Anal. Calcd. for $C_{16}H_{14}S$: C, 80.64; H, 5.92. Found: C, 81.00; H, 6.15.

Seven grams of 3-(β-phenylethyl)-benzothiophene, 20 ml. of acetic anhydride, 30 ml. of glacial acetic acid and 35 ml. of 30% hydrogen peroxide[14] were refluxed for 1.5 hours. At the end of the reflux time, 150 ml. of ice-water was added, followed by 40 g. of sodium hydroxide. The mixture was extracted with 300 ml. of benzene. After evaporating the benzene on a steam-cone, and allowing to stand at room temperature for 24 hours, white crystals were formed. After recrystallizing the product twice from 95% ethanol, 2.9 g. (36%) of 3-(β-phenylethyl)-benzothiophene-1-dioxide was obtained; m.p. 89.5–90.5°.

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 70.99; H, 5.41.

(14) F. G. Bordwell, *et al.*, THIS JOURNAL, **71**, 1704 (1949).

To a solution of 2.0 g. of 3-(β-phenylethyl)-benzothiophene-1-dioxide in 100 ml. of absolute ethanol, 0.08 g. of 5% palladium on animal charcoal was added, and the material was hydrogenated[15] under an initial pressure of 45.6 p.s.i. The hydrogenation was continued for 1 hour even though no more hydrogen was taken up after the first 20 minutes. After filtering and evaporating to 25 ml. on a steam-cone and chilling in an ice–salt-bath, a nearly colorless, pasty oil was initially deposited followed later by white crystals. The crystals (1.2 g.) melted at 75–77° and after two recrystallizations from ethanol melted at 78.5–80.0°.

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.54; H, 5.92. Found: C, 70.37; H, 5.88.

(15) F. G. Bordwell, *et al.*, *ibid.*, **72**, 1985 (1950).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND THE NATIONAL INSTITUTES OF HEALTH]

Studies on Carboline Anhydronium Bases

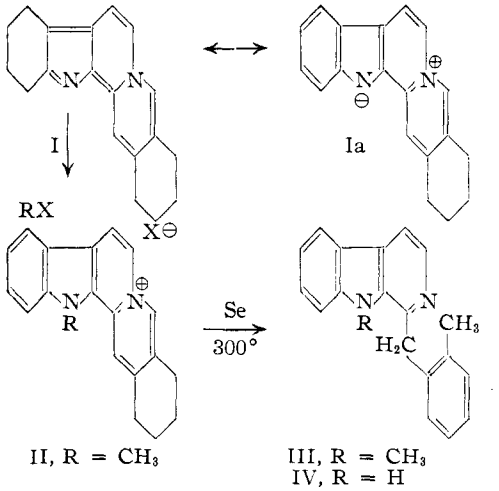
BY BERNHARD WITKOP[1]

RECEIVED AUGUST 15, 1952

Methylsempervirine chloride (II), the quaternary salt from the markedly hypotensive alkaloid sempervirine (I ⇄ Ia) on treatment with selenium yields N-methylyobyrine (III) and yobyrine (IV). On refluxing with sodium borohydride in methanol II furnishes methylhexahydrosempervirine in which the position of the double bond may be at $\Delta_{14,15}$ (in analogy to the formation of arecoline from methyl nicotinate) or possibly at $\Delta_{15,20}$ (IX) or $\Delta_{20,21}$ (X). N-Methylyohimbane (VIII), an isomer of methyloctahydrosempervirine (VII) was prepared by the methylation of yohimbane; on catalytic oxidation with platinum catalyst in glacial acetic acid it formed the cation (XIII) of methyltetradehydroyohimbane. The latter dehydrogenation at room temperature is considered the model reaction for the dehydrogenation of tetrahydroharmans in the plant leading to sempervirine, serpentine, alstonine and other anhydronium bases. Spectrophotometric and pharmacological data together with some observations in the 2-carboline series are presented.

Robinson has suggested the name *anhydronium bases* for the colored anhydro derivatives of aromatic onium hydroxides of which he prepared representatives in the 3-,[2] 4- and 2-carboline,[3] quindoline, indophenazine and other series.[3] Within the last few years, the alkaloids sempervirine[4,5] serpentine,[6] alstonine[6,7] and cryptolepine,[8] have been recognized as naturally occurring anhydronium bases of the 3-carboline and quindoline type. Recent reports on the beneficial effect of serpentine hydrochloride on patients suffering from hypertension[9] has again directed attention to natural and synthetic anhydronium bases, especially in the yohimbine series, and some recent studies on dehydrogenation and hydrogenation in this series, together with related observations made several years ago, are reported in this paper.

Sempervirine, isolated from the American yellow jasmine[10] and later from *Mostuea Buchholzii*[11] was recognized as the first naturally occurring anhydronium base (I ⟷ Ia) by R. B. Woodward[4] who predicted correctly the absence of an NH-imino band[12] in the infrared spectrum of sempervirine (Fig. 1a). The unusually high dipole moment of I (7–8 *D*[5,13] in benzene or dioxane) offers good evidence for the actual existence of Ia which adds alkyl halides[4,5] in the reverse fashion in which tertiary bases in this series normally react. The proof for the position of the methyl group in methylsempervirine chloride (II) was (besides the latter



(1) National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

(2) With regard to nomenclature, *cf.* J. M. Gulland, R. Robinson, J. Scott and S. Thornley, *J. Chem. Soc.*, 2926 (1929).

(3) J. W. Armit and R. Robinson, *ibid.*, **127**, 1604 (1925).

(4) R. B. Woodward and B. Witkop, THIS JOURNAL, **71**, 379 (1949).

(5) R. Bentley and T. S. Stevens, *Nature*, **164**, 141 (1949).

(6) E. Schlittler and H. Schwarz, *Helv. Chim. Acta*, **33**, 1463 (1950).

(7) R. C. Elderfield and A. P. Grey, *J. Org. Chem.*, **16**, 1506 (1951).

(8) E. Gellert, R. Hamet and E. Schlittler, *Helv. Chim. Acta*, **34**, 642 (1951).

(9) N. K. Chakravarty, M. N. Rai Chaudhuri and R. N. Chaudhuri, *The Indian Medical Gazette*, 348 (1951). The alkaloid tested there, according to a private communication from Dr. H. Schwarz, Ottawa, proved to be identical with serpentine.

(10) For a review, *cf.* L. Marion, "The Indole Alkaloids," in "The Alkaloids," edited by R. H. F. Manske and H. L. Holmes, Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 432.

(11) E. Gellert and H. Schwarz, *Helv. Chim. Acta*, **34**, 779 (1951).

(12) *Cf.* O. E. Edwards and L. Marion, THIS JOURNAL, **71**, 1695 (1949).[8]

(13) K. A. Jensen, *Acta Chem. Scand.*, **3**, 1447 (1949).

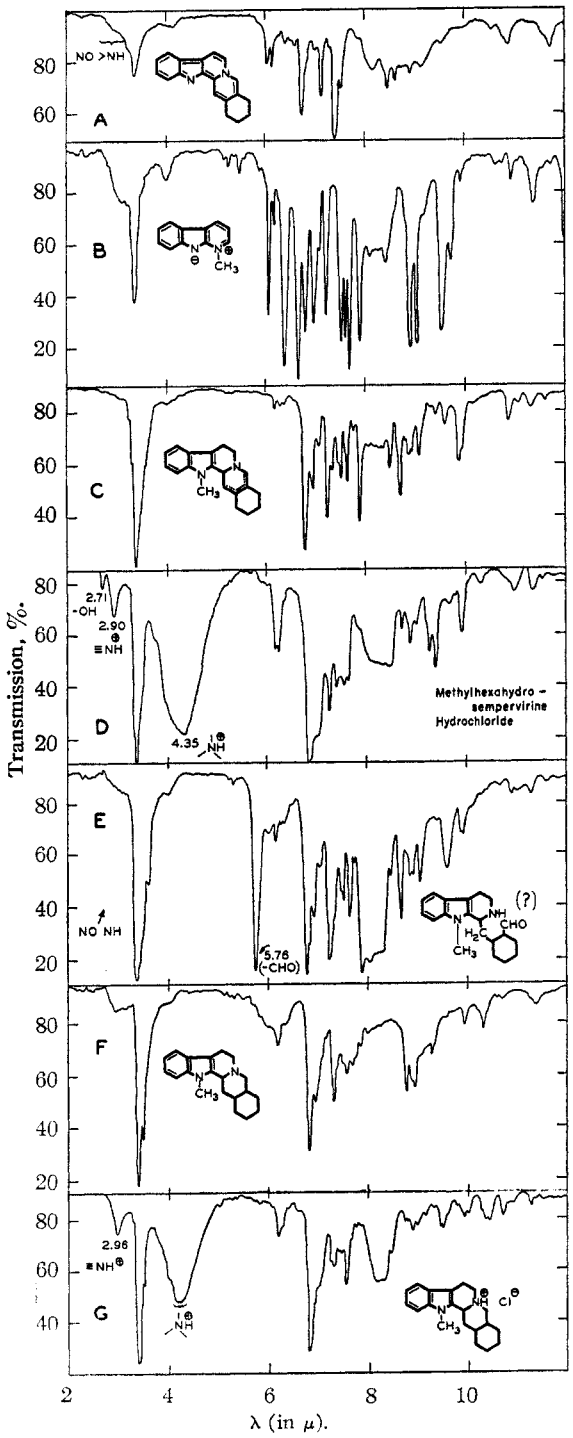
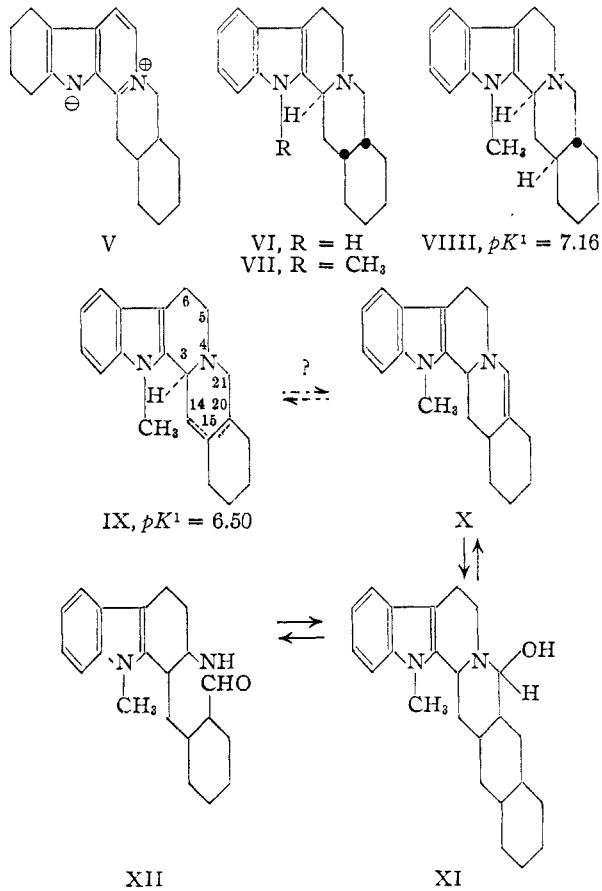


