refluxed for 1 hr. and then taken to dryness *in vacuo*. In the usual manner the mixture was separated into acidic, neutral and basic fractions. The acid fraction amounted to a few mg. of an ether-soluble oily product with a strong odor reminiscent of butyric or hexahydrobenzoic acid and showed a strong infrared band at 5.85 μ. The ether-soluble neutral fraction was negligible. The ether-soluble basic fraction (120 mg.) was slightly yellow with a powerful green fluorescence. It was purified on a small column of alumina. By careful elution with 10-cc. portions of chloroform–benzene (1:1), the *indoxyl fraction* was obtained pure enough for spectral characterization.

A crystalline fraction from ether, m.p. 142°, was analyzed: C, 67.19; H, 8.33 (Calcd. for $C_{19}H_{26}N_2O_2\cdot 1^1/_2H_2O$: C, 66.83; H, 8.56).

Infrared Spectrum of Indoxyl Fraction ($CHCl_3$).—2.88 μ (NH); 3.05; 4.07 (ammonium); 5.89s (CO of indoxyl); 6.15s (phenyl); 6.72–6.78 (sharp doublet); 7.23w; 7.45m; 7.55m; 8.57m; 9.07s; 10.35m; 11.25w; 11.57w.

Ultraviolet Spectrum of Indoxyl Fraction (95% EtOH).—$\lambda\lambda_{max}$ 392, 290, 234 mμ (log ϵ was not determined because there was not enough material to make a solution of known concentration); *cf.* isoquinamine: $\lambda\lambda_{max}$ (log ϵ): 397 (3.51); 255 (4.0); 232 (4.46).

Oxindole Fraction.—Elution with pure chloroform gave a colorless fraction whose spectral characteristics agree with an oxindole or dioxindole structure. Analysis of a sample, obtained crystalline on trituration with ether (m.p. 295–315° dec.) showed C, 68.65; H, 8.69 (Calcd. for $C_{19}H_{26}N_2O_2\cdot H_2O$: C, 68.64; H, 8.49. Calcd. for $C_{19}H_{26}N_2O\cdot HCl$: C, 68.26; H, 8.14). There was insufficient material for a chlorine determination. The high m.p. and part of infrared data support the salt, the method of preparation and the ultraviolet spectrum and oxindole band do not.

Infrared Spectrum ($CHCl_3$).—2.89 (sharp and narrow NH); 3.13 (broad on band); 3.98 (zwitterion or salt?). 5.84vs (CO of oxindole); 6.15s; 6.80s; 7.25m; 7.37m; 7.53s; 8.52w; 8.72w; 8.88w; 9.08s; 9.34w; 9.55w; 9.82m; 10.05m; 10.19m; 11.20w; 11.58m. By comparison dioxindole showed the following bands (Nujol): 2.92; 3.15; 5.85s; 6.13s; 6.80s; 7.14m; 7.39m; 7.65w; 7.82m; 7.89m; 8.12w; 8.35s; 8.48s; 8.68w; 9.01s; 9.35m; 9.86w; 10.70w; 10.96vw; 11.52w.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 282 (2.32); 249 (3.42); *cf.* gelsemine: 282 (2.69); 252 (3.33).

A similar compound had been obtained before from a preparation of 2 g. of base V, when the latter was not extracted immediately with ether but left in contact with strong alkali overnight. Most of the collected product was easily soluble in ether. However, there remained a small part which was almost insoluble in ether but soluble in chloroform. On slow evaporation from acetone it formed buttons of birefringent needles, showing a crystalline transformation into slim rods at 212–240°, 273° subliming. 278–281° melting with decomposition. Found: C, 68.57; H, 8.65; N, 8.14. For calcd. values see above.

The infrared spectra of this oxindole (or dioxindole) fraction showed the following bands ($CHCl_3$): 2.70w; 2.78sh; 3.15 (broad); 4.05w; 5.83vs; 6.18s; 6.37vs; 6.84vs; 7.25vw; 7.37s; 7.55m; 7.67w; 7.88w; 8.76w; 8.84–8.88m; 9.24w; 9.81m; 10.15w; 10.38m; 10.70m; 11.55m.

Catalytic Peroxidation of Quebrachamine to the Hydroperoxy Base VI.—A solution of 300 mg. of quebrachamine in 5 cc. of glacial acetic acid was added to a suspension of platinum, obtained by reduction of 100 mg. of PtO_2 in 3 cc. of glacial acetic acid, and shaken under oxygen. One molar equivalent of oxygen (25.3 cc.) was taken up in 90 minutes.

(38) Originally the hydriodide was considered to be the methiodide and the $LiAlH_4$ reduction erroneously interpreted to involve loss of a methyl group; *cf.* B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 4474 (1953).

No oxygen uptake was observed when ethyl acetate served as the solvent. The solution was filtered from the catalyst and brought to *p*H 9 by adding 4 *N* KOH at 0°. A negligible amount of basic material separated and was discarded. Concentrated alkali was added at 0°. The resulting base was extracted into ether, in which it was not very soluble. Some of the base crystallized at the interface and was collected by filtration. The residue from the ether extract as well as the crystals from the interface were recrystallized from acetone. Short colorless needles were obtained, m.p. 183° (yellow melt, evolution of gas). The compound turned starch–iodide paper blue.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 73.08; H, 8.04; N, 9.24.

Infrared Spectrum ($CHCl_3$).—2.84 μ (weak, broad band); 3.16 (shallow, broad band); 3.98 (shoulder); 4.35vw; 6.20vw; 6.36s; 6.85vs; 7.26w; 7.9w; 7.52w; 8.76m; 8.90m; 9.88w; 10.40m; 11.55m. When VI was left in chloroform solution for two days, a strong new band at 3.17 and a weak band at 5.74 μ developed.

