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The Conversion of Tetrahydroharman Alkaloids into Derivatives of Linear Pyrroquinolones[1]

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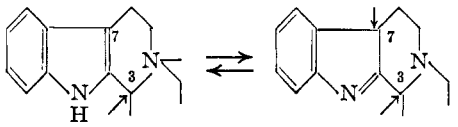
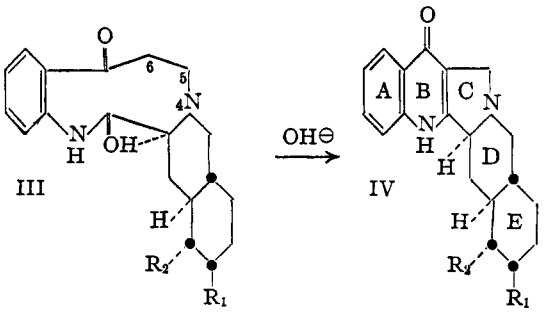
The ozonization of yohimbine, yohimbane and N-methyltetrahydronorharman (VIIb) leads to 9-membered cyclic lactams which easily undergo a base-catalyzed intramolecular condensation (Camps reaction) to derivatives of linear pyrroquinolones (IVa, IVb, IVc). Clemmensen reduction of IVa yields the *tetrahydroquinoline analog (VI) of yohimbine.* The ozonization of tetrahydroalstonine is interpreted.

Position 3 in the tetrahydroharman I and positions 3 and 7 in the indolenine tautomer (II) are likely sites,[3] labilized by the adjacent >C=C< or



I II

>C=N group[4] for the initial attack of oxidants. Biochemical oxidation in the plant of an alkaloid of this type, *e.g.*, of yohimbine, at position 7 would be expected to lead, *via* labile hydroperoxy or hydroxyindolenine[5] intermediates, to the structure III[6] in which rings B and C together form now a 9-membered cyclic lactam.



	R_1	R_2
a	OH	$COOCH_3$
b	OH	COOH
c	H	H
d	=O	H

	R_1	R_2
a	OH	$COOCH_3$
b	OH	COOH
c	H	H
d	=O	H

As the oxidant we used ozone hoping to get preponderantly incipient attack at C_7 followed by ozonolytic cleavage of the indole double bond. In ethyl acetate as solvent yohimbine on treatment with ozone gave a peroxidic non-crystalline compound which might be derived from the hydroperoxide tautomer[7] of the stable isozonide; the latter would not be capable of existence in this case.[8] Since ozonization in dimethylformamide[9] produced only amorphous products, 80% acetic acid was used. On neutralization with bicarbonate of the aqueous solution of the residue of the ozonized solution there was obtained in up to 54% yield a bright yellow crystalline compound which had the composition, the ultraviolet (Table I) and infrared absorption (Fig. 1) characteristic of a γ-quinolone.[10]

TABLE I

ULTRAVIOLET SPECTRA IN ETHYL ALCOHOL

The figures in brackets are inflection points

Compound	λ_{max}	log ε
Quinolone (IVa) from yohimbine	327	4.09
	314	4.03
	236	4.46
Quinolone from tetrahydroalstonine[25]	328	4.11
	315	4.08
	240	4.62
Quinolone (IVc) from yohimbane	328	4.25
	314	4.15
	242	4.63
2,3-Cyclopenteno-4-quinolone[10]	331	4.13
	317	4.09
	238	4.48
1,4-Aza-8,9-benz-4-methylcyclononedi-2,7-one (IX)	302	2.84
	226	3.99
1-Aza-8,9-benzcyclononadi-2,7-one[10]	[300]	2.84
	226	4.12
	[292]	2.88

Either the mild basic action of sodium bicarbonate or the basicity of the free lactam III must have been sufficient to effect intramolecular cyclization to the linear pyrroloquinolone derivative IVa analogous to the base-catalyzed Camps reaction leading from 1-aza-8,9-benzcyclononadi-2,7-one to 2,3-cyclopenteno-4-quinolone.[10] Aside from the fact that a 9-membered lactam exclusively yields the linear γ-quinolone on treatment with base,[10] the path to an α-quinolone in the case of IIIa is

(1) Oxidation Mechanisms. X. Previous paper in this series: B. Witkop and H. M. Kissman, THIS JOURNAL, **75**, 1975 (1953).

(2) National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md.

(3) B. Witkop, THIS JOURNAL, **75**, 3361 (1953).

(4) Even lacking double bond activation, the equivalent positions in other alkaloids, *e.g.*, carbons 9 in strychnine and codeine, are (aut)oxidizable to hydroxy derivatives such as ψ-strychnine [*cf.* R. Huisgen, *Angew. Chem.*, **62**, 531 (1950)] or hydroxycodeine [Ach and L. Knorr, *Ber.*, **36**, 3068 (1903)]. ψ-Strychnine has been found in strychnos extracts by Warnat, and a compound of the composition and melting point of Knorr's hydroxycodeine, presumably formed in either case by autoxidation or enzymatic processes has been isolated from opium [private communication from Dr. L. F. Small]. The analogous 3-hydroxyyohimbine has not been found yet in nature but its synthesis is being attempted.

(5) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2196 (1951).

(6) The stereochemical assignments in III and IV which are based on the elimination and epimerization reactions of yohimbine and its congeners, have been used by Dr. G. Stork in his fall lecture on indole alkaloids at Harvard University, 1949–1950. New experimental material and a thorough discussion of the subject is found in the paper by M.-M. Janot, R. Goutarel, A. Le Hir, M. Amin and V. Prelog, *Bull. soc. chim.*, 1085 (1952).

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

(8) *Cf.* R. Criegee and G. Wenner, *Ann.*, **564**, 9 (1949).

(9) *Cf.* B. Witkop, *ibid.*, **556**, 103 (1944).

(10) B. Witkop, J. B. Patrick and M. Rosenblum, THIS JOURNAL, **73**, 2641 (1951).

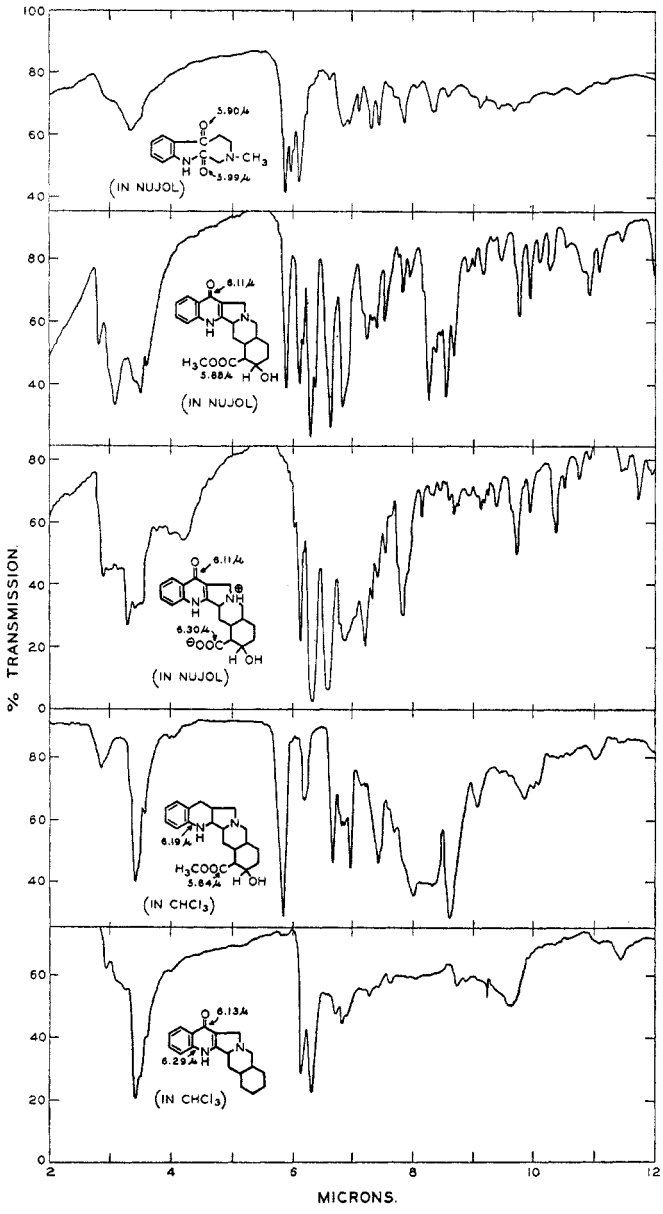
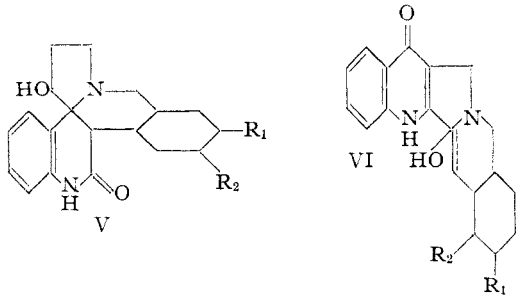


Fig. 1.—Infrared spectra in Nujol and chloroform.

blocked since the hypothetical intermediate V is unable to form an aromatic system.



The fact that the quinolone IVa was obtained in a *yellow* and in a *colorless* form and crystallized with one or two molecules of water, methanol or ethanol, prompted us to investigate carefully the possibility of having the hydroxyquinolone VI in hand. However, the hydrochloride, methiodide and picrate were not derived from the anhydro compound[11] (VI, no hydroxyl, dotted double bond), as the analyses and ultraviolet spectra demonstrated. Therefore, the chromoisomerism of IVa is *not* a result of the presence of a chromophore system >C=C—C=C—C=O as in metathebainone.[12]

As a γ-quinolone IVa is soluble in dilute aqueous base.[10] The action of base on the quinolone could lead to the formation of an anion at position 3. The quinolone from yohimbene (or ψ-yohimbine), if different from IVa, should be converted to IVa by a base-catalyzed epimerization. With yohimbene not easily available, we are at present trying to effect the same type of epimerization *via* the methiodide. Stronger action of base gives the zwitterionic amino acid IVb (infrared spectrum Fig. 1), the hydrochloride of which could also be obtained from IIIa by acid treatment. Diazomethane gave neither the N-methyl- nor 4-methoxyquinoline derivative; the latter would have been interesting for pharmacological testing, since its structure is somewhat reminiscent of dictamnine,[13] belonging chemically to the group of cardioactive[14] fagara alkaloids. The quinolone IVa itself was devoid of any noteworthy pharmacological action.[15]

In order to obtain a pharmacologically more promising compound the reduction of the quinolone IVa was tried by various methods. By the use of mossy zinc in hydrochloric acid a high-melting product was obtained in small yield which on the basis of the ultraviolet and infrared absorption is probably the tetrahydroquinoline derivative VI, the paucity of which has not permitted pharmacological tests yet. This course of reduction of a γ-quinolone is reminiscent of similar observations of Stoll and Rutschmann[16] in the lysergic acid series.

The simplest compound possessing the pentacyclic yohimbine skeleton, *viz.*, yohimbane,[17] which we prepared from yohimbone by the Huang-Minlon[18] modification of the Wolff–Kishner reaction in over 90% yield, was also ozonized and gave the quinolone $C_{19}H_{22}N_2O$ (IVc) as shiny tan plates. Yohimbane was further

TABLE II

	Yohimbane	"*Chano*isodesoxyyohimbol"
M.p., °C.	205–206	206
Methiodide, m.p., °C.	296–301	Progressive charring at 280
Methiodide, m.p., °C.	256–258	254

(11) *Cf.* Salt formation of hydroxyevodiamine to give the hydroxyevodiaminium (or isoevodiamine) cation: T. Ohta, *J. Pharm. Soc. Jap.*, **65**, 15 (1945); *C. A.*, **45**, 5697 (1951).

(12) L. F. Small and E. Meitzner, THIS JOURNAL, **55**, 4602 (1933).

(13) Y. Asahina, T. Ohta and M. Inubuse, *Ber.*, **63**, 2045 (1930).

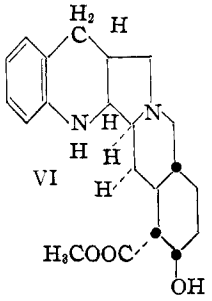
(14) V. Deulofeu, *Arquiv. faculdade Nacl. Med. (Rio de Janeiro)*, **1**, 80 (1946).

(15) We are indebted to Prof. A. P. Richardson, Department of Pharmacology, Emory University, Georgia, for the pharmacological assay.

(16) A. Stoll and J. Rutschmann, *Helv. Chim. Acta*, **33**, 67 (1950).

(17) J. Jost, *ibid.*, **32**, 1297 (1949).

(18) D. Todd, *Org. Reactions*, **4**, 410 (1948).

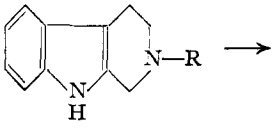


VI

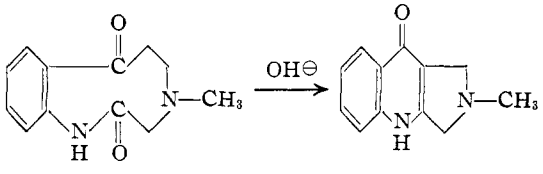
characterized by its two diastereoisomeric methiodides of opposite rotations, $[\alpha]^{22}D$ +35.7° and −36.6° which are considered identical with the methiodides of a compound previously named *chano*isodesoxyyohimbol[19] now believed to be identical with yohimbane (Table II).

We report in the Experimental on attempts to oxidize yohimbane or one of its methiodides with potassium ferricyanide in order to oxidize position 3 to a hydroxyl or keto[20] group, hoping to get to a proptopine analog in the yohimbine series. Failing to achieve oxidative opening we tried reductive fission of the allylamine bond between positions 3, 4 of yohimbane methiodide and methosulfate by the Wieland[21] or Robinson[22] modifications of the Emde degradation and by the action of sodium borohydride. However only starting material or yohimbane was recovered. Yohimbone, on ozonolysis, yielded only tars or unchanged starting material, but not IVd.

The cyclic lactam VIII (infrared spectrum, Fig. 1) was obtained in very small yield by the ozonization of N-methyltetrahydronorharman (VII), prepared by a somewhat different route than previously.[23] Its ultraviolet spectrum (Table I) shows

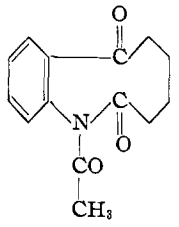


VII a, R = CHO
b, R = CH_3

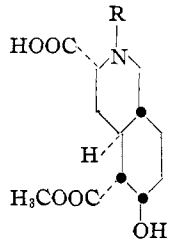


VIII IX

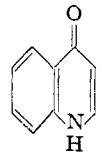
a similar inhibition of resonance of the chromophoric aminophenone system as the analogous 1-aza-8,9-benzcyclononadi-2,7-one.[10] Since N-methylyohimbane was a more suitable compound for catalytic oxidation than yohimbine,[3] we tried ozonolysis of an N-substituted indole, using N-acetyltetrahydrocarbazole as a model compound, which on ozonolysis in ethyl acetate gave a compound $C_{14}H_{15}NO_4$, rather than the expected X.[23a] The ozonolysis of similar N-acetyl compounds in the tetrahydroharman series may be of future use.



X



XI, R = H or CH_3



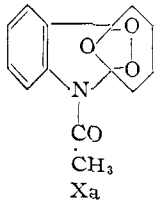
XII

When we treated amorphous ozonized yohimbine, prior to neutralization with bicarbonate, with zinc dust at 250° we expected the lactam IIIa, presumably present, as a Mannich base to undergo a cleavage characteristic of such β-aminoketones.[24] Although we have so far not been able to prove the presence of *o*-aminoacetophenone (rupture between position 5,6) or γ-quinolone (XII) (rupture between positions 4,5 and formation of *o*-aminophenyl vinyl ketone) or of the basic fragment (XI), experiments will be continued in this direction, since XI, which still contains all 5 asymmetric centers present in yohimbine so to speak *in nuce*, would be an interesting model compound to study the stereochemical course of the many epimerization and elimination reactions that make the chemistry of yohimbine, corynanthine, etc., so colorful.

There can be little doubt that the mysterious *ozonization product* from *tetrahydroalstonine* obtained by Elderfield and Gray[25] resulted from the parent lactam by base (in this case sodium carbonate)-catalyzed intramolecular cyclization to the γ-quinolone. The ultraviolet absorption spectrum of this quinolone (Table I) is almost identical with that of IVa.

Whether this sequence of reactions, which is not strictly analogous to the conversion of tryptophan into kynurenic acid, may occur in the plant, must be left open at this point.

(23a) NOTE ADDED IN PROOF:—Compound X, however, was obtained by D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 612 (1953) by ozonolysis of 9-acetyltetrahydracarbazole in acetic acid, emphasizing again the important role the solvent plays in these reactions. The compound $C_{14}H_{15}NO_4$, m.p. 244–245° (232° reported by O. and S.), is formulated there as the acetyl ozonide (Xa), a view which we do not share.



Xa

(19) B. Witkop, THIS JOURNAL, **71**, 2559 (1949). At the time "*chano*-isodesoxyyohimbol" was made, yohimbane was not known yet. The positive Ehrlich and Hopkins–Cole reactions may have been caused by traces of accompanying *chano*desoxyyohimbol. The lack of samples has not permitted direct comparison yet.

(20) *Cf.* C. Schöpf and W. Braun, *Ann.*, **465**, 138 (1928).

(21) *Cf.* H. Wieland and O. Müller, *ibid.*, **545**, 66 (1940).

(22) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 789 (1932).

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

(24) Some examples for this type of cleavage: febrifugine → 3-(β-ketopropyl)-4-quinazolone [B. L. Hitchings, S. Gordon, F. Ablondi, C. F. Wolf and J. H. Williams, *J. Org. Chem.*, **17**, 19 (1952)]; cuscohygrine → hygrine + N-methylpyrroline (?) [K. Hess and R. Bappert, *Ann.*, **441**, 137 (1925)]; lobeline → acetophenone and fluorene [H. Wieland and O. Dragendorff, *ibid.*, **473**, 83 (1929); kynurenine → *o*-aminoacetophenone.

(25) R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, **16**, 506 (1951).

Experimental[26,27]

Ozonolysis of Yohimbine.—After many variations of the experimental conditions the following directions were found to give reproducible results and the maximum yields. A solution of 6 g. (17.8 millimoles) of yohimbine in 200 ml. of acetic acid and 25 ml. of water was cooled in an ice-water bath and treated with a 50% excess of ozone for 23 minutes. The ozone was produced in a Welsbach laboratory ozonator model T23. The rate of flow of ozone was 1.18 millimoles per minute. The average rate of flow of ozone varied in different experiments from 0.7 to 1.2 millimoles per minute and the amount of ozone used ranged from the theoretical to 50% excess. In one experiment it was found that at the calculated end-point 67% of the ozone was still being absorbed; at 60% excess 54% was absorbed and at 100% excess 45% was absorbed. Excess sulfur dioxide acted on the ozonization mixture for 1 to 3 minutes. The brown solution was evaporated in a desiccator over sulfuric acid. Bigger batches were concentrated *in vacuo* at a temperature not exceeding 50° to one-fourth of the original volume and then evaporated further in a vacuum desiccator. The brown, tarry residue was dissolved in about 10 ml. of water and poured into sufficient sodium bicarbonate solution to arrive at a *p*H of 7–8. Some dark tar and some light-yellow solid separated. The addition of chloroform to the mixture resulted in the formation of more solid, which was further increased on shaking in a separatory funnel with more chloroform. The tan-brown or light-yellow solid (yield of crude material was 2.3 g., 35%, maximum yield obtained was 54%) was collected and dissolved in methanol giving a brown solution from which a first crop of bright lemon yellow needles was obtained in 17% yield. The mother liquor was concentrated and further crops were taken until finally a brown tar remained. The chloroform fraction contained only dark tarry material.

The recrystallized, analytically pure yohimbine-quinolone (IVa) had no definite melting point but darkened around 210° and started decomposing around 275°. It was readily soluble in cold 0.1 *N* HCl, 0.1 *N* NaOH and 2 *N* acetic acid, sparingly soluble in cold but readily in hot methanol; sparingly soluble in boiling chloroform, benzene and ethyl acetate; and insoluble in 10% sodium carbonate, ether and cold water but to some extent (about 0.05%) in boiling water. From runs in which only methanol was used as the solvent the quinolone IVa crystallized with 2 molecules of methyl alcohol.

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot 2CH_3OH$: C, 63.88; H, 7.47; N, 6.48; OCH_3, 7.17. Found: C, 63.83; H, 7.41; N, 6.70; OCH_3, 8.27.

Recrystallization of this material from ethyl acetate did not significantly alter the analysis: C, 64.27; H, 7.41; OCH_3, 7.86. Recrystallization from ethanol gave an *ethanol adduct.*

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot C_2H_5OH$: C, 66.64; H, 7.30; N, 6.76; OCH_3, 7.48. Found: C, 66.45; H, 7.47; N, 6.28; OCH_3, 10.13.

Recrystallization of the methanol adduct from boiling water gave some discolored material which was filtered off; the clear pale yellow solution deposited on standing long deep-yellow needles of the *quinolone dihydrate.*

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot 2H_2O$: C, 62.36; H, 6.97; N, 6.93; OCH_3, 7.65. Found: C, 62.30; H, 7.08; N, 7.14; OCH_3, 7.92.

The result of boiling yohimbine-quinolone dihydrate with acetone indicated no incorporation of acetone into the molecule. Yohimbine-quinolone-dihydrate (100 mg.) was refluxed in 80 ml. of acetone for six hours. A Soxhlet containing $MgSO_4$ was used to remove water. The solution was evaporated to dryness and the yellow solid recrystallized from acetone. Some decomposition had occurred as the mother liquor was brown. Deep yellow needles were obtained which on heating became red at 220°, and charred progressively up to 330°. The analysis does not check for the addition of one acetone and the loss of one water ($C_{24}H_{28}N_2O_5$, calcd. C, 67.91; H, 6.65; N, 6.60), nor for the starting material but is fairly close to that of yohimbine-quinolone with two molecules of methyl alcohol of crystallization, although no methanol was used in the experiment.

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot 2CH_3OH$: C, 63.88; H, 7.47; N, 6.48. Found: C, 63.86, 63.44; H, 7.17, 6.97; N, 6.59.

The infrared spectrum reveals some change from the starting material in that the 5.8 μ band is weaker and broader.

Ozonolysis of Yohimbine in Ethyl Acetate.—A solution of 4 g. of yohimbine in 200 ml. of freshly distilled ethyl acetate was treated with an excess of ozone. The white precipitate which formed during the reaction was collected. The top of the filter cake became brown in a short time. The white solid on heating became progressively yellow from 130°, finally caramel colored and started melting at 145°. The infrared spectrum seemed to be indicative of the ketolactam structure. The material liberated iodine and gave an acid reaction on *p*H paper. The material was insoluble in benzene, chloroform, ethyl acetate and dilute hydrochloric acid, soluble in methanol, ethanol, acetone, N,N-dimethylformamide and dilute sodium hydroxide.

Anal. Found: C, 53.31; H, 5.89.

In another run the precipitate formed (0.17 g. from 2 g. of yohimbine) was yellow, melted at 183–200° and had no carbonyl absorption in the infrared.

Ozonolysis in N,N-Dimethylformamide.—A solution of 3 g. of yohimbine in 100 cc. of N,N-dimethylformamide was treated with a slight excess of ozone. Sulfur dioxide was introduced for about one minute. The solvent was removed *in vacuo.* Addition of ethyl acetate precipitated a yellow-orange amorphous solid which was soluble in water, gave an acid reaction and did not liberate iodine. It was insoluble in chloroform. The infrared spectrum indicated new carbonyl absorption. The material was not amenable to crystallization.

White Modification of Yohimbine-quinolone (IVa).—When yellow yohimbine-quinolone was converted into its white hydrochloride (see below) and then regenerated from an aqueous solution of this salt by the addition of sodium bicarbonate solution it appeared as white needles. A portion of the colorless material, when left in sunlight, became bright yellow. The yellow color also appeared on heating to 120°. The material could be recrystallized from methanol to give fine white needles which in the aggregate had a pale yellow tinge.

Rotation.—Attempts to obtain the rotation of yellow yohimbine-quinolone in acetic acid or in pyridine were unsuccessful because the solutions became red in a short time and even cloudy in the case of pyridine. Thus methanol was used as the solvent and the quinolone sample used was the colorless modification. A solution of 80.3 mg. of colorless yohimbine-quinolone in 10 ml. of methanol was obtained by mild warming. The average observed rotation was $\alpha = +0.823$; $[\alpha]^{20}D$ +103°. Repetition without using heat to effect solution gave $[\alpha]^{20}D$ +107.5°.

Hydrochloride.—A solution of 200 mg. of yohimbine-quinolone (IVa, crystallized from ethanol) in 20 ml. of 1 *N* HCl was evaporated in a desiccator. When the deep red solution had evaporated to about 10 ml., white needles appeared. The solution was allowed to go to dryness leaving a red solid. After three recrystallizations from water colorless needles were obtained. On the hot-stage the white needles became yellow at 188°, bright orange at 220°, then brown and finally formed a brown tar at 245°. The analysis is in agreement with the quinolone hydrochloride trihydrate.

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot HCl \cdot 3H_2O$: C, 55.10; H, 6.77; N, 6.32. Found: C, 55.04; H, 6.62; N, 6.26.

Picrate.—The picrate of yohimbine-quinolone was precipitated by the addition of a saturated aqueous solution of picric acid to a solution of the quinolone in 0.1 *N* HCl. The crystalline yellow solid on heating darkened progressively from 240° and did not melt up to 350°. For analysis the compound was recrystallized from methanol.

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot C_6H_3N_3O_7$: C, 54.25; H, 4.56; N, 11.72. Found: C, 54.10; H, 4.50; N, 11.46.

Methiodide.—The quinolone was dissolved in methanol, treated with a large excess of methyl iodide and allowed to concentrate overnight. The product was precipitated with ether. On recrystallization from methanol it gave a white crystalline powder which on heating became yellow at 240°,

(26) All melting points are corrected (Kofler block). The analyses were carried out by Dr. W. C. Alford and his associates in the microanalytical laboratory of the National Institutes of Health.

(27) We are indebted to Miss Marie Johnson for her skillful and diligent technical assistance.

progressively darkened and became viscous at 280°. The material was hygroscopic.

Anal. Calcd. for $C_{21}H_{24}N_2O_4 \cdot CH_3I \cdot H_2O$: C, 50.00; H, 5.54; N, 5.30; CH_3O, 5.87. Found: C, 50.05; H, 5.50; N, 5.31; CH_3O, 6.83.

The infrared spectrum was recorded for the second crop and showed the quinolone band at 6.13 μ, excluding a methoxyquinoline derivative. The ultraviolet spectrum in ethanol showed the intact chromophore of the γ-quinolone (IVa): $\lambda\lambda_{max}$ (log ϵ) 321 (3.83); 310 (3.86); 243 (4.34); 239 (4.33).

Methylation of IVa with diazomethane in methanol so far has not been successful and gave back chiefly quinolone methanol adduct (Found: C, 63.17; H, 7.11), though the infrared spectrum of this material showed a new band at 6.06 μ.

Free Acid (IVb) from the Quinolone Ester Base IVa. A. Alkaline Hydrolysis.—A solution of 500 mg. of yohimbine-quinolone (IVa) in 20 ml. of 5% aqueous sodium hydroxide was refluxed for two hours. The initially yellow solution became red. The color returned to yellow on longer standing. The solution was neutralized with 2 *N* acetic acid and concentrated *in vacuo*. The resulting white precipitate was recrystallized from methanol. The white solid became pink very readily. The infrared spectrum (Fig. 1) showed the carboxyl band at 6.28–6.32 μ typical of zwitterions and amino acids such as yohimbic acid which has a band at 6.26 μ. The compound became very dark on heating to 200° but did not melt.

Anal. Calcd. for $C_{20}H_{22}N_2O_4 \cdot 2^1/_2H_2O$: C, 60.16; H, 6.82; N, 7.02. Found: C, 60.40; H, 6.67; N, 7.01.

From mother liquors there was obtained more material the analysis of which indicated a dihydrate.

Anal. Calcd. for $C_{20}H_{22}N_2O_4 \cdot 2H_2O$: C, 61.51; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.57; N, 6.95.

Picrate.—The mother liquor was used to prepare the picrate, a yellow solid which on heating darkened progressively from 200° and by 242° was black (Kofler). There was no melting up to 350°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4 \cdot C_6H_3N_3O_7 \cdot H_2O$: C, 51.91; H, 4.52; N, 11.64. Found: C, 51.67; H, 4.64; N, 11.75.

B. Acid Hydrolysis.—Yohimbine-quinolone (100 mg.) dissolved in 5 *N* HCl (20 ml.) was heated at 100° for 4 hours. Some decomposition occurred. The dark material was removed and the red solution evaporated to dryness. Crystallization from alcohol gave a white powder. The infrared spectrum showed bands at 5.77 and 5.90 μ (the hydrochloride of yohimbic acid has a band at 5.82 μ). On heating the compound became black at 270–280° without melting.

Anal. Calcd. for $C_{20}H_{22}N_2O_4 \cdot HCl \cdot {}^1/_4H_2O$: C, 60.76; H, 6.00; N, 7.08. Found: C, 60.71; H, 6.04; N, 6.66.

Clemmensen Reduction of the Quinolone (IVa).—Following the procedure of Stoll and Rutschmann,[16] but using amalgamated mossy zinc instead of zinc dust and double the amount thereof (20 g.), 1.5 g. of the quinolone in 30 ml. of acetic acid was refluxed under stirring. Concentrated hydrochloric acid was added in 10-ml. portions every two hours. The refluxing time was 6 hours. The solution was concentrated *in vacuo* and re-esterified with methanol and HCl. The final residue was poured into concentrated ammonium hydroxide. The precipitate was collected, dried and extracted with hot methanol. This solution was evaporated, the residue extracted with chloroform and chromatographed on alumina. All fractions had very similar infrared spectra. The solids obtained did not melt on heating to 350°. For purification for analysis the middle fractions were dissolved in methanol and precipitated with benzene.

Anal. Calcd. for $C_{21}H_{28}N_2O_3 \cdot H_2O$: C, 67.4; H, 8.07; N, 7.5. Found: C, 67.69; H, 7.29; N, 7.35.

Although the analysis for hydrogen would fit better a H_{26}-compound, the ultraviolet spectrum supports a tetrahydroquinoline structure: compound VI, 296 (3.36), 250 (3.94), 212 (4.38).

Further reductions of the quinolone IVa were tried with excess sodium borohydride in methanol; only starting material was recovered. Catalytic hydrogenation with Adams catalyst in ethanol did not lead to the uptake of hydrogen. In acetic acid with palladium on carbon 2 moles of hydrogen was consumed. The main bands of non-crystalline fractions obtained in this way showed bands in the infrared at 5.79, 6.12, 6.46 μ, not identical with the product (VI) from the Clemmensen reduction.

Yohimbane.—Yohimbone[28] was reduced by means of the Huang-Minlon modification of the Wolff–Kishner method. The yield of crude product, m.p. 185–203°, from 2 g. of yohimbone was 1.77 g. (93%). Recrystallization from methanol afforded 1.26 g. (66%) of white needles, m.p. 204–205°. Two samples were prepared for analysis. One (A) was dried *in vacuo* at 100° for two hours. The other (B) was dried over phosphorus pentoxide at room temperature and atmospheric pressure overnight.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found (A): C, 81.45; H, 8.59; N, 10.07. (B): C, 77.17, 77.06; H, 7.53, 7.49; N, 9.01. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3OH$: C, 76.88; H, 9.03; N, 8.97. Calcd. for $C_{19}H_{24}N_2 \cdot H_2O$: C, 76.51; H, 8.72.

Yohimbane Methiodides. Methiodide A (296–301°).—A solution of 400 mg. (2 millimoles) of yohimbane in 20 ml. of dry ether was treated with 1 g. of methyl iodide. The yellow solution after standing overnight, was evaporated to dryness. Recrystallization from methanol gave a white crystalline powder, recrystallized a second time for analysis, m.p. 296–301°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3I$: C, 56.87; H, 6.44; N, 6.64. Found: C, 57.04; H, 6.68; N, 6.76. Rotation $[\alpha]^{20}D$ +35.7° (5.6 mg. in 10 ml. of methanol).

Methiodide B (256–258°).—The more soluble methiodide was precipitated from the methanolic mother liquors by the addition of ether. Crystallization from methanol–ether afforded a small amount of fine white needles, m.p. 256–258° (yellow melt).

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3I$: C, 56.87; H, 6.44. Found: C, 57.49; H, 6.78. Rotation, $[\alpha]^{20}D$ −36.6° (2.9 mg. in 2 ml. of methanol).

Yohimbane Methochloride.—This compound was prepared for testing for curare activity. Freshly precipitated silver chloride from about 1 g. of silver nitrate was added to a solution of 211 mg. (0.5 millimole) of unrecrystallized yohimbane methiodide A in 50 ml. of aqueous methanol (80%). The mixture was stirred by means of a magnetic stirrer for 48 hours at room temperature. Removal of the silver salts by filtration and concentration of the yellow filtrate afforded a yellow solid which on crystallization from *n*-propanol gave short white needles not melting on heating, charring at 284–290°. The analytical sample was dried at 60° *in vacuo* for 24 hours.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3Cl \cdot {}^1/_2H_2O$: C, 70.67; H, 8.30; N, 8.24. Found: C, 70.25; H, 8.05; N, 8.10. Rotation, $[\alpha]^{20}D$ +40.0° (5.1 mg. in 2 ml. of methanol).

Pharmacological Test.[15]—3.875 mg. of yohimbane methochloride per kg. dog failed to cause a noticeable myoneural blockade.

Methylyohimbane Methosulfate.—A solution of 500 mg. of yohimbane in 15 ml. of benzene was refluxed with 2 g. of dimethyl sulfate for one hour. Some white solid had precipitated and more appeared on the addition of ether. The precipitate was collected and washed with ether. Recrystallization from ethanol gave a white crystalline powder, m.p. 305° (dec.).

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot (CH_3)_2SO_4$: C, 62.09; H, 7.44; N, 6.90. Found: C, 61.81; H, 7.31; N, 6.99. Rotation, $[\alpha]^{20}D$ −23.8° (5.7 mg. in 2 ml. of methanol).

Yohimbane Methopicrates. A. *via* the Quaternary Ammonium Base from Yohimbane Methiodide (A).—Thallous hydroxide (1 millimole) was prepared by mixing aqueous solutions (about 10 ml. each) of 352.4 mg. (0.5 millimole) of thallous sulfate and 160 mg. (0.501 millimole) of barium hydroxide octahydrate. The barium sulfate was removed by filtration and the filtrate was added to a solution of 211 mg. (0.5 millimole) of unrecrystallized yohimbane methiodide A in 100 ml. of methanol. A fine yellow precipitate of thallous iodide developed immediately. After about 20 minutes the mixture was filtered and the colorless filtrate was evaporated to dryness. The dry, yellowish residue was extracted with a large amount of absolute ethanol. The yellow solution on evaporation left a brown glassy residue which after washing with chloroform gave an almost white solid which melted over a wide range (starting about 197°). This residue was converted to a yellow-brown

(28) B. Witkop, *Ann.*, **554**, 83 (1943).

picrate which was recrystallized from aqueous methanol, m.p. 230–233°.

Anal. Calcd. for $C_{20}H_{27}N_2 \cdot C_6H_2N_3O_7$: C, 59.64; H, 5.58. Found: C, 60.36; H, 5.80.

B. **Directly from Yohimbane Methiodide (A).**—An excess of saturated aqueous solution of picric acid was added to an aqueous methanol solution of 50 mg. of yohimbane methiodide (A). The yellow precipitate was dried and on crystallization from methanol–acetone afforded small, lemon yellow plates, m.p. 247–248°, mixed m.p. with picrate from the hydroxide 230–243° (softening at 215°).

Conversion of Methylyohimbane Methosulfate to Yohimbane.—Whereas yohimbane methiodide (A) was recovered unchanged on treatment with excess sodium borohydride in methanol and on attempted Emde reduction, the methosulfate lost its methyl group in the latter reaction. To a solution of 100 mg. of methylyohimbane methosulfate in 25 ml. of hot water (about 60°) 10 g. of 5% sodium amalgam was added. In a few minutes a white precipitate started forming. The mixture was warmed for one hour. The greyish solid was collected (90 mg.) and crystallized from methanol. White needles were obtained, m.p. 205°, undepressed on admixture with yohimbane. The infrared spectra were essentially identical.

Quinolone (IVc) by Ozonolysis of Yohimbane.—A solution of 2 g. (7.13 millimoles) of yohimbane in 80 ml. of acetic acid and 20 ml. of water was treated with a threefold excess of ozone. At one-twentieth of the theoretical time 80% of the ozone was being absorbed and at three times the theoretical time 20% of the ozone was still being absorbed. The reaction mixture was treated with sulfur dioxide and taken to dryness in a vacuum desiccator. The brown tarry residue which was insoluble in water was dissolved in chloroform. The addition of an aqueous sodium bicarbonate solution caused some tar to separate which on rubbing became a brown solid. This solid on treatment with methanol gave an almost white solid which was quite insoluble in most solvents but could be dissolved in 50% aqueous methanol. On concentration to a small volume about 10 mg. of small shiny tan plates was obtained. The material became black on heating at 280–300° but did not melt.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.31; H, 7.56; N, 10.10.

From the mother liquor sufficient material was obtained for an ultraviolet spectrum which showed the characteristic bifurcation of quinolones at 315 and 328 mμ.

In another run 2 g. of yohimbane in 80% aqueous acetic acid was treated with an uncalculated excess of ozone. After treatment with sulfur dioxide the solution was concentrated *in vacuo* at 50° to one-fourth the original volume. The remainder of the solvent was removed in the desiccator. Treatment of the residue with water yielded a brown solution and a brown gum. The solution was made alkaline with sodium carbonate; a yellow-brown precipitate was formed, the infrared spectrum of which was suggestive of the quinolone structure; only a trace of solid material was obtained on working up with methanol. The brown gummy residue after several triturations with water was dissolved in 1 *N* HCl. On neutralization with sodium carbonate a yellow-brown solid precipitated. One-half of this solid was dissolved in 1 *N* HCl and converted into the picrate which was recrystallized from methanol; yellow microcrystalline powder, m.p. 200–220° with a crystalline transformation at 160°. The sample for analysis was dried *in vacuo* at 100° for 15 hours.

Anal. Calcd. for $C_{19}H_{22}N_2O \cdot C_6H_3N_3O_7 \cdot H_2O$: C, 55.86; H, 5.04. Found: C, 55.88; H, 4.86.

The other portion of the material from which the picrate was obtained was recrystallized from methanol to give bright yellow needles (10 mg.). The analytical sample was recrystallized from ethanol and dried *in vacuo* at 60° for two hours. On heating the clear yellow needles became opaque at 143–147° (loss of solvent). At about 243° sprouting was observed. Progressive darkening started at about 260°.

Anal. Calcd. for $C_{19}H_{22}N_2O \cdot C_2H_5OH$: C, 74.18; H, 8.23; N, 8.05. Found: C, 74.61; H, 8.25; N, 8.15.

Attempted Ozonolysis of Yohimbone.—A solution of 2 g. of yohimbone in 80 ml. acetic acid and 20 ml. water was treated with ozone for the calculated length of time. The reaction mixture was worked up in the usual manner. From the crude brown product the only crystalline material obtained was yohimbone (60 mg. was recovered).

N^b-Formyl-1,2,3,4-tetrahydronorharman (VIIa).—A solution of 1.58 g. of 1,2,3,4-tetrahydronorharman[28] in 30 ml. of 90% formic acid at 70° was treated with 10 ml. of acetic anhydride added over 20 min. The temperature of the solution was kept at 70–80° for an additional 40 minutes. The dark brown solution was then poured into 10% NaOH. The white precipitate was collected, dried and crystallized from ethyl acetate. White cubes (0.9 g., 50%), m.p. 171°, were obtained. Recrystallization from methyl alcohol afforded needles, m.p. 170–172° (capillary).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 72.12; H, 6.27; N, 13.98.

N^b-Methyl-1,2,3,4-tetrahydronorharman[29] (VIIb).—To a solution of 0.75 g. of powdered lithium aluminum hydride in 100 ml. of dry, freshly distilled tetrahydrofuran, 2.34 g. (0.0117 mole) of N^b-formyl-1,2,3,4-tetrahydronorharman (VIIa) was added causing a mild exothermic reaction. The solution was refluxed for three hours, then cooled, and ice was added. The resulting white solid, consisting mostly of aluminum hydroxide, was removed by filtration. The filter cake was washed with methyl alcohol. The combined wash solution and filtrates were concentrated on the steam-bath whereupon a white solid precipitated. The precipitate was collected and crystallized from methyl alcohol. The yield of product melting at 203–205° (uncor.) (lit. 216–217°[23]) was 1.86 g. (85%). Recrystallization from benzene–methanol afforded short pale yellow needles melting at 208–210° (uncor.).

1,4-Aza-8,9-benz-4-methylcyclononadi-2,7-one (IX).—A solution of 400 mg. (2.04 millimoles) of N^b-methyl-1,2,3,4-tetrahydronorharman in 75 ml. of ethyl acetate was treated with a stream of ozone for 7 to 8 minutes (theoretical time required 6.3 minutes). During the reaction, a considerable yellow precipitate formed. On attempted crystallization from methanol, the yellow material became brown and sticky. Some brown solid was obtained from the alcohol solution in small amount. The ethyl acetate mother liquor on evaporation afforded a brown oil which on mixing with a little methanol gave an almost white solid. Infrared spectrum: 5.90 μ, 5.98 μ, 6.12 μ; shoulder at 2.90–3.10 μ. This material on crystallization from ethyl acetate yielded short white needles which on heating underwent a crystalline transformation at 213–220°, became yellow and opaque at 230° and finally melted with decomposition at 300–320°. The ultraviolet absorption spectrum indicated the ketolactam structure (VIII). When 1 mg. of this compound was warmed with 0.1 *N* caustic alkali and neutralized again, the ultraviolet spectrum showed the bifurcation characteristic of the expected γ-quinolone (IX) at 328 and 315 μ.

Ozonolysis of N-Acetyltetrahydrocarbazole.—A solution of 2.13 g. (10 millimoles) of N-acetyltetrahydrocarbazole[30] in 200 ml. of ethyl acetate was treated with ozone with cooling in an ice-water bath. Near the end of the ozonization a white solid precipitated which was soluble in chloroform and sparingly soluble in benzene. The sample prepared for analysis was recrystallized from a mixture of these solvents, white crystalline powder, m.p. 244–245°. The infrared spectrum showed bands in the carbonyl region at 5.86–5.88 μ with shoulders at 5.81 and 5.98 μ.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.80; N, 5.36. Found: C, 64.22; H, 6.12; N, 5.55.

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(29) Catalytic hydrogenation of *nor*harman methiodide (m.p. 233°) in ethyl alcohol with platinum oxide led to the uptake of almost one mole of hydrogen, but the starting material was recovered from this reaction almost quantitatively. This hydrogenation will probably work in the presence of base.

(30) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **119**, 1831 (1921).