Fig. 1.—Infrared absorption spectra in chloroform solution.

synthesis[14]) the rearrangement to N-methylyobyrine (III) by the action of selenium at 300°. The compound was compared directly with a synthetic specimen[15,16] obtained through the kindness of Dr. P. L. Julian. Some yobyrine (IV) was also formed in the reaction as a result of dealkylation. The loss of alkyl groups from nitrogen as well as from carbon is a common phenomenon in selenium dehydrogenations.[17] The separation of III from IV was easily effected by chromatography in ether. N-Methylyobyrine (III) is much less strongly absorbed on alumina than yobyrine (IV) with its free indole imino group.

The Reduction of Methylsempervirine Chloride with Sodium Borohydride.—Reduction of sempervirine with platinum in acetic acid yields two (possibly diastereoisomeric) octahydrosempervirines (V), (m.p. 207–210° and 155–160°)[18] and (in alcoholic solution) another octahydrosempervirine identical with racemic alloyohimbane (VI, R = H).[19,20]



Reduction of methylsempervirine methosulfate with zinc in acetic acid yields a tertiary base, a methyloctahydrosempervirine (m.p. 187–189°, probably VII) which has not been characterized beyond its melting point.[5] N-Methylyohimbane (m.p. 179°), prepared by the methylation of yohimbane,[21] is apparently another isomer of octahydromethylsempervirine and probably best represented by VIII. Still another hydrogenation product, a

(14) R. B. Woodward and W. M. McLamore, THIS JOURNAL, **71**, 379 (1949); in the meantime these authors succeeded in synthesizing sempervirine itself by using the lithium derivative of unmethylated harman in the condensation with 2-isopropoxymethylenecyclohexanone.

(15) P. L. Julian and H. C. Printy, THIS JOURNAL, **71**, 3206 (1949).

(16) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).

(17) *Cf.* "Dehydrogenation with sulfur, selenium and platinum," P. A. Plattner, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 21.

(18) H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

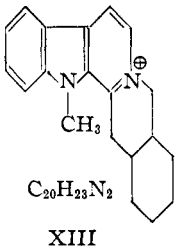
(19) A. Le Hir, R. Goutarel and M.-M. Janot, *Compt. rend.*, **235**, 63 (1952); *Bull. soc. chim.*, 1091 (1952).

(20) Rings D and E in the alloyohimbane series are probably *cis*-locked. The "α-position" (below the plane) of the hydrogen at C_3 is probably the same as in yohimbine, which is obtained analogously by the catalytic hydrogenation of tetradehydroyohimbine: M.-M. Janot, personal communication and *Bull. soc. chim.*, 1086 (1952).

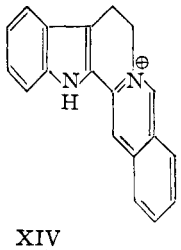
(21) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

methylhexahydrosempervirine (presumably IX, *i.e.*, *rac*-N-methyl, $\Delta_{14,15}$ or $\Delta_{15,20}$-yohimbane, m.p. 137–139°), was obtained when methylsempervirine chloride was refluxed in methanol with excess sodium borohydride. This base still clearly contains the indole chromophore (λ_{max} (log ϵ) 229 (4.58); 287 (3.87)) as shown by infrared and ultraviolet spectral comparison with N-methylyohimbane (VIII, Fig. 1, C) prepared by methylation of yohimbane.[21] The double bond which must be present in this compound may be placed in positions 14, 15 or 20.[22] The reasons in favor of $\Delta_{15,20}$ are: (i) catalytic hydrogenation with platinum in ethanol fails to reduce IX; the inertness of diquaternary double bonds is known from the steroid as well as rubremetine[23] series. (ii) The pK^1 value for IX (measured in 80% cellosolve) is about 0.7 lower than for N-methylyohimbane (VIII), comparable to similar decreases in basicity when going from an allylamine to the saturated system.[24] The isomeric allylamine with $\Delta_{14,15}$ must also be considered (see below). The alternative structure X would be expected to have a pK higher than VIII, although (as Prof. Prelog kindly pointed out in a private communication) there may be many intermediate pK values of N-substituted Δ^2-piperideines between the two extreme cases, Δ^2-N-methylpiperideine[24] and neostrychnine. The possibility of double bond migration[25] has not been ruled out yet. The hydrochloride of IX in dilute chloroform solution shows infrared bands compatible with the carbinol amine form XI (Fig. 1D). However solutions of dry hydrochloride of IX in dry chloroform showed no band at 2.71 μ and showed the same absorption in that region as N-methylyohimbane hydrochloride (Fig. 1G). Indication for the existence of XII comes from the infrared spectrum of the first chloroform fractions resulting from the chromatographic purification on alumina of the crude reduction product. These fractions showed a strong band at 5.76 μ (Fig. 1E) indicative of an unconjugated aldehyde[26] and yielded picrate C, analyzing for the picrate of an oxygen free base possibly derived from X. The striking dichroism[27] and the much lower melting point of this picrate support the assumption of a Δ_2-piperideine. Attempted reduction of IX in ethanol or glacial acetic acid failed and yielded back the hydrochloride of the starting material. The final decision on the exact location of the double bond and the possibility of double bond isomerism in methylhexahydrosempervirine (IX or X) cannot be made at this time.

Chloroform solutions of methylhexahydrosempervirine (IX or X) turn green and fluorescent on exposure to air and light. This phenomenon is probably not connected with the unsaturation of the molecule since N-methylyohimbane (VIII) behaves likewise. The catalytic autoxidation of N-methylyohimbane in glacial acetic acid with platinum catalyst, after uptake of one mole, leads to the picrate of XIII, a homolog of tetradehydroyohimbane,[20] showing the three ultra-



$C_{20}H_{23}N_2$



XIII	XIV
λ_{max} (log ϵ)	λ_{max} (log ϵ)[29]
362 (4.06)	352 (4.51)
310 (4.18)	281 (3.97) [*Cf.* XXXI·HCl, Table I]
257 (4.38)	252 (4.53)
	239 (4.55)

violet absorption peaks characteristic of the cations of serpentine, tetradehydroyohimbine and other anhydronium bases of this type.[28] Compound XIV[29] has an ultraviolet spectrum different from XIII as well as isoyobyrine (XXXI) hydrochloride. XIII in strong alkaline solution apparently does not form a carbinol base; the spectra of yobyrone in neutral[30] and acidic solution straddle λ_{max} of XIII (see Table I).

The conversion of N-methylyohimbane to a tetradehydro derivative of the alstonine, serpentine, etc., type by autoxidation is very suggestive of a similar dehydrogenation occurring in the plant.[31] In the case of yohimbine the same transformation has been effected by the use of lead tetraacetate,[32] or palladium black in the presence of maleic acid.[33,34] Catalytic oxidation of yohimbine (partial formulas XV ⇄ XVa) in glacial acetic acid also leads to the slow uptake of oxygen and to the formation of several oxidation products, some possessing a strong green fluorescence. In contrast to N-methylyohimbane, where dehydrogenation of Ring C supervenes, in yohimbine molecular

(22) The so-called *chano*isodesoxyyohimbol (B. Witkop, THIS JOURNAL, **71**, 2564 (1949)) for which a similar position of the double bond was discussed, is in all likelihood identical with yohimbane, *cf.* B. Witkop and S. Goodwin, *ibid.*, **75**, 3371 (1953).

(23) H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 391 (1952), and ref. 39.

(24) *Cf.* R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942).

(25) The ease and direction of double bond migrations into and out of conjugation with nitrogen apparently depends on the size and rigidity of the ring system: whereas migration of the former type has been observed with strychnine → neostrychnine, the reverse migration of a double bond in a Δ^3-pyrroline to give a Δ^4-pyrroline under the action of platinum catalyst, preceded by an unusually long "log period" was noticed with the anhydro compound from the two 3-hydroxystachydrines: J. W. Cornforth and A. J. Henry, *J. Chem. Soc.*, 597 (1952).

(26) The Schiff test for the compound was negative as it also is for the aldehyde base from the ozonization of the vinyldesbase from tetrahydroberberine [H. W. Bersch, *Arch. Pharmaz.*, **284**, 218 (1951)]. The absence of an NH-band in the infrared spectrum, though possibly due to similar interaction of the two functional groups, weakens the argument.

(27) A similar change from *yellow* to *red* accompanies the rearrangement of the picrate of Δ_3-N-methyl-2-phenyl-dihydroquinoline to that of Δ_2-N-methyl-2-phenyl-dihydroquinoline: J. Meisenheimer, *Ber.*, **58**, 2328 (1925). The latter compound seems to be an exception to the rule that Δ_3-N-methylpiperideines are stronger bases than their Δ_2-isomers (*cf.* R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942)).

(28) H. Schwarz, *Experientia*, **6**, 330 (1950).

(29) G. A. Swan, *J. Chem. Soc.*, 1720 (1949).

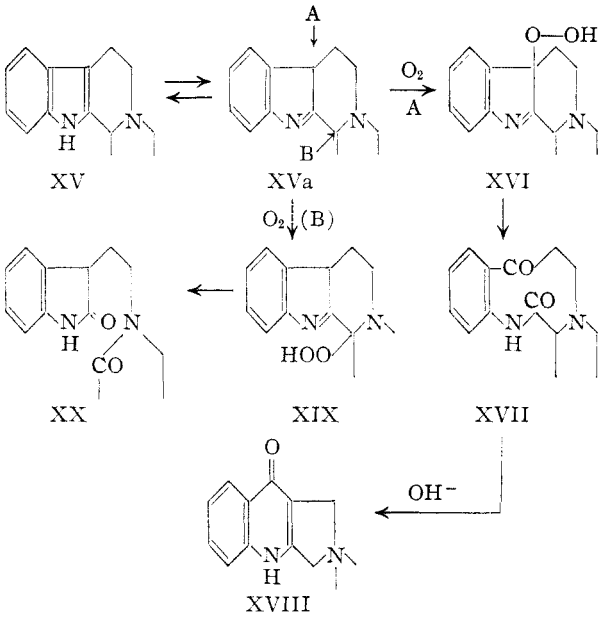
(30) V. Prelog, *Helv. Chim. Acta*, **31**, 588 (1948).

(31) *Cf.* P. Karrer, R. Schwyzer and A. Flam, *ibid.*, **35**, 857 (1952).

(32) G. Hahn, E. Kappes and H. Ludewig, *Ber.*, **67**, 686 (1934).

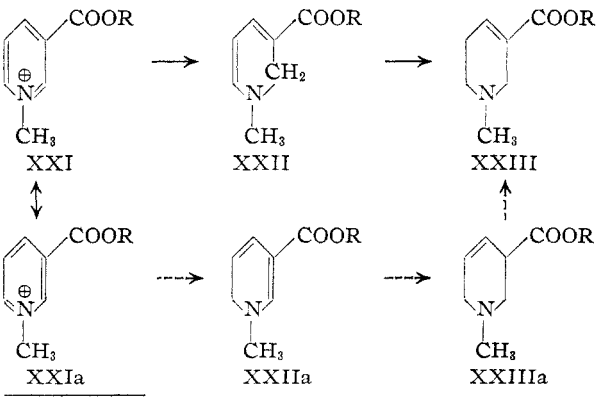
(33) R. Majima and S. Murahashi, *Proc. Imp. Acad. (Tokyo)*, **10**, No. 6 (1934); collected papers *Faculty Sci. Osaka Imp. Univ.*, **2**, 342 (1935); *C. A.*, **30**, 3437 (1936).

(34) R. Schwyzer, *Helv. Chim. Acta*, **35**, 867 (1952), prepared flavocorynanthyrine from desmethoxytetrahydrocorynantheine alcohol using essentially Majima's method without mentioning it.



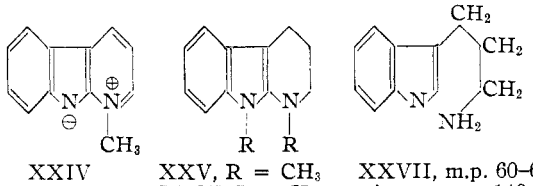
oxygen can attack according to schemes A and B (XVa). Scheme A leads, *via* XVI, XVII, to γ-quinolones,[35] a route so far not substantiated by the isolation of such alkaloids. Route B, analogous to the autoxidation of cycloöctenoindole,[36] could lead to a hydroperoxide XIX rearranging to an oxindole derivative XX. Scheme B might offer a possibility of linking gelsemine with the yohimbine series. Such autoxidation experiments are in progress.

That sodium borohydride reduces methylsempervirine to a hexahydro derivative deserves a word of comment. The reduction of tertiary[37] and quaternary heterocyclic bases[38] to unstable dihydro compounds by lithium aluminum hydride is well known. Further reduction has not been observed even in the case of rubremethinium bromide.[39] The reduction of the methiodide of ethyl nicotinate (XXI) with potassium borohydride[40] to give arecoline (XXIII) is an example strikingly similar to the reduction of sempervirine methiodide to methylhexahydrosempervirine. It seems that in such



pyridinium or aromatic quinolizinium systems the double bonds –RN=CH– as well as –NR—C=C– are amenable to reduction. The alternate pathway XXIa → XXIIa → XXIIIa has not been eliminated yet, since the isomerization of XXIIIa to XXIII was not disproved. By analogy the double bond in methylhexahydrosempervirine might be placed at $\Delta_{14,15}$, a position compatible with the *pK* measurements.

Like free sempervirine, the anhydronium base from α-carboline (prepared by a new method using polyphosphoric acid in the Ullmann reaction) methosulfate[3] (XXIV, infrared spectrum shown in Fig. 1B) remains unchanged on refluxing with sodium boron hydride. Its methiodide (XXIV,



XXIV XXV, R = CH_3 XXVI, R = H XXVII, m.p. 60–64° picrate, m.p. 146–149°[41]

methyl instead of negative charge at N(a)) reacts and forms a compound which, though not yet obtained crystalline, may be XXV. The reduction of α-carboline with sodium in butanol gave in small yield a compound m.p. 82–84°, picrate m.p. 134°, which is considered to be the interesting tetrahydro-α-carboline XXVI rather than homotryptamine XXVII.[41] Further work on the use of sodium borohydride on quaternary cyclic Schiff bases[42] is in hand.[43]

Appendix.—Prior to the settlement of the structure for sempervirine a number of isomers having the formula $C_{19}H_{16}N_2$ were considered[30] and rejected,[4,5,12,29] since no pentacyclic structure of the yohimbine type with partly hydrogenated rings offered an explanation for the characteristic ultraviolet spectrum and the strong basicity ($pK_A \sim 10.6$) of sempervirine. At that time, the isomer XXX was synthesized (using essentially P. L. Julian's route[44]) *via* the intermediates XXVIII and XXIX. This isomer showed no spectral relationship to sempervirine (Table I).

The methiodide and methochloride were also prepared in order to obtain spectrophotometric and pharmacological data (Tables I and II). Tests for curariform and toxic activity of related compounds in this series have been made before.[45–47] In these tests we have also included methylsempervirine chloride (II), isoyobyrine (XXXI)[44,48,49] methochloride and dihydroyobyrine (XXXII)[44]

(35) B. Witkop and S. Goodwin, THIS JOURNAL, **75**, 3371 (1953).
(36) B. Witkop, J. B. Patrick and M. Rosenblum, *ibid.*, **73**, 2641 (1951).
(37) F. Bohlmann, *Ber.*, **85**, 390 (1952).
(38) *Cf.* W. C. Brown, *Organic Reactions*, **6**, 469 (1951).
(39) P. Karrer and O. Rüttner, *Helv. Chim. Acta*, **33**, 291 (1950).
(40) J. J. Panouse, *Compt. rend.*, **233**, 1200 (1951).
(41) R. Majima and T. Hoshino, *Ber.*, **58**, 2046 (1925).
(42) The reduction of Schiff base methiodides by lithium aluminum hydride to give secondary amines is mentioned in an article by K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 951 (1952). *Cf.* J. J. Panouse, *Compt. rend.*, **233**, 260 (1951).
(43) B. Witkop and J. B. Patrick, in preparation.
(44) P. L. Julian, W. J. Karpel, A. Magnani and E. W. Meyer, THIS JOURNAL, **70**, 180 (1948).
(45) B. Witkop, *Ann.*, **554**, 125 (1943).
(46) P. Karrer and P. Waser, *Helv. Chim. Acta*, **32**, 409 (1949).
(47) P. Karrer, C. H. Eugster and P. Waser, *ibid.*, **32**, 2381 (1949).
(48) According to Karrer (ref. 46) this compound would be named "tetradehydrotetrabyrine." We prefer the name isoyobyrine as suggested previously in *Ann.*, **558**, 92 (1947).
(49) B. Witkop, *ibid.*, **554**, 122 (1943).