Microtitration.—A 0.01 *M* solution in 50% water–alcohol showed 12.3 *p*H units at 20°. The microtitration gave values of *pK* 12.13 and 9.65. In 80% methyl Cellosolve (starting *p*H 12.28) *pK* inflection points at 11.0 and 5.5 were observed on titration with 0.01 *N* HCl. The neutralization equivalent was within 2% of theory.

Hydrochloride.—The addition of HCl gas to a chloroform solution of the hydroperoxide yielded tufts of needles, sintering and partial melting 180–185°, subliming in needles at 210°, melting again at 275–278°. Found: C, 61.76; H, 7.49; N, 7.33. (Calcd. for $C_{19}H_{26}N_2O_2 \cdot HCl \cdot H_2O$: C, 61.95; H, 7.93; N, 7.60.)

Conversion of the Hydroperoxide VI into the Base V. A. By Sublimation *in Vacuo*.—A small sample of the hydroperoxide was warmed in a molecular still to 180° (0.001 mm.). The crystalline material, washed down from the "cold finger," crystallized from ether in prisms, m.p. 188°, undepressed on admixture with base V, m.p. 188. The picrate was prepared (m.p. 172°) and identified with the picrate of base V by mixed m.p. and analysis.

B. By Rearrangement of the Hydroperoxide in Chloroform.—A solution of 0.5 g. of hydroperoxide VI in 40 cc. of chloroform, containing a few drops of a 4 *N* solution of HCl in ether, was refluxed until the test with potassium iodide–starch paper was negative. This took 50 minutes. From the chloroform solution there crystallized on cooling clear colorless prisms of a hydrochloride, m.p. 285–287° (sublimation 200–240°). Found: C, 65.68; H, 8.71; N, 8.12; Cl, 11.51. Calcd. for $C_{19}H_{26}N_2O \cdot HCl \cdot {}^3/_4H_2O$: C, 65.52; H, 8.25; N, 8.04; Cl, 10.6.

The infrared spectrum of this hydrochloride was practically identical with that of base V (2.73; 3.14; 4.06w; 6.18vs).

The mother liquors were fractionated on a column of 20 g. of alumina using 10-cc. portions of chloroform for elution. Fractions 4 and 5 (24 mg.) were ether-soluble, gave an ether-insoluble hydrochloride and showed the following bands in the infrared; 3.05 (broad); 5.98vs; 6.21s; 5.97vs; 6.01vs; 6.21s; 6.37m; 6.73vs. The ultraviolet spectrum showed only very weak absorption at 310 mμ where *o*-acylaminophenones absorb. A later fraction 13 (5 mg.) showed the following infrared bands: 3.10 (broad); 5.73s; 6.18s; 6.34s.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

The Self-condensation of 1,2,5-Trimethyl-3,4-diacetylpyrrole[1]

BY D. BRUCE BRIGHT[2]

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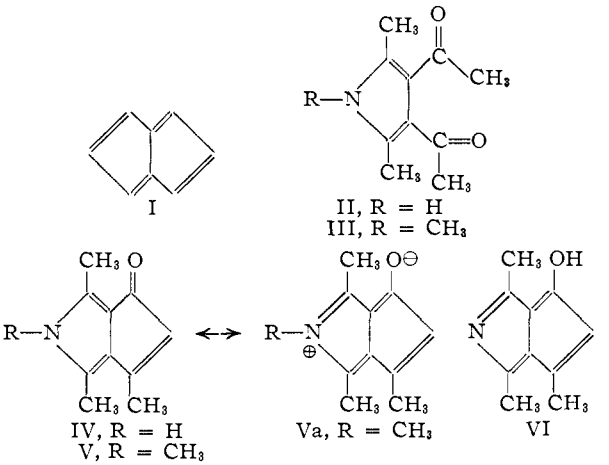
1,2,5-Trimethyl-3,4-diacetylpyrrole condenses in the presence of sodium isopropoxide to give two products to which structures VIII and IX have been assigned as the most probable. The formation and reactions of these products are discussed in connection with the possible aromaticity of the pentalene system, and it is concluded that no significant resonance stability of the pentalene type is present in an apparently favorable case.

With the exception of a few dibenzo-derivatives,[3] previous attempted syntheses of the pentalene system[4] (I) have been unsuccessful. The present work is concerned with the attempted synthesis of an azapentalene. This plan was chosen because the nitrogen analog would be expected to have about the same resonance energy as the carbocycle and the fact that suitable starting materials were readily available. The scheme adopted was to start with a suitably substituted pyrrole nucleus and to form the second five-membered ring by a cyclization reaction. The attempted cyclization of 2,5-dimethyl-3,4-diacetylpyrrole (II) with several basic catalysts was unsuccessful, presumably because of the initial formation of the salt from the acidic N–H group rather than an active methyl group.

Such a cyclization would have resulted in the formation of the bicyclic product IV or its enol VI, a hydroxytrimethylazapentalene. To test the feasibility of this type of cyclization, 1,2,5-trimethyl-3,4-diacetylpyrrole (III), in which the N–H group is substituted, was subjected to treatment with sodium isopropoxide in isopropyl alcohol. The expected product (V) was not obtained but instead two compounds (A and B) whose analyses



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(2) Department of Chemistry, Purdue University, Lafayette, Indiana.

(3) C. T. Blood and R. P. Linstead, *J. Chem. Soc.*, 2263 (1952).

(4) For a review see J. W. Cook, "Progress in Organic Chemistry," Vol. III, Butterworths Publications, Ltd., London, 1955, p. 68.