[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. X. Yohimbine (Part 2). The Synthesis of Yobyrine, Yobyrone and "Tetrahydroyobyrine"

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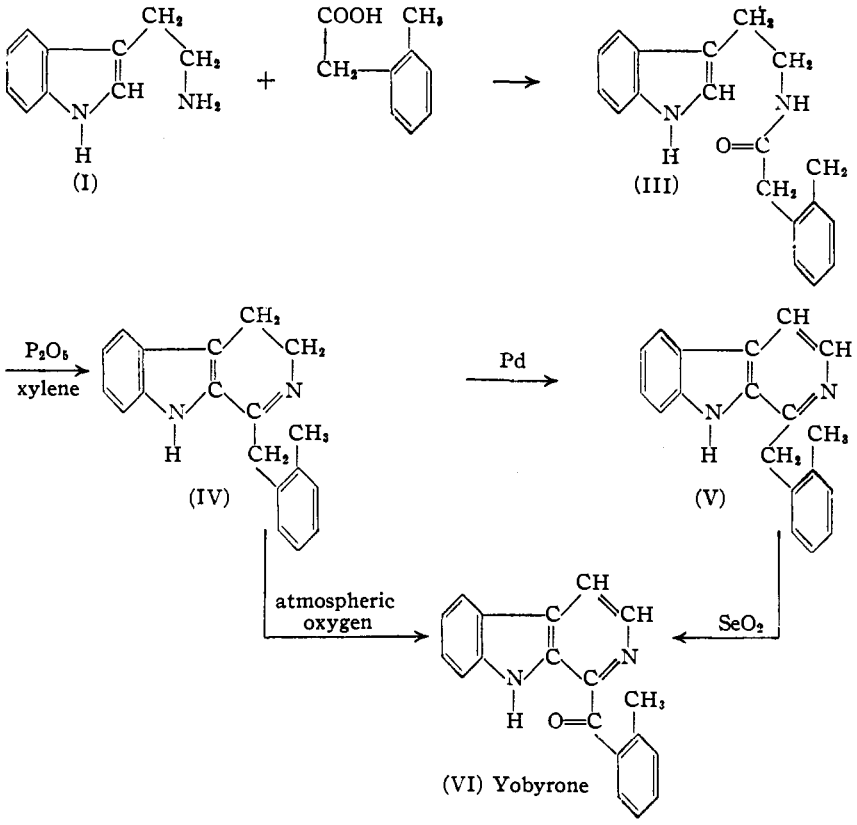
In a previous communication[1] we have adduced new evidence and discussed investigations of others to show that on dehydrogenation of the alkaloid yohimbine with selenium, cleavage of the molecule takes place at the nitrogen atom of the tetrahydroisoquinoline nucleus. The reaction was first discovered by Mendlik and Wibaut[2] who gave the names yobyrine and tetrahydroyobyrine to the two principal products arising from this degradation, in the mistaken notion that both of them possessed the same fundamental ring skeleton. Recently Witkop[3] has given convincing evidence to indicate that yobyrine is 3-*o*-xylyl-4-carboline (V). Several years ago Scholz,[4] in a beautiful piece of work, proposed for "tetrahydroyobyrine" the structure XIII. Thus the name is a misnomer and "tetrahydroyobyrine" is actually 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole.



In the present communication we are reporting the successful synthesis of both yobyrine and "tetrahydroyobyrine."[5] Our synthesis of yobyrine is, generally speaking, an application of the procedure worked out by Späth and Lederer[6] for the Harmala alkaloids. *o*-Tolylacetic acid (II) was prepared in 65% yield from *o*-xylene *via* *o*-xylyl bromide secured by the method of Atkinson and Thorpe.[7] This acid was condensed with tryptamine (I)[8] and the amide thus formed subjected to ring closure with phosphorus pentoxide in boiling xylene to produce dihydroyobyrine (IV). Dehydrogenation of IV with palladium black gave yobyrine (V).[9]

A novel synthesis of yobyrone (VI) was discovered in the atmospheric oxidation of dihydroyobyrine (IV). This compound had previously been prepared by the oxidation of yobyrine with chromic acid[4] and with selenium dioxide.[3,9] Comparison of our synthetic yobyrine and yobyrone with the products of natural origin showed their identity in all respects.

For final proof of structure and synthesis of "tetrahydroyobyrine" (XIII), the other principal degradation product of yohimbine with selenium, we needed 3-*n*-butyrylisoquinolines. 3-Acylisoquinolines have hitherto been unknown and a procedure had to be devised for their preparation.

(1) Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

(2) (a) Mendlik and Wibaut, *Rec. trav. chim.*, **48**, 191 (1929); (b) **50**, 91 (1931); (c) Wibaut and Van Gastel, *ibid.*, **54**, 85 (1935).