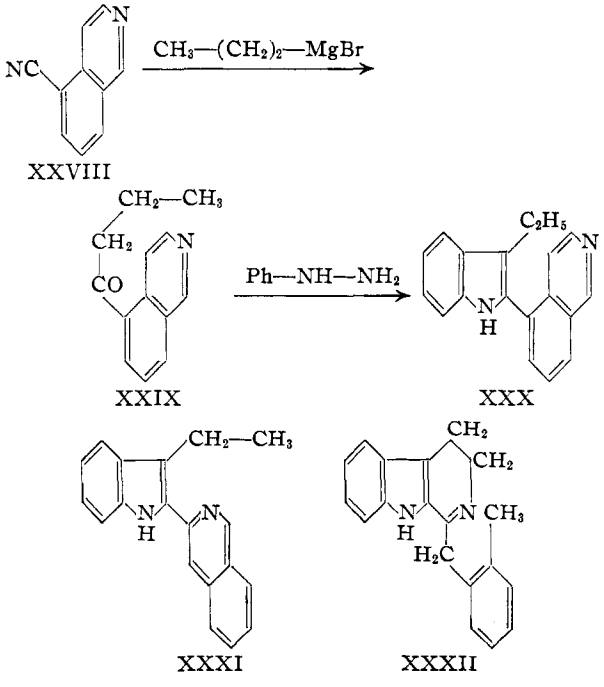
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA IN ETHANOL

The figures in brackets are inflection points.

Compound	Tertiary free base λ_{max} (log ϵ)	Cation λ_{max} (log ϵ)	Type of cation	Δ, λ_{max} cation − λ_{max} base
Isoyobyrine (XXXI)	333(4.42) 246(4.51) 233(4.48)	342(4.24) 235(4.59) [410(3.19)]	Hydrochloride	+9
5-[β-Ethylindyl]-isoquinoline (XXX)[a]	[350(3.63)] 322(3.79) 283(4.09)	326(3.74) 284(4.12)	Methiodide	+4
		366(3.96) 338(3.93)	Methiodide	+44 +(18)
Dihydroyobyrine[44] (XXXII)	320(4.21)			
		355(4.30)	Benzyl bromide	+35
Yobyrone	387(3.89) 293(4.31)	402(3.52)	Hydrochloride	+9
Tetradehydro-N-methylyohimbane (XIII)		362(4.06) 310(4.18) 257(4.38)	Picrate or hydrochloride; no change on addition of base	....
3,4-Dihydro-7,8-benzindolo-[2′,3′,-1,2]pyridocoline (originally proposed for sempervirine[30])	352(4.46) 342(4.36)			No appreciable shift apparent in neutral[29] or acid solution[12]
α-Carboline	347(3.72) 338(3.70) 288(4.23) 228(4.61)	[340(3.55)] 308(4.02) 269(4.15) 263(4.04) 245(4.14)	Methochloride	
2-Methyl-α-*iso*carboline	405(3.37) 324(4.01) 281(4.31)			
C-Curarine-III	Not known yet	362(4.20) 298(3.61) 237(4.03)	Methochloride (ref. 50)	....
3,4-Dihydro-1-methyl-5,6-methylenedioxyisoquinoline	317(3.77) 276(3.62) 229(4.28)	365(3.91) 304(3.74) 244(4.25)	Hydrochloride[51]	+48

[a] The positional effect of substitution on the indylisoquinolines XXX and XXXI is reminiscent of the band shifts observed with various indoloquinolines: Clemo and Felton, *J. Chem. Soc.*, 671 (1951); 1658 (1952).



methochloride. The latter is an isomer of C-Curarine-III chloride,[50] equally lacking curariform activity and showing a maximum (Table I) closer to that of C-Curarine III than all the other compounds listed in Table I, except the hydrochloride of 3,4-dihydro-1-methyl-6,7-methylenedioxyisoquinoline.[51,52] The last column in Table I lists the differences (in mμ) between the absorption peak of the (tertiary or quaternary) cation and that of the parent tertiary base. This difference, owing to the bathochromic effect of salt formation, is almost always positive, provided no chemical changes, such as hydration, shift of the >C=N—bond, or internal addition of

(50) *Cf.* H. Wieland, B. Witkop and K. Bähr, *ibid.*, **558**, 144 (1947).

(51) J. L. Bills and C. R. Noller, THIS JOURNAL, **70**, 957 (1948).

(52) Such a 3,4-dihydroisoquinoline component is also present in O-methylpsychotrine (H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 391 (1952)). The analogous dihydro compounds in the β-carboline series show the following maxima (measured in ethanol):

	λ_{max} base	λ_{max} hydrochloride
Harmaline	316 (4.32)	324 (4.32)
Dihydronorharman	320 (4.17)	360 (4.28)

The dihydronorharman was prepared according to C. Schöpf and H. Steurer, *Ann.*, **558**, 132 (1947). Analogous surprising differences were observed between harmine and norharmane (F. Pruckner and B. Witkop, *Ann.*, **554**, 127 (1943)).

TABLE II

PHARMACOLOGICAL ACTIVITY OF SOME QUATERNARY BASES

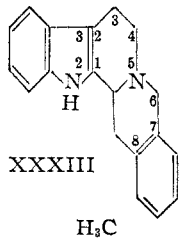
These tests were kindly carried out by Dr. E. F. Van Maanen in the Pharmacological Institute of Dr. O. Krayer at Harvard University.

Compound	Frogs (injected in left dorsal lymph sac) Doses, mg./kg.	Effects	Mice (injected intravenously) Doses, mg./kg.	No. of animals	Dead	Alive	Effects
Methylsempervirine[a] chloride (II)	10	After 4 hr. slight excitation, 6 hr. normal					
	1–5	.....					
Isoyobyrine (XXXI) methochloride	3	None	1	2	..	2	Quick respiration, 1 minute
	6	Slightly paralyzed after 2 hr. normal	2	2	..	2	
			3	2	..	2	Respr. slow for 1 min. then normal
			4	1	..	1	
			5	6	2	4	4 showed convulsions, respr. slow, in 1 min. normal or dead
			5.5	6	6	..	Struggling convulsions, respr. slow, dead or normal within 1 min.
			6	6	5	1	
Phenylhydrazone of 5-*n*-butyrylisoquinoline methochloride	0.1–30	None	10–20	3	..		None
			40	4	1	3	Convulsions, paralysis, then normal or dead
			50	6	2	4	
			70	4	4	..	
			100	1	1	..	Died instantly
5-[β-Ethylindyl]-isoquinoline (XXX) methochloride	2–20	None					
	50	Increasing paralysis after 1–3 hr. Dead after 5 hr.					
Dihydroyobyrine (XXXII) methochloride	5–30	None					

[a] Semipervirine itself has a fatal dose in dogs of 64 mg./kg., as Dr. N. C. Moran in the laboratory of Prof. A. P. Richardson found, and has only partial adrenolytic action. The most striking feature of its pharmacological action, according to Drs. Richardson and Moran, is the fall in blood pressure first noticed at 0.25 mg./kg. dog, which became more pronounced as the dose was increased. This effect will be studied further, since at this time nothing definite is known about the mechanism of hypotensive drug action.

functional groups occur. We have commented previously[53] on the diagnostic value of these figures.

At a time when the smooth reduction of cyclic lactams by lithium aluminum hydride[38] was not fully explored the easy reduction of oxindole to dihydroindole[54] prompted us to apply the same reaction to ketoyobyrine[55] which had just been elucidated at that time. Similar reductions have been reported in connection with the sempervirine problem by several authors.[12,29] A base $C_{20}H_{20}N_2$ was obtained from ketoyobyrine in this reduction.



