The collected material from the above-described zone I was a sirup that crystallized on the addition of anhydrous methanol; yield 0.19 g. (fraction J), $[\alpha]^{29}D$ −37.6° (*c* 4, water). This material was combined below to form fraction K.

An amount of 12 g. of fraction G above was dissolved in 180 ml. of water and to this was added 1020 ml. of purified dioxane. The resultant solution was chromatographed in 5-ml. portions as described above for fraction B. Zones were obtained that were located in the same positions as those found in fraction B. The collected material from the bottom zones yielded a sirup that was not further investigated; yield 1.4 g. The material from the top zones was found to contain diheterolevulosan, identified by optical rotation, which was isolated as described above; yield 0.32 g. The collected material from the middles zones crystallized in part from methanol; yield 1.2 g., $[\alpha]^{28}D$ −39.0° (*c* 4, water). This crystalline material was combined with fraction J above to form fraction K which was further purified from methanol and 90% ethanol and was identified as diheterolevulosan II; m. p. 250–252° (dec.) undepressed on admixture with material obtained by the acid treatment of D-fructose, $[\alpha]^{28}D$ −39.0° (*c* 4, water).

*Anal.* Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.31; H, 6.20.

The material was non-reducing toward Fehling solution and yielded the above-described hexaacetate of diheterolevulosan II.

## Summary

1. Diheterolevulosan (di-D-fructopyranose 1,-2′:2,1′-dianhydride, I) and a new di-D-fructose dianhydride, designated diheterolevulosan II, have been isolated in crystalline form by chromatographic methods from the products obtained by the action of heat or of hydrogen chloride upon concentrated aqueous solutions of D-fructose.

2. Periodate analysis of diheterolevulosan II (II) favors, but does not prove, a 1,2′:2,1′-dianhydride structure (III) formed between a mole of D-fructopyranose and one of D-fructofuranose.

3. The amorphous "heterolevulosan" of Pictet and Chavan is shown by chromatographic methods to be a complex mixture, the principal constituent of which is diheterolevulosan II.

COLUMBUS, OHIO RECEIVED FEBRUARY 16, 1948

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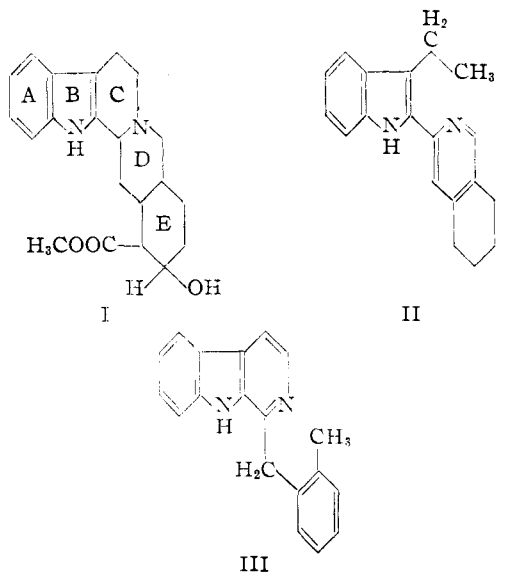
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

# The Structure of Ketoyobyrine

BY R. B. WOODWARD AND BERNHARD WITKOP

The selenium dehydrogenation of yohimbine (I) gives two bases, tetrahydroisoyobyrine (II), yobyrine (III) and ketoyobyrine, a neutral substance of the formula $C_{20}H_{16}ON_2$. The study of the basic products was of primary importance in deducing the structure of yohimbine, and the structures of the bases have been established beyond question.[1,2] On the other hand, no satisfactory formulation of ketoyobyrine has been forthcoming. Scholz[3] originally put forward the expression (IV); the facts that ketoyobyrine is optically inactive, that it is the product of a drastic dehydrogenation reaction, and in particular that it has no basic properties, are incompatible with that formula. The outstanding phenomenon in the chemistry of ketoyobyrine is the smooth cleavage of the molecule by amyl alcoholic potassium hydroxide to hemellitylic acid and norharmane.[3,4] This behavior has been adduced in support of an alternative formula (V),[2] which, however, still cannot be reconciled with the neutral character of the molecule.