(3) Witkop, *Ann.*, **554**, 83 (1943).

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

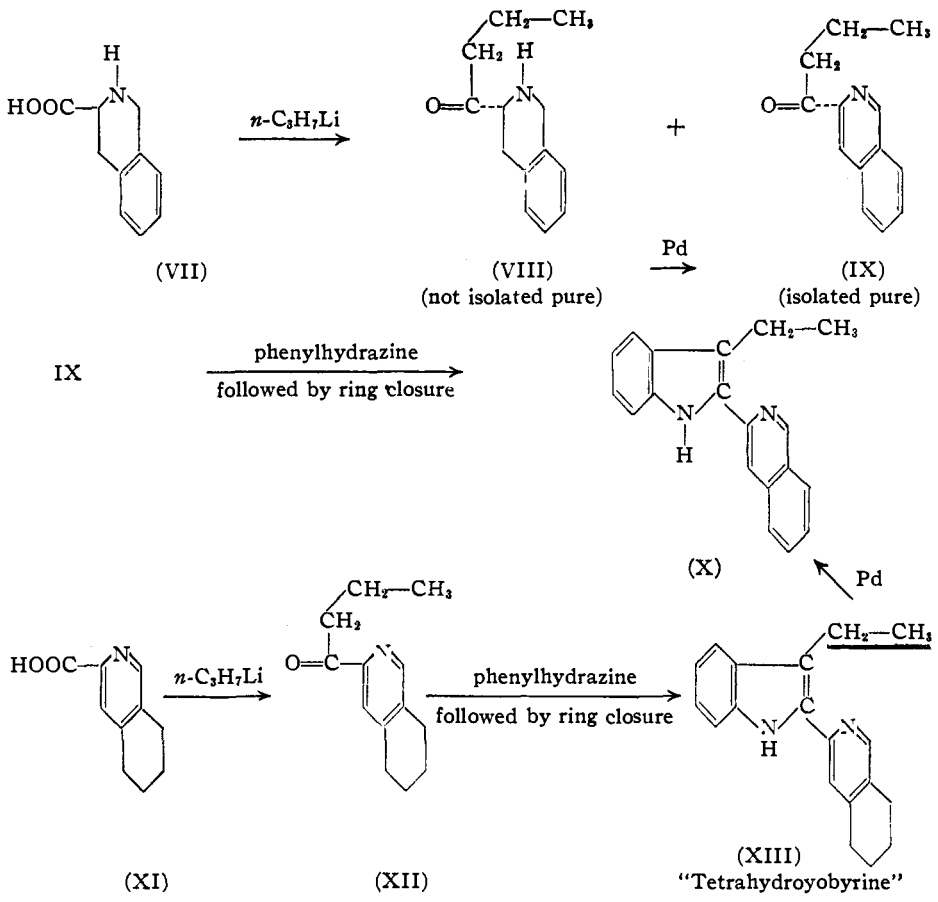
(5) We have employed the name tetrahydroyobyrine in quotation marks throughout the manuscript rather than the proper chemical name. This is done purely for clarity because the name "tetrahydroyobyrine" is so strongly embedded in the literature that confusion might result if we discarded it, even though it is a misnomer.

(6) Späth and Lederer, *Ber.*, **63**, 120, 2102 (1930).

(7) Atkinson and Thorpe, *J. Chem. Soc.*, 1695 (1907).

(8) Hoshino and Majima, *Ber.*, **58**, 2042 (1925).

(9) After the submission of our original manuscript, the English Journal in which there appeared an almost identical synthesis of yobyrine by Clemo and Swan, *J. Chem. Soc.*, 617 (1946), was received by our library. This part of our original manuscript has, therefore, been abbreviated to include only a skeleton description of the synthesis of yobyrine and such new data in connection therewith as Clemo and Swan did not report.



A modification of the procedure of Pictet and Spengler[10] for the preparation of 3-carboxy-1,2,3,-4-tetrahydroisoquinoline (VII) from β-phenylalanine, gave the acid in 61% yield. On treating this acid with *n*-propyllithium,[11] a mixture of 3-butyryl-1,2,3,4-tetrahydroisoquinoline (VIII) and its dehydrogenation product, 3-butyrylisoquinoline (IX), was obtained. The ketone (VIII) resisted isolation in pure form but IX could be obtained in pure crystalline form and characterized. The mixture on dehydrogenation with palladium black gave pure IX. When the Fischer indole synthesis with phenylhydrazine was applied to either IX or the mixture of VIII and IX, 2-(3-isoquinolyl)-3-ethylindole (X) was obtained, identical with the product secured from "tetrahydroyobyrine" by dehydrogenation with palladium black.[3] Thus the constitution of "tetrahydroyobyrine" is firmly established by this complete synthesis of its dehydrogenation product.