XXXIII

According to m.p. and analysis this compound is possibly 7,8-(2,3-tolu)-1,2-(2,3-indolo)-3,4,6,9-tetrahydropyridocoline (XXXIII), the homolog of the catalytic reduction product of norketoyobyrine[29] and an isomer of a compound obtained by P. L. Julian by a novel type of cyclization[16] also brought about by lithium aluminum hydride.[56]

Experimental[57,58]

Methylsempervirine Chloride (II).—Methylsempervirine iodide,[59] prepared from sempervirine and methyl iodide in chloroform solution, was suspended in methanol and freshly prepared silver chloride was added in excess. After stirring and warming for a few minutes the silver halides were separated by centrifugation. The methanol extract on evaporation left the methochlorides as a brown crystalline residue which on recrystallization from hot water formed yellow rods, charring increasingly on warming to 300° (reported 330–332°[14]). The methochloride is easily soluble in water. In sufficient dilution the yellow aqueous shows a strong blue fluorescence. When poured into alkali a solution of the

(53) B. Witkop, J. B. Patrick and H. Kissman, *Ber.*, **85**, 949 (1952).

(54) The claim that only N-methyloxindoles are amenable to this reaction (ref. 15) has been disproved by the lithium aluminum hydride reduction of gelsemine: M. Kates and L. Marion, THIS JOURNAL, **72**, 2308 (1950).

(55) R. B. Woodward and B. Witkop, *ibid.*, **70**, 2409 (1948).

(56) The reverse transformation, *viz.*, oxidation of methylsempervirine base with alkaline potassium ferricyanide (*cf.* Decker, *J. prakt. Chem.*, **47**, 39 (1893); W. H. Perkin, *J. Chem. Soc.*, **113**, 518 (1918)) and dehydrogenation with palladium to N-methyldehydroketoyobyrine was tried without success. The quaternary quinolinium bases seem to be unusually stable as shown by their stability to oxidizing agents as well as by spectral evidence (L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952)). It could be argued that formation of a carbinol base from the methyl sempervirinium cation, and further transformations, might influence the aromaticity of two fused pyridine rings (rather than one, as is the case in the berberinium series) (*cf.* ref. 5), but this mode of reasoning does not explain the behavior of XIII.

(57) All melting points are corrected (Kofler block), all boiling points are uncorrected.

(58) The technical assistance of Miss Catherine Donaher is gratefully acknowledged.

(59) W. G. C. Forsyth, S. F. Marrian and T. S. Stevens, *J. Chem. Soc.*, 582 (1945).

methochloride remains clear for a few seconds; then the solution becomes cloudy and a flocculent precipitate is formed.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot CH_3Cl \cdot {}^1/_2H_2O$: C, 72.38; H, 6.09; N, 8.94. Found: C, 72.33; H, 6.21; N, 8.72.

Sempervirine Methopicrate.—Aqueous picric acid precipitated the yellow flocculent picrate from a solution of sempervirine methochloride in water. Recrystallization from acetone yielded yellow-brown prisms, m.p. 233–235°, clear dark melt (reported 239–240°).[14]

Anal. Calcd. for $C_{20}H_{19}N_2 \cdot C_6H_3N_3O_7 \cdot {}^1/_2H_2O$: C, 59.43; H, 4.23; N, 13.33. Found: C, 59.68; H, 4.13; N, 12.93.

Rearrangement of Sempervirine Methochloride by Selenium. A. N-Methylyobyrine (III).—An intimate mixture of 50 mg. of sempervirine methochloride and of 25 mg. of black powdered selenium was heated to 295–300° for ten minutes.[30] This operation was repeated with seven more portions. The combined reaction products were extracted several times with a total of 120 ml. of boiling benzene. The benzene solution was poured onto a column of 20 g. of aluminum oxide (Brockmann). The following fractions were obtained.

Fraction	Eluent	Ml.	Description	Compound
I	Benzene	150	.....	.....
II	Ether	50	Colorless oil, picrate m.p. 233–235°	N-Methylyobyrine
III	Ether	100	Colorless oil and crystals, hydrochloride m.p. 229°	N-Methylyobyrine
IV	Ether	500	Colorless needles, hydrochloride m.p. 240°	Yobyrine
V	Ether	500		

Fraction I, about 10 mg. of a colorless oil, was dissolved in hot 0.1 *N* hydrochloric acid and aqueous picric acid was added. The crystalline picrate was collected, dried and recrystallized from acetone as golden-yellow glistening needles, m.p. 233–235°.

Anal. Calcd. for $C_{20}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 60.58; H, 4.11. Found: C, 60.38; H, 4.15.

On admixture with a sample of synthetic N-methylyobyrine[15,16] picrate (m.p. 233°) no depression was observed. Fraction II, partly crystalline colorless oil, was microsublimed at 0.01 mm. The crystalline sublimate formed at a bath temperature of about 150° was readily soluble in ether. The hydrochloride of this base was obtained as short colorless prisms from hot 0.1 *N* hydrochloric acid, m.p. 229°. The solutions, especially in dilution, showed a strong blue fluorescence.

Anal. Calcd. for $C_{20}H_{18}N_2 \cdot {}^3/_4H_2O$: C, 71.14; H, 6.16; N, 8.33. Found: C, 71.05; H, 6.28; N, 8.14.

In order to avoid loss of hydrogen chloride the compound was dried only at room temperature for 6 hours; the hydrochloride, properly dried, is probably anhydrous. The mixed melting point of this hydrochloride with yobyrine hydrochloride (m.p. 241°) showed a distinct depression (222°). From a solution of the pure hydrochloride in water alkali precipitated the free N-methylyobyrine which crystallized from benzene in rosettes, m.p. 98°. On recrystallization from methanol–water the melting point was raised to 103°. Purest synthetic N-methylyobyrine is reported to melt at 106°.[15,16] The infrared spectrum of the free base in chloroform lacked the strong NH band at 2.87 μ characteristic of yobyrine. The ultraviolet spectrum in ethanol showed the four typical maxima also present in yobyrine: 351, 339, 291 and 239 mμ.[60,61] A Herzig–Meyer determination carried out with a sample of the hydrochloride from mother liquors gave a value of 4.87% NCH_3, a value much higher than the blanks usually run in this series.[62]

B. Yobyrine (IV).—Fractions III and IV were combined and distilled at 0.01 mm. at 150° (bath). The oily distillate thus obtained was first washed with a small portion of cold ether. The remaining less ether-soluble fraction was taken up in warm ether. On cooling, colorless fine needles appeared, m.p. 207°, which after recrystallization from benzene melted at 212°, undepressed on admixture with a sample of purest yobyrine (m.p. 216°). The infrared spectra in chloroform solution of yobyrine from sempervirine and from yohimbine were identical.

Hydrochloride.—The hydrochloride, described previously,[63] was found to melt at 240° (dec.) rather than to sinter at that temperature.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot HCl$: C, 73.90; H, 5.51; N, 9.09. Found: C, 73.93; H, 5.59; N, 8.84.

Picrate.—The picrate also previously described,[62,63] melted at 245–250° (reported 239°, 250°) and gave the following analysis.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 59.88; H, 3.82; N, 13.97. Found: C, 59.58; H, 3.70; N, 13.65.

Reduction of Sempervirine Methochloride with Sodium Borohydride. Methylhexahydrosempervirine (Presumably IX).—Sempervirine methochloride (1.7 g.) was dissolved in 20 ml. of methanol and refluxed for two hours in the presence of 1.5 g. of sodium borohydride. The methanol was removed *in vacuo*, the residue was triturated with water and the aqueous suspension was extracted with chloroform. The chloroform extract, after drying and evaporation, left a yellow-brown residue which was extracted exhaustively with ether. The residue of this ether extract left 1.25 g. of a slightly yellow crystalline base appearing from methanol in fine colorless needles, m.p. 133.5–136°, and, after a second recrystallization from the same solvent, m.p. 137–139°.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.19; H, 8.28; N, 9.58. Found: C, 81.99; H, 8.16; N, 9.30.

Microtitration.—Purest methylhexahydrosempervirine was dissolved in cellosolve and titrated with 0.1 *N* HCl; found, pK_a 6.50; equiv. wt., 303 (calcd. 292).[64]

In a number of previous reductions the method for the isolation of the ether-soluble base differed in that the initial brown-red chloroform extract was chromatographed over aluminum oxide. From a reduction of 0.2 g. of sempervirine methochloride using chloroform as eluent the following fractions were obtained.

Fraction	Wt., mg.	Description	Infrared spectrum	Derivatives
I	58	Yellowish oil	5.76μ (strong), unconjug. aldehyde	Picrate C, m.p. 155–158°
II	40			
III	18	Yellow-brown crystals on standing	Weak band 5.85μ	Picrate B, m.p. 188–192°
IV	9			
V	10		No band below 6.0μ	
VI	27			

Attempted Hydrogenation of Base $C_{20}H_{24}N_2$ (IX).—When 91 mg. of the base in 4 ml. of ethanol was stirred under hydrogen in the presence of platinum catalyst from 50 mg. of platinum oxide, no hydrogen uptake was observed, even after the addition of a few drops of ethanolic hydrogen chloride. When 90 mg. of the base was reduced in 4 ml. of glacial acetic acid with 90 mg. of platinum, the hydrogenation was stopped after the uptake of 7 ml. of hydrogen after 105 min. The basic part was worked up in the usual fashion from aqueous solution by the addition of alkali and extraction with ether. Since crystallization of the free base proved difficult, a few drops of aqueous 2 *N* hydrochloric acid were added to a fairly concentrated solution of the base in methanol. On slow evaporation there appeared colorless needles which were washed with acetone and ether, showing then the characteristic double melting point (182–189 and 235–240°) of the hydrochloride of the starting material (see below), undepressed on admixture.

Catalytic Oxidation.—When 40 mg. of $C_{20}H_{24}N_2$ was shaken under oxygen in 4 ml. of ethyl acetate in the presence of 50 mg. of reduced platinum oxide 3.4 ml. of oxygen were taken up in the course of three hours. After filtration from the catalyst and evaporation of the solvent, the residue from methanol solution on slow concentration at room temperature deposited yellow short rods exhibiting a strong, green fluorescence in alcoholic solutions, m.p. 278–280°; found:

(60) F. Pruckner and B. Witkop, *Ann.*, **554**, 132 (1943).
(61) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 618 (1946).
(62) B. Witkop, THIS JOURNAL, **71**, 2559 (1949).
(63) B. Witkop, *Ann.*, **554**, 111 (1943).
(64) I am indebted to Dr. Charles Wiesner for arranging for these measurements.

C, 53.84; H, 5.98; λ_{max} 372 (low extinction); *cf.* autoxidation of hydrochloride in chloroform solution.

Hydrochloride.—From a solution of base IX in ether addition of ethereal hydrogen chloride caused the precipitation of the hydrochloride as a colorless crystalline powder, m.p. 170°, viscous dark-orange melt, 205° resolidification to needles melting at 225° (dark melt). The solution of the hydrochloride in chloroform shows two distinct bands at 2.71 and 2.90 μ characteristic of hydrochlorides of carbinolamines.

Anal. Calcd. for $C_{20}H_{26}N_2O\cdot HCl$: C, 69.16; H, 7.85; N, 8.07. Found: C, 69.56; H, 8.15; N, 8.27.

On drying to constant weight at the temperature of refluxing ethyl acetate the above hydrochloride lost 5.36% of its weight; calculated for 1 mole of water, 5.19%.

Anal. Calcd. for $C_{20}H_{24}N_2\cdot HCl$: C, 72.94; H, 7.66. Found: C, 72.44; H, 7.62.

Chloroform solutions of this hydrochloride in contact with air and light on standing for five days or longer developed a strong green fluorescence (λ_{max} 365 mμ) and three new characteristic bands in the infrared, *viz.*, 5.85, 6.00 and 6.11 μ.

Picrate A.—The solution of the above hydrochloride in water gave, on addition of aqueous picric acid, the crystalline yellow picrate which after one recrystallization from methanol showed m.p. 177–185°, after a second recrystallization from the same solvent the m.p. was 170–172°.

Anal. Calcd. for $C_{20}H_{26}N_2O\cdot C_6H_3N_3O_7$: C, 57.88; H, 5.42; N, 12.98. Found: C, 57.46; H, 5.44; N, 12.42.

Picrate B.—When the picrate was prepared directly from the free tertiary base (IX) in methanol by the addition of methanolic picric acid the picrate appeared in yellow needles, m.p. 176–182°, after second recrystallization 188–192°.

Anal. Calcd. for $C_{20}H_{24}N_2\cdot C_6H_3N_3O_7\cdot CH_3OH$: C, 58.59; H, 5.67; N, 12.66. Found: C, 58.63; H, 5.96; N, 12.32.

Picrate C, Presumably Derived from the Isomeric Base X.—The combined fractions I and II from the chromatographic purification of the chloroform solution containing the crude amino aldehyde (XII) were converted to the picrate in aqueous solution. The dried picrates were extracted in the cold with small portions of methanol removing a picrate more soluble in methanol, tufts of fine yellow needles, m.p. 177–181° (found: C, 60.94; H, 5.10). The picrate fraction less soluble in methanol was recrystallized from acetone. On slow crystallization, one obtained what seemed to be a mixture of well-formed yellow and red rods which were separated mechanically, showing both the same m.p. 155–158°. On closer inspection the apparent difference in color was due to a striking case of *pleochroism*. The free base, prepared from 15 mg. of this picrate, was not obtained crystalline.

Anal. Calcd. for $C_{20}H_{24}N_2\cdot C_6H_3N_3O_7$: C, 59.89; H, 5.22; N, 13.43. Found: C, 59.97; H, 5.26; N, 12.96.

From the acetone mother liquor there was obtained on standing a picrate fraction, m.p. 152–156°, which analyzed correctly for an isomer of picrate B.

Anal. Calcd. for $C_{20}H_{24}N_2\cdot C_6H_3N_3O_7\cdot CH_3OH$: C, 58.59; H, 5.67; N, 12.66. Found: C, 58.73; H, 5.50; N, 12.75.

Reaction of $C_{20}H_{24}N_2$ with Methyl Iodide.—When 50 mg. of the base IX in 20 ml. of absolute ether was left standing overnight with excess methyl iodide in the presence of 2,6-lutidine, a white microcrystalline powder separated. A solution of this compound in chloroform on slow evaporation deposited clear slightly yellow plates, m.p. 260–264° (dec.); found: C, 42.10, 42.20; H, 4.67, 4.79; N, 7.06. The infrared spectrum of this compound in chloroform showed bands at 2.98, 5.85 (weak), 6.12 μ, not present in the starting material (2,6-lutidine methiodide, m.p. 233°).

N-Methylyohimbane (VIII).—To a solution of 0.28 g. of yohimbane[21] in 20 ml. of dry benzene was added 41 mg. (5% more than 1 milliequivalent) of potassium chips. The solution was refluxed for 2.5 hours with mechanical stirring. To the cooled suspension of the flocculent potassium salt in benzene was poured 0.15 g. of methyl iodide in 2 ml. of benzene. The reaction mixture was stirred for another 2 hours and then left overnight. After removal of the potassium iodide by filtration, the benzene solution was evaporated to dryness and the residue recrystallized from methanol, from which N-methylyohimbane appeared in a mush of lissom needles, m.p. 174–177°, yield 85%. For further purification and to test the homogeneity the compound was subjected to the standard chromatographic adsorption for colorless substances according to Reichstein and Shoppee.[65] Using the binary solvent pair hexane–benzene about 80% of the base appeared in the fractions obtained by elution of the column with benzene–hexane 3:1. The material melted at 179°; however, the analysis gave values for carbon which were consistently 1.1–1.3% too low. Finally, a sample microsublimed at 150° (bath) and 0.7 mm. gave correct figures.

Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.63; H, 8.91; N, 9.52. Found: C, 81.82; H, 8.73; N, 9.51.

Microtitration.—Purest N-methylyohimbane was titrated in 80% cellosolve with 0.1 *N* HCl; found: pK_A 7.16; equiv. wt., 298.7 (calcd. 294.4).[64]

Hydrochloride.—From an ethereal solution of methylyohimbane on addition of ethereal hydrochloric acid the hydrochloride separated as a colorless microcrystalline powder, melting in a range from 180–200° (melt not clear until 260°).

Anal. Calcd. for $C_{20}H_{26}N_2\cdot HCl\cdot H_2O$: C, 68.76; H, 8.36; N, 8.02. Found: C, 68.39; H, 8.27; N, 8.43.

The infrared spectrum of this hydrochloride in chloroform shows only one band in the OH–NH region, *viz.*, at 2.96 μ.

Picrate.—The picrate, prepared from aqueous solution, recrystallized from methanol, formed deep yellow shiny needles, m.p. 188–190.5° (clear, dark yellow melt); on admixture with picrate B of the base $C_{20}H_{24}N_2$ there was a distinct depression: sintering 165°, melting 173–185°.

Anal. Calcd. for $C_{20}H_{26}N_2\cdot C_6H_3N_3O_7\cdot {}^1/_2H_2O$: C, 58.65; H, 5.68. Found: C, 58.41; H, 5.88.

Methiodide.—A solution of N-methylyohimbane in acetone containing excess methyl iodide deposited the crystalline methiodide on standing, m.p. 280–284° (dec.).

Anal. Calcd. for $C_{20}H_{26}N_2\cdot CH_3I\cdot {}^1/_4H_2O$: C, 57.27; H, 6.76; N, 6.36. Found: C, 57.20; H, 6.65; N, 5.95.

When a solution of this methiodide in methanol was refluxed for several hours in the presence of excess sodium boron hydride, the chloroform-soluble part of the dry residue from the reaction gave a picrate, m.p. 206–208°, identical with the following methopicrate directly prepared from the methiodide.

Methopicrate.—This picrate crystallized in tufts of golden yellow needles from methanol, m.p. 206–208° (clear melt).

Anal. Calcd. for $C_{21}H_{29}N_2\cdot C_6H_3N_3O_7$: C, 60.21; H, 5.99; N, 13.00. Found: C, 60.11; H, 6.12; N, 12.77.

Methyltetrahydrosempervirinium Picrate (XIII) by the Catalytic Oxidation of N-Methylyohimbane (VIII).—When 0.37 g. of N-methylyohimbane in 4 ml. of glacial acetic acid was shaken under oxygen in the presence of 200 mg. of prereduced platinum oxide, 29.4 ml. of oxygen was taken up in the course of 22 hours. After filtration from the platinum the solution was made strongly alkaline and extracted with ether. Most of the residue from the dried ether extracts was taken up in a large volume of pentane (green fluorescence) and filtered through a column containing 20 g. of aluminum oxide. Pentane and benzene failed to elute anything. The first fractions eluted with 100% chloroform showed a strong green fluorescence, were pentane-soluble and showed three characteristic bands at 5.85, 6.07 and at 6.18 μ similar to the three new bands present in solutions of autoxidized base $C_{20}H_{24}N_2$. Further elution with chloroform and methanol yielded yellow fractions whose infrared spectra were almost identical with the preceding pentane-soluble fraction. However, these latter fractions could be washed with chloroform in the cold for purification, and the residue was dissolved in 0.1 *N* hydrochloric acid under gentle warming and converted into the picrate. This picrate, after washing with methanol in the cold, was recrystallized from acetone containing 5–10% water and formed yellow rectangular prisms, m.p. 213–216° (dec.).

Anal. Calcd. for $C_{20}H_{23}N_2\cdot C_6H_3N_3O_7$: C, 60.00; H, 5.04; N, 13.46. Found: C, 60.33; H, 4.89; N, 13.15.

α-Carboline (2-Carboline).—N-α-Pyridyl-*o*-phenylenediamine was prepared from phenylenediamine and 2-bromopyridine (rather than 2-chloropyridine[66]) following the pro-

(65) T. Reichstein and C. W. Shoppee, *Dis. Faraday Soc.*, 305 (1949).

(66) W. Lawson, W. H. Perkin, Jr., and R. Robinson, *ibid.*, **125**, 632 (1924).

cedure worked out in the norharmane series.[67] When 2 g. of 1-α-pyridylbenzotriazole was mixed with 23 g. of polyphosphoric acid one obtained a thick white paste which turned green on standing. The paste was heated in an oil-bath to 175° until frothing subsided and the color had changed to a light brown. After cooling, the reaction product was thoroughly mixed with water and then brought to *p*H 8 with alkali. Repeated extraction with ether gave an ether-soluble, slightly greenish crystalline base, which on crystallization from benzene formed long shiny needles, m.p. 210–212° (0.8 g., 50% yield).

α-Carboline Hydrochloride.—Prepared from ethereal solution with ethereal hydrochloric acid the hydrochloride formed a colorless crystalline powder, m.p. 195–199° with effervescence (loss of HCl). In striking contrast to norharmane hydrochloride the solution of 2-carboline hydrochloride in water or alcohol does not show a blue fluorescence until base is added.

Anal. Calcd. for $C_{11}H_8N_2 \cdot HCl$: C, 64.70; H, 4.41; N, 13.69. Found: C, 64.72; H, 4.63; N, 13.59.

α-Carboline Picrate.—The picrate previously reported (m.p. 260–264°[67]) but not analyzed appeared from acetone in canary-yellow needles, only slightly soluble in all usual solvents, m.p. 272–274° (dec.).

Anal. Calcd. for $C_{11}H_8N_2 \cdot C_6H_3N_3O_7$: C, 51.38; H, 2.77; N, 17.64. Found: C, 51.50; H, 3.01; N, 17.50.

α-Carboline Methosulfate.—The methosulfate described previously[3] (no m.p., no analysis) crystallized from hot alcohol in colorless needles, m.p. 254–258°.

Anal. Calcd. for $C_{11}H_8N_2 \cdot (CH_3)_2SO_4 \cdot 1^1/_2H_2O$: C, 50.16; H, 5.43. Found: C, 50.39; H, 5.03.

2-Methyl-α-isocarboline Methiodide.[68]—2-Methyl-α-isocarboline (XXIV), m.p. 140°, prepared from α-carboline methosulfate according to Robinson,[3] was left in ether–acetone solution in the presence of methyl iodide at room temperature. After 24 hours, the almost colorless flat brief needles were collected and washed with ether: they sublimed without melting at 266°.

Anal. Calcd. for $C_{13}H_{13}N_2I$: C, 48.17; H, 4.04; N, 8.64. Found: C, 47.97; H, 3.99; N, 8.66.

Whereas there was no fading of color when 2-methyl-α-isocarboline was refluxed with excess sodium borohydride in methanol, and starting material was isolated after the attempted reduction, the same experiment carried out with 2-methyl-α-carboline methiodide gave, after evaporation of the methanol, a yellow-brown residue, which was mostly soluble in hexane. The free base, after fractionation with various solvents, did not crystallize.[69] The hydrochloride was prepared from ethereal solution as a slightly orange precipitate, the aqueous solution of which gave a picrate becoming flocculent and pulverulent on rubbing; no sharp melting point, softening and increasing darkening on heating.

Anal. Calcd. for $C_{13}H_{14}N_2 \cdot C_6H_3N_3O_7 \cdot 1^1/_2H_2O$: C, 50.23; H, 4.44; N, 15.41. Found: C, 50.90; H, 4.26; N, 16.18.

Reduction of α-Carboline with Sodium in Butanol.—In analogy to the preparation of tetrahydronorharmane,[70] 0.2 g. of α-carboline was refluxed in 10 ml. of absolute butanol while a large excess of sodium metal (1 g.) was added together with sufficient butanol to keep the solution clear. After cooling the reaction mixture was decomposed with water and extracted with ether. The stronger base present in the combined ether extracts went into the first extraction with 0.1 *N* hydrochloric acid. Subsequent extractions with stronger hydrochloric acid gave starting material. The first aqueous acidic fractions were made alkaline and extracted with ether. The residue from the ether extract was extracted first with hot pentane then with hexane. On cooling there appeared from the hexane solution 8 mg. of beautiful colorless platelets, m.p. 82–83°.

Anal. Calcd. for $C_{11}H_{12}N_2 \cdot {}^1/_3H_2O$: C, 74.15; H, 7.2; N, 15.7. Found: C, 74.41; H, 7.94; N, 15.16.

The infrared spectrum shows one strong NH band at 2.86 μ, no bands between 6.0–6.75 μ. The Ehrlich reaction is dark red on warming, disappearing on cooling, reappearing on warming, etc., and turning dark blue-green on addition of nitrous acid.[71]

Picrate.—The preparation of the picrate on a small scale is difficult. From aqueous solution the picrate appears either in the form of rosettes of brown-red needles on prolonged standing from an originally reddish turbid solution or as a yellow crystalline powder on scratching. Recrystallization from methanol produces glass-hard red prisms, becoming yellow on crushing, m.p. 134°. Quebrachamine picrate shows a similar *chromoisomerism*.

The Synthesis of 5-(β-Ethylindyl)-isoquinoline (XXX). 5-Isoquinolyl *n*-Propyl Ketone (XXVIII).—The addition of 15.4 g. of 5-cyanoisoquinoline (V, m.p. 138°)[72] in 50 ml. of absolute benzene to the Grignard reagent prepared from 12.3 g. of *n*-propyl bromide in ether gave an immediate reddish-brown precipitate which slowly changed to deep red on refluxing overnight. Excess dilute hydrochloric acid was added and, after refluxing for two hours to hydrolyze the ketimine, the mixture was made alkaline and extracted with benzene. The precipitated magnesium hydroxide was removed by centrifugation and the dry benzene extract evaporated *in vacuo*. The dark residue (18.5 g.) was distilled at 0.02 mm. pressure and the fraction of b.p. 130–140° was collected. Since crystallization from ether–petroleum ether, or petroleum ether alone, gave only oily products, the material easily soluble in petroleum ether was converted to the crystalline hydrobromide by addition of an ethereal solution of hydrogen bromide. Recrystallization from a small volume of ethyl alcohol yielded stout prisms, m.p. 185° (subl.); total yield 26%.[73]

Anal. Calcd. for $C_{13}H_{13}NO \cdot HBr$: C, 55.71; H, 4.64; N, 5.0. Found: C, 55.47; H, 4.84; N, 4.76.

Picrate.—Prepared from aqueous solution, the picrate appeared in yellow needles on recrystallization from acetone, m.p. 196°. The picrate of 5-cyanoisoquinoline melts at 234°.

Anal. Calcd. for $C_{13}H_{13}NO \cdot C_6H_3N_3O_7$: C, 53.2; H, 3.73. Found: C, 52.78; H, 3.72.

Phenylhydrazone.—Refluxing the oily ketone, prepared from purest hydrobromide, with a slight excess of phenylhydrazine in absolute alcohol for four hours on the water-bath gave on evaporation in the desiccator crystals which after two recrystallizations from methanol–water formed slightly yellow prisms, m.p. 168°.

Anal. Calcd. for $C_{19}H_{19}N_3$: C, 78.89; H, 6.57; N, 14.5. Found: C, 78.82; H, 6.91; N, 14.36.

5-Isoquinolyl *n*-Propyl Ketone Phenylhydrazone Methiodide.—The tertiary phenylhydrazone could be recovered unchanged after refluxing in methanol containing excess methyl iodide. Formation of the methiodide, however, readily occurred in acetone solution even without refluxing. The crystalline precipitate thus obtained and increased by the addition of ether formed beautiful yellow rods on recrystallization from methanol, m.p. 238°.

Anal. Calcd. for $C_{19}H_{19}N_3 \cdot CH_3I$: C, 55.68; H, 5.15; N, 9.74. Found: C, 55.71; H, 5.17; N, 9.63.

(67) E. Späth and K. Eiter, *Ber.*, **73**, 721 (1940); *cf.* K. Eiter, *Monatsh.*, **81**, 405 (1950).

(68) The preparation of this compound and the attempted reduction was carried out by Dr. J. B. Patrick.

(69) The infrared spectrum of the purified non-crystalline base showed the following absorption peaks: no OH or NH bands, 5.84μ (weak), 6.17μ(medium), 6.35μ(strong). The ultraviolet comparison showed the similarity of the absorbing system of the two reduction products.

Compound	λ_{max} (log ε) in ethanol
Base from the $NaBH_4$ reduction of 2-methyl-α-carboline methiodide (presumably XXV)	290 (3.84) mμ
Base from the reduction of α-carboline (presumably XXVI)	293 (3.75)
	285 (3.81)

The spectrum of the latter compound is, surprisingly enough, not appreciably shifted by acid or base. Though N-methylation at the indole imino group shifts λ_{max} in yohimbane (282) to 286 in N-methylyohimbane, the shift to even longer wave lengths may well be explained by the nitrogen substituent in α-position of the indole ring. This assumption is substantiated by the absorption λ_{max} 295 (3.85), 286 (3.88) of quebrachamine, in which such an arrangement is present (B. Witkop, unpublished data).

(70) *Cf.* V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2132 (1950).

(71) For the non-isolated reduction product from α-carboline with sodium in isoamyl alcohol, Lawson, Perkin and Robinson[66] describe the Ehrlich reaction as magenta on warming and stable on cooling, an indication that reductive fission may have occurred under their more drastic conditions.

(72) F. T. Tyson, THIS JOURNAL, **61**, 183 (1939).

(73) *Cf.* L. F. Fieser and E. B. Hershberg, *ibid.*, **62**, 1640 (1940).

5-Isoquinolyl *n*-Propyl Ketone Phenylhydrazone Methochloride.—A suspension of freshly prepared silver chloride in water was added to a solution of the above methiodide in methanol. After removal of the silver halides the solution was evaporated to dryness in the desiccator and the residue was recrystallized from methanol–ether (1:4) affording slightly yellow glistening prisms, m.p. 224° (dec.).

Anal. Calcd. for $C_{19}H_{19}N_3 \cdot CH_3Cl \cdot H_2O$: C, 69.12; H, 6.98. Found: C, 69.52; H, 7.29.

5-(β-Ethylindyl)-isoquinoline (XXX).—When 0.32 g. of the phenylhydrazone of 5-butyrylisoquinoline was dissolved in 10 ml. of absolute alcohol, saturated at 0° with dry hydrogen chloride, refluxed for 90 minutes, and was then, after the addition of 30 ml. water, placed in the ice box, yellow-red needles of the hydrochloride of 5-(β-ethylindyl)-isoquinoline, m.p. 222-225° (215 mg.) deposited. The base prepared from this hydrochloride from aqueous solution with alkali immediately crystallized in fine short needles (215 mg.) appearing on recrystallization from methanol slightly yellow scales, m.p. 180.5°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.82; H, 5.88; N, 10.29. Found: C, 83.55; H, 6.12; N, 9.95.

Methiodide.—The methiodide was prepared in methanol or chloroform solution with excess methyl iodide at room temperature; slightly yellow prisms for methanol–ether, m.p. 231°.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot CH_3I$: C, 57.97; H, 4.58; N, 6.76. Found: C, 58.11; H, 4.44; N, 6.94.

Methochloride.—The methochloride prepared in the usual fashion from the methiodide with silver chloride, crystallized from ethanol–ether as a yellowish microcrystalline powder, m.p. 258°. Recrystallization from ethanol yielded clusters of yellowish needles, m.p. 263° (effervescence).

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot CH_3Cl$: C, 74.54; H, 5.90. Found: C, 74.69; H, 5.83.

Isoyobyrine (XXXI) Methiodide.—When 250 mg. of isoyobyrine was left in ethanolic solution for 50 hours at 40° in the presence of excess methyl iodide, the residue still contained about 100 mg. of ether-soluble starting material. The methiodide is moderately soluble in ethanol and can be recrystallized from ethanol or acetone, yellow cubes, showing softening over a range of 210–230°.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot CH_3I$: C, 57.97; H, 4.58. Found: C, 57.74; H, 4.66.

Isoyobyrine (XXXI) Methochloride.—The methochloride prepared from the methiodide in methanol with silver chloride, was recrystallized from alcohol, tufts of yellow needles, softening and decomposing between 215–225°. The compound had to be dried at 100° *in vacuo;* samples dried at 60° still retained 1/4 mole of water.

Anal. Calcd. for $C_{19}H_{16}N_2 \cdot CH_3Cl$: C, 74.54; H, 5.90. Found: C, 74.65; H, 6.22.

Dihydroyobyrine (XXXII) Methiodide.—Freshly recrystallized colorless dihydroyobyrine[22] was dissolved in a small volume of methanol and excess methyl iodide added. On standing, yellow needles crystallized which, after recrystallization from methanol, melted at 259–263°.

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot CH_3I$: C, 57.89; H, 5.09; N, 6.73. Found: C, 57.56; H, 5.46; N, 6.84.

Dihydroyobyrine (XXXII) Methochloride.—The methiodide in methanolic solution was converted to the methochloride with freshly precipitated silver chloride. The methochloride crystallized from ethanol–ether in buttons of pale yellow crystals, m.p. 214–216°.

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot CH_3Cl$: C, 73.98; H, 6.48; N, 8.64. Found: C, 73.56; H, 6.65; N, 8.42.

Dihydroyobyrine (XXXII) Benzyl Bromide.—When 50 mg. of dihydroyobyrine was refluxed with 1 ml. of benzyl bromide in 3 ml. of isopropyl ether for one-half hour, the compound obtained after evaporation to dryness and chromatographic purification in acetone over aluminum oxide crystallized from acetone–water in glistening yellow scales identical with *yobyrone* (m.p. 185°). In another experiment, 180 mg. of dihydroyobyrine in 20 ml. of benzene was refluxed for one hour with 1 ml. of benzyl bromide. The yellow glistening cubes that had separated by that time were collected and washed with benzene; they softened at 170–180°, resolidified and then showed m.p. 238–243°.

Anal. Calcd. for $C_{26}H_{25}N_2Br \cdot 1^1/_4H_2O$: C, 66.67; H, 5.89. Found: C, 66.61; H, 5.60.

Reduction of Oxindole to Dihydroindole.—Since oxindole is only moderately soluble in ether, 1 g. was placed in the thimble of an extractor[74] containing 100 ml. of ether and a slight excess of lithium aluminum hydride. After four hours of refluxing all oxindole was in solution. After decomposition of excess hydride by the cautious addition of ice the solution was made so strongly alkaline as to keep the aluminate in solution. Several extractions with 50-ml. portions of ether yielded a violet colored extract from which the basic constituents were removed by extraction with 2 *N* hydrochloric acid. From this extract, by the use of alkali and ether, 0.12 g. of an oily fraction was obtained with a strong odor reminiscent of naphthalene. The picrate, recrystallized from methanol, appeared in needles, m.p. 176° (dark melt), reported m.p. 172°.[75]

Anal. Calcd. for $C_8H_9N \cdot C_6H_3N_3O_7$: C, 48.97; H, 3.48; N, 16.1. Found: C, 48.80; H, 3.18; N, 15.78.

Reduction of "Ketoyobyrine" with Lithium Aluminum Hydride.—The above thimble method was applied to 0.25 g. of pure "Ketoyobyrine." After refluxing for about 60 hours practically all of the only slightly ether-soluble compound had gone into solution. After decomposition with ice and water the dried ether extract on standing deposited pale-yellow prisms, presumably XI, m.p. 190°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.33; H, 7.01; N, 9.72. Found: C, 83.19; H, 7.04; N, 9.85.

The ether mother liquors on evaporation left a yellow-red crystalline residue which was distilled at 160° (bath) and 0.001 mm. The distillate gave yellow-red prisms from ether, m.p. 188°. The residue from the distillation crystallized from a small volume of methanol in dark red prisms, m.p. 240–242°; found: C, 67.06; H, 5.61.

Acknowledgment.—Part of this work, done at Harvard, was supported by a grant-in-aid of Research Corporation, New York. The author gratefully remembers many stimulating discussions with Dr. R. B. Woodward. Dr. M. M. Janot, Paris, kindly and generously supplied most of the sempervirine used in this investigation.

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(74) *Cf. Organic Reactions,* **6**, 491 (1951).
(75) E. Ferber, *Ber.,* **62**, 189 (1929).