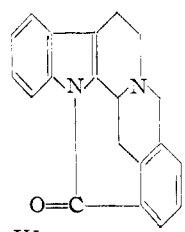

I



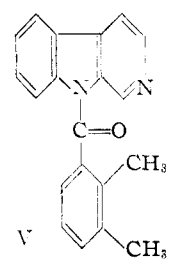

II




III




IV




V

In this communication, it is shown that in fact ketoyobyrine[5] has the structure (VI). This formula was deduced from that of yohimbine (I) on the basis of these considerations: (i) when yohimbic acid is heated with selenium, loss of the

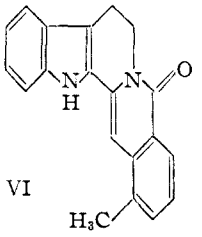
(1) Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).

(2) Witkop, *Ann.*, **554**, 83 (1943); *cf.* Clemo and Swan, *J. Chem. Soc.*, 617 (1946); Julian, *et al.*, THIS JOURNAL, **70**, 180 (1948).

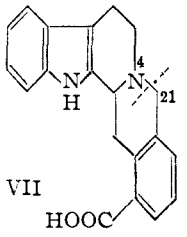
(3) Scholz, Diss. Eidgen. Techn. Hochschule, Zürich, 1934.

(4) Mendlik and Wibaut, *Rec. trav. chim.*, **50**, 91 (1931).

(5) It is clear that the term ketoyobyrine is a misnomer, but in view of long-established usage, we feel that a change is not desirable.

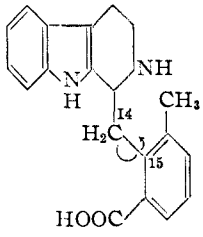


VI

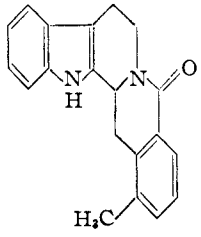


VII

hydroxyl group through dehydration may be followed to some extent by the dehydrogenation of ring E; (ii) the resulting intermediate (VII), as a benzylamine, should be subject to ready reduction cleavage between N.4 and C.21,[6] to give (VIII); (iii) by rotation through 180° about the



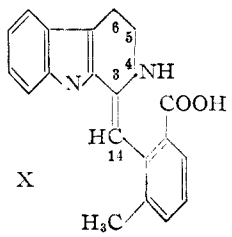
VIII



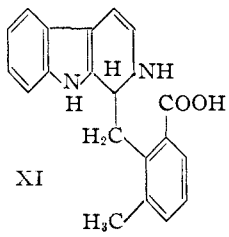
IX

C.14-C.15 bond, (VIII) is in a position to undergo lactamization to (IX); (iv) selenium may effect the further dehydrogenation of the dihydroisoquinolone (IX) to (VI). It is noteworthy that the latter contains a fully aromatic isoquinolone system, and that a compound of that structure should exhibit the high stability characteristic of ketoyobyrine.

The remarkable cleavage of ketoyobyrine by amyl alcoholic potassium hydroxide to norharmane and hemellitylic acid is readily explicable in terms of the structure (VI). Thus, opening of the amide link gives (X). The $\Delta^{3,14}$ double bond of

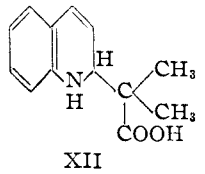


X



XI

(X) migrates to $\Delta^{5,6}$ by three prototropic shifts, for each of which ample analogy is available, *viz.*, enamine $\left(\underset{14}{HC}=\underset{3}{C}-NH\right) \rightarrow$ ketimine[7] $\left(\underset{14}{CH_2}-\underset{3}{C}=N\right)$ ketimine $\left(-\underset{3}{C}=N-\underset{5}{CH_2}\right) \rightarrow$ isomeric ketimine[8] $\left(-\underset{3}{CH}-N=\underset{5}{CH}\right)$, and finally ketimine $\rightarrow$ enamine[7] $\left(N=\underset{5}{CH}-\underset{6}{CH_2} \longrightarrow NH-\underset{5}{CH}=\underset{6}{CH}\right)$. The resulting dihydropyridine derivative (XI) then suffers loss of the side chain through the base-catalyzed process $N-CH-\overset{14}{CH_2}-C=C-COOH$, $HO^{\ominus} \longrightarrow H$, giving norharmane and 2,3-dimethylbenzoic acid. The cleavage is analogous to that of the dihydroquinoline derivative (XII), which leads to quinoline and isobutyric acid[9]; the driving force for the reaction is derived from the aromatization of the pyridine ring in either case, and the reaction is facilitated by the attachment of a carboxyl group either directly (in the case of XII) or through a

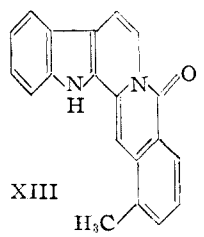


XII

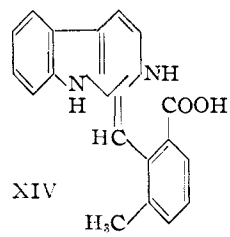
double bond (in the case of XI) to the carbon atom which must accept the electron pair from the broken bond.

The formula (VI) implies that in ketoyobyrine the yohimbine ring system is not fully aromatized. In accordance with that view, we have found that when ketoyobyrine is heated at 280° in the presence of palladium black, exactly one mole of hydrogen is released, and a new substance, $C_{20}H_{14}ON_2$, m. p. 345°, for which we propose the name dehydroketoyobyrine, is formed. The ultraviolet spectrum of the new compound differs considerably from that of its progenitor (*cf.* Fig. 1). It is clear that the structure (XIII) may be assigned to dehydroketoyobyrine.

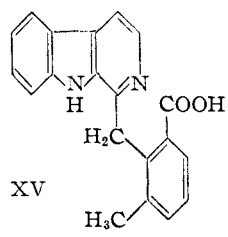
In marked contrast to ketoyobyrine, dehydroketoyobyrine, when treated with hot amyl alcoholic potassium hydroxide, is converted smoothly to a colorless *amino acid*, $C_{20}H_{16}O_2N_2$, which reverts readily to its precursor on heating, alone, or in a variety of solvents, *e. g.*, even on attempted recrystallization from alcohol. The nature of these changes is clear. Following the cleavage of the



XIII



XIV



XV

(6) Emde and Kull, *Arch. Pharm.*, **274**, 173 (1936).

(7) *Cf.* Auwers and Wunderling, *Ber.*, **64**, 2748, 2758 (1931); **65**, 70 (1932).

(8) Shoppee, *J. Chem. Soc.*, 696 (1932); 1225 (1931).

(9) Staudinger and Klever, *Ber.*, **39**, 968 (1906); **40**, 1149 (1907).

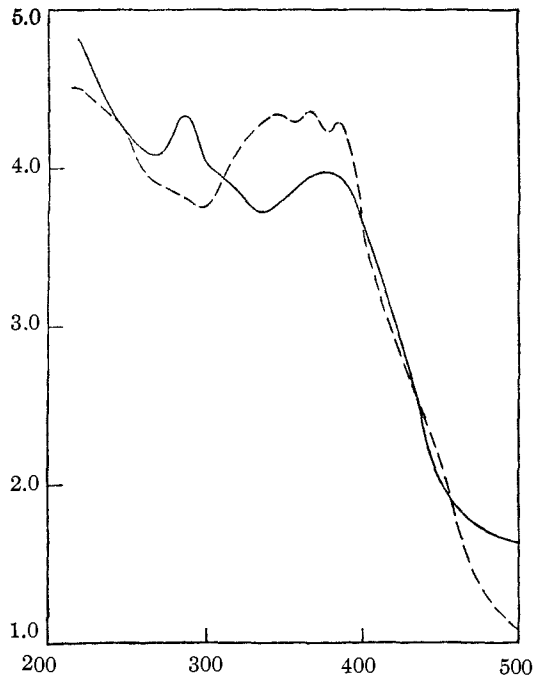
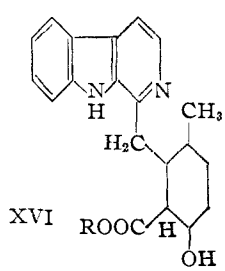


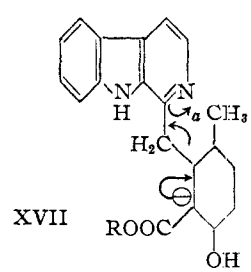

Fig. 1.—Dehydroketoyobyrine, —; ketoyobyrine ----.

amide link of (XIII) with the formation of (XIV), ring C becomes aromatic through migration of the $\Delta^{3,14}$ double bond to the $\Delta^{3,4}$ position. In this way, we arrive at the conclusion that the amino acid $C_{20}H_{16}O_2N_2$ is carboxyyobyrine (XV). This view is substantiated by the identity of the ultraviolet absorption spectrum of the amino acid in alkaline solution[10] with that of yobyrine[11] (III) (*cf.* Fig. 2). The reconversion of (XV) to (XIII) is readily understandable in the light of the well-known lability of the α-substituted pyridine ⇄ α-pyridone methine equilibrium. When attempts were made to effect the decarboxylation of (XV) to yobyrine itself, the facile reconversion to (XIII) supervened, and dehydroketoyobyrine was the sole isolable product.

The new view of the constitution of ketoyobyrine affords new support for the attachment of the carboxyl group of yohimbine at C.16. Hitherto the acceptance of this position has depended upon the formation of harmane and *m*-toluic acid from




XVI




XVII

(10) The spectrum was determined under alkaline conditions in order to minimize any possible additional contribution to absorption as a result of the conjugation of the carboxyl group of (XV) with the benzenoid ring.

(11) Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

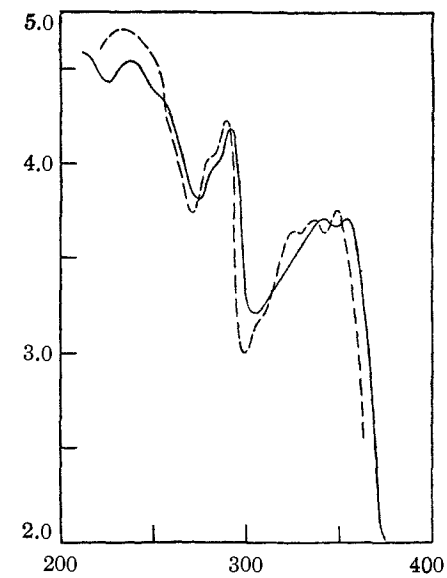



Fig. 2.—Carboxyyobyrine (sodium salt), —; yobyrine, ------.

"tetradehydroyohimbine"[12] (XVI)[2] on boiling with amyl alcoholic potassium hydroxide. The inference from this change is relatively clear, but the structural value of the evidence has been subject to some question in view of the fact that the nature of the cleavage has been obscure, the more so, since, in this reaction, scission of the C.14-C.15 bond occurs, in sharp contrast to the breaking of the C.3-C.14 bond of ketoyobyrine under very similar conditions. We should like to point out that the course of the cleavage of (XVI) is explicable in terms which we have applied elsewhere to the drastic alkaline degradation of alicyclic acids.[13] Thus, removal by base of the hydrogen atom, α to and activated by, the carbomethoxy group of (XVI) gives an anion (XVII), which undergoes a simple electronic shift (XVII, arrows), with cleavage of the C.14-C.15 bond; the acceptance of the liberated electron pair by C.14 is, of course, facilitated by the adjacent pyridine ring (*cf.* XVII, arrow *a*). The addition of a proton to the heterocyclic fragment leads to harmane, and the further changes which lead to *m*-toluic acid from the hydroaromatic fission product are unexceptional. We may point out that the course of this cleavage is in general terms very similar to that of ketoyobyrine, and that the difference in the actual points of cleavage receives a rational explanation in terms of the particular molecular environment present in the one or the other case.

In these circumstances, we consider that the attachment of the carbomethoxy group of yohimbine at C.16 is now entirely free of ambiguity.

## Experimental

**Ketoyobyrine.**—The crude product obtained from the selenium dehydrogenation of yohimbic acid in about 4%

(12) Hahn, Kappes and Ludewig, *Ber.*, **67**, 686 (1934).

(13) Woodward and Brutschy, THIS JOURNAL, in press.

yield was first recrystallized from acetic acid (charcoal) and then extracted from a thimble with alcohol, in which it is moderately soluble; bright yellow rectangular prisms, m. p. 315–320°[14] (dark melt).

*Anal.* Calcd. for $C_{20}H_{16}ON_2$: C, 79.97; H, 5.37 Found: C, 79.98; H, 5.37.

**Dehydroketoyobyrine.**—A mixture of 100 mg. of ketoyobyrine and 200 mg. of palladium black was heated to 280° (metal-bath). After about fifteen minutes exactly the equivalent of one mole of hydrogen had been liberated; prolonged heating or higher temperature did not increase the amount of hydrogen (8.5 cc.). From the reaction mixture the dehydroproduct was obtained either by sublimation (280°, 0.001 mm.), or by recrystallization from a thimble with ethyl alcohol (twenty-four hours). The compound is very sparingly soluble in ethanol and forms fans of short needles of a yellowish-green color. The yield is almost quantitative. The crystals when powdered or sublimed have the same yellow color as ketoyobyrine and in solution they exhibit a similar powerful fluorescence; melting point 345–350° (transformation into prisms at 310°, mixed melting point with ketoyobyrine, 305–310°).

*Anal.* Calcd. for $C_{20}H_{14}ON_2$: C, 80.53; H, 4.69. Found: C, 80.32; H, 4.92.

**Carboxyyobyrine.**—Dehydroketoyobyrine (0.2 g.) was heated under reflux in 4 cc. of amyl alcohol containing 2 g. of caustic potash. A clear yellow solution was obtained after fifteen minutes, whereas ketoyobyrine requires many hours to go into solution under the same conditions. After ten hours water was added and the mixture was extracted with ether. The ethereal layer contained traces of ketoyobyrine, if that was a contaminant of the starting material, and traces of a fluorescent base yielding a picrate (4 mg.), m. p. 255°, showing no depression on admixture with norharmane picrate. The aqueous alkaline layer contained an acid which on acidification with glacial acetic acid separated as a colorless flocculent precipitate. When the alkaline cleavage was carried out in a glass vessel, silicic acid was precipitated first by adding mineral acid to the alkaline solution to *p*H 8.5. The flocculent amino acid (180 mg.) was obtained crystalline when its solution in dilute ammonia was allowed to stand overnight in a slightly evacuated desiccator. In another run, carboxyyobyrine was obtained in beautiful fine needles when it was reprecipitated from dilute alkaline solution with just the necessary amount of acetic acid and was allowed to stand for two days. The colorless aqueous acidic solution of the acid shows the characteristic pure blue harmane fluorescence. On heating the compound becomes yellow at about 100° and shows then the same melting point as dehydroketoyobyrine. For the analysis the substance has to be dried at room temperature.

*Anal.* Calcd. for $C_{20}H_{16}O_2N_2 \cdot H_2O$: C, 71.85; H, 5.40. Found: C, 71.46; H, 5.49.

**Reconversion to Dehydroketoyobyrine.**—When recrystallization of carboxyyobyrine was attempted by extracting it from a thimble with methanol in which the amino acid is sparingly soluble, all the yellow material which had crystallized overnight from the alcoholic solution consisted of dehydroketoyobyrine, m. p. 345°. When 20 mg. of carboxyyobyrine mixed with 40 mg. of soda lime was heated *in vacuo* to 350°, no yobyrine could be isolated from the negligible sublimate. The residue gave some dehydroketoyobyrine.

**Acknowledgment.**—We are indebted to Miss Adelaide Sutton who, through the courtesy of Dr. Elkan R. Blout (Polaroid Corporation, Cambridge), measured the ultraviolet spectra.

## Summary

The structure of ketoyobyrine has been shown to be that of a lactam derived from carboxyyobyrine.

(14) All melting points are corrected.

CAMBRIDGE 38, MASS. RECEIVED MARCH 15, 1948

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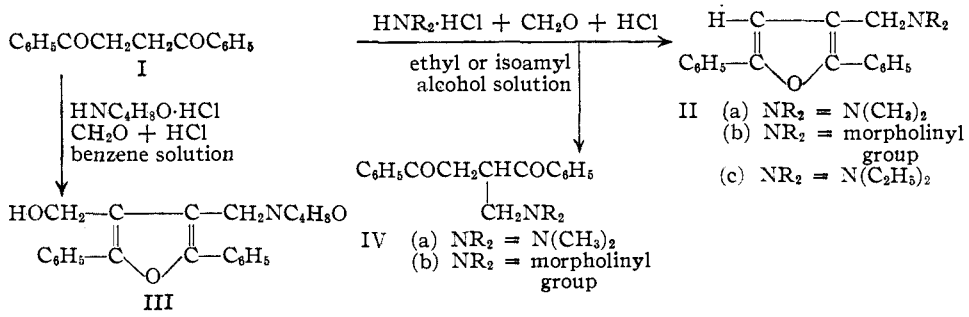
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

# The Mannich Reaction with 1,2-Dibenzoylethane[1,2]

BY PHILIP S. BAILEY[3] AND ROBERT E. LUTZ

The Mannich reaction has been carried out with 1,2-dibenzoylethane, using secondary amine hydrochlorides and paraformaldehyde in ethyl or isoamyl alcohol solution and in benzene solution.[4]




In ethanol solution, using dimethylamine and morpholine hydrochlorides and refluxing for forty-eight hours, the products were the respective substituted furans (IIa and IIb), both of which have previously been made by other methods.[5] When

(1) A portion of the work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

(2) Presented in combination with a paper from The University of Texas at the Chicago meeting of the American Chemical Society, April, 1948.

(3) Holder of Philip Francis du Pont Fellowships, 1942–1944. Present location, The University of Texas, Austin, Texas.

(4) For a discussion of the use of benzene as a solvent in the Mannich reaction see Fry, *J. Org. Chem.*, **10**, 259 (1945).

(5) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).