To complete the synthesis of "tetrahydroyobyrine" itself, 3-carboxy-5,6,7,8-tetrahydroisoquinoline (XI) was prepared by the method of Scholz.[4] Treatment with propyllithium gave the desired ketone, namely, 3-butyryl-5,6,7,8-tetrahydroisoquinoline (XII), an oil which was readily purified and characterized by means of its crystalline picrate. This ketone underwent the Fischer indole reaction, giving "tetrahydroyobyrine" (XIII) identical in all respects with the product of natural origin. Taken together these syntheses of 2-(3-isoquinolyl)-3-ethylindole (X) and 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole ("tetrahydroyobyrine") (XIII) represent virtually a complete synthesis of "tetrahydroyobyrine" and demonstrate conclusively the constitution of this product.

Experimental

Tryptamine (VI).—The method of Hoshino and Majima[8] was found to be the simplest route to this substance. For good yields of the amine, it was found desirable to employ ethyl iodide instead of the bromide for the Grignard complex.

***o*-Tolylacetic Acid (VII).**—*o*-Xylene was brominated by the method of Atkinson and Thorpe[7] to obtain *o*-xylyl bromide. The bromide was converted into the nitrile by treating it with potassium cyanide in the manner described in "Organic Synthesis" for the preparation of benzyl cyanide.[12] The nitrile was hydrolyzed to the acid by refluxing for five hours with 55% sulfuric acid. Upon cooling, the crystalline acid was filtered, washed with cold water and dried. It was recrystallized from aqueous methanol, m. p. 87–88°. The yield based on *o*-xylene was 65% and this procedure, therefore, constituted a very convenient route to the acid.

***o*-Tolylacetyltryptamine (VIII).**—At room temperature, mixing tryptamine with *o*-tolylacetic acid produces the

(10) Pictet and Spengler, *Ber.*, **44**, 2034 (1911).

(11) Gilman and Van Ess, THIS JOURNAL, **55**, 1258 (1933); Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940).

(12) "Organic Syntheses," Coll. Vol. I, 107 (1941).

acetate salt of the amine, m. p. 170°. To prepare the amide 4.5 g. of tryptamine and 5.0 g. of the acid were heated at 195–200° for forty minutes. During the first twenty minutes there was vigorous liberation of water from the melt. After cooling, the brown residue was dissolved in ether and washed with 2% bicarbonate solution and 2% hydrochloric acid to remove unchanged acid and amine. The amide was obtained from the concentrated ethereal solution by the addition of petroleum ether (b. p. 35–60°). There was obtained 6.75 g., m. p. 96–97°. Recrystallized from ether–petroleum ether it melted at 97°.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.05; H, 6.90. Found: C, 78.12; H, 7.04.

Ring Closure of *o*-Tolylacetyltryptamine (VIII) to Dihydroyobyrine (IX).—To a refluxing solution of dry xylene containing 0.58 g. of the amide there was added portionwise under an atmosphere of nitrogen 5.0 g. of phosphorus pentoxide over a forty-minute period. Heating was continued for an additional fifteen minutes. The mixture was cooled in an ice-bath and 30 ml. of 5% hydrochloric acid was added slowly with agitation. Enough methanol was added to dissolve the red gummy product upon vigorous agitation. The neutral products were removed from the acidic solution by ether extraction. The dihydroyobyrine (IX) was obtained from the acidic solution by basifying and extracting with ether. Crystallization from ether–petroleum ether (b. p. 35–60°) gave 0.35 g., m. p. 175–177°. Upon recrystallization from ether–petroleum ether it was obtained as clusters of fine white needles, m. p. 178–179°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61. Found: C, 83.27; H, 6.65.

The mother liquor of crystallization on standing turned red and upon slow evaporation of the solvent, yellow crystals separated from the solution. They were digested with cold methanol and filtered, m. p. 172–175°. A mixed melting point with the dihydroyobyrine (IX) gave a depression. The compound distilled at 195–200° bath temperature (0.009 mm.) as a yellow oil which solidified on cooling. Crystallization from methanol gave yellow plates, m. p. 185°, which when admixed with known yobyrone gave no depression in melting point. It was found advisable, therefore, when recrystallizing the dihydroyobyrine to filter the product promptly to avoid contamination with yobyrone.

Yobyrine (IV) by Dehydrogenation of Dihydroyobyrine (IX).—An intimate mixture of 0.5 g. of dihydroyobyrine and 0.5 g. of palladium black was heated to 185–190° in a metal-bath at 20–25 mm. pressure for a half hour. Upon direct distillation, the product had a tendency to sublime. There was obtained 0.4 g. of colorless oil distilling at 200–205° bath temperature (0.001 mm.) which quickly crystallized on cooling, m. p. 209–211°. Crystallization from benzene gave 0.35 g. of needles, m. p. 211–212°. A sample crystallized from aqueous methanol also gave needles, m. p. 213°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 83.90; H, 5.90.

It was identical in every respect with the yobyrine obtained from the dehydrogenation of yohimbine with selenium by the method of Mendlik and Wibaut.[2] The yobyrine from natural sources melted at 213° and a mixed melting point with the synthetic yobyrine showed no depression.

Samples of the synthetic and natural yobyrine were each oxidized with selenium dioxide in boiling xylene[2] to yield yobyrone. In each instance, the yobyrone distilled at 190–195° bath temperature (0.008 mm.) and gave yellow plates on crystallizing from methanol, m. p. 185°. A mixed melting point of the two samples gave no depression.

The absorption spectrum of the synthetic material showed maxima at 237, 289, 327, 337 and 348mμ and minima at 269 and 299mμ, the same values as displayed by material of natural origin.[9]

3-Carboxy-5,6,7,8-tetrahydroisoquinoline.—This acid was prepared by the ozonization of tetrahydroyobyrine[2] essentially according to the method of Scholz.[4] However, it has been found that unless precautions are taken to ensure the decomposition of the ozonide, considerable difficulty is experienced in working up the reaction mixture. This is best accomplished by allowing the ozonized reaction mixture, after the addition of water, to stand for three–four hours at room temperature before proceeding. In this fashion 2.55 g. (72%) of the intermediate amide, m. p. 150–151°, was obtained from 3.2 g. of tetrahydroyobyrine. The amide was then hydrolyzed as described by Scholz[4] but for a period of eight hours. The product, 3-carboxy-5,6,7,8-tetrahydroisoquinoline, m. p. 203–206° dec., was obtained in a 95% yield.

3-*n*-Butyryl-5,6,7,8-tetrahydroisoquinoline.—A solution of *n*-propyllithium in 90 ml. of anhydrous ether was prepared under nitrogen from 1.0 g. of lithium metal and 10.5 g. of *n*-propyl bromide. Titration of an aliquot of the ethereal solution indicated the presence of 2.6 g. of *n*-propyllithium. After dilution to 125 ml. with anhydrous ether, 1.5 g. of 3-carboxy-5,6,7,8-tetrahydroisoquinoline was added to the ether solution. The mixture was stirred for eighteen hours, then decomposed with ice and extracted with ether. The ether extract was washed with water and the basic material separated with 3% hydrochloric acid. The acidic solution was made alkaline with 5% sodium hydroxide solution and extracted with ether. After washing the ethereal solution with water and drying, the solution was concentrated. There remained 1.5 g. of a light brown oil. Upon distillation at 6×10^{-3} mm., there was obtained 0.85 g. of a pale yellow oil which came over at 130–135° bath temperature. This material was not analytically pure but was employed for further experimentation. For purification for analysis the ketone was converted into the picrate which was recrystallized twice from methanol. The picrate was then decomposed and the base distilled.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.54; N, 6.71.

The picrate of this ketone, lemon yellow crystals, melted at 128° after recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.66 Found: C, 52.90; H, 4.96.

"*Tetrahydroyobyrine.*"—A mixture of 691 mg. of crude 3-*n*-butyryl-5,6,7,8-tetrahydroisoquinoline and 414 mg. of phenylhydrazine was heated *in vacuo* on the steam-bath for one-half hour (water loss, 59 mg.). The mass was taken up in 25 ml. of anhydrous ethanol and while chilled in an ice-bath, saturated with dry hydrogen chloride. After standing at room temperature for one hour, the mixture was refluxed for one and one-half hours. The solution was then chilled in an ice-bath and the solid hydrochloride separated by filtration. This material, 0.2 g., is being further investigated. The filtrate was concentrated under partial vacuum with gentle warming to remove the ethanol. The residue was covered with ether and shaken with 5% sodium hydroxide solution. The ether extract was washed with water, dried and concentrated. There remained 0.9 g. of a brown gum which was crystallized from 3 ml. of methanol. This gave 180 mg. of pale yellow crystals which melted at 158–162°. A second crop of 100 mg., m. p. 154–157°, was isolated from the mother liquor. The total yield amounted to 30%. The "tetrahydroyobyrine" after purification by sublimation at 4×10^{-2} mm. and crystallization from methanol melted at 164.5°. It showed no depression in melting point when mixed with an authentic sample of "tetrahydroyobyrine."

3-Carboxy-1,2,3,4-tetrahydroisoquinoline.—This acid was previously prepared by Pictet and Spengler.[10] However, the following procedure is much simpler and has given consistently better results. A mixture of 75 g. of β-phenylalanine, 170 ml. of formalin (36%, neutral) and 575 ml. of concentrated hydrochloric acid was heated on a steam-bath for one-half hour with occasional swirling. After the addition of another 75 ml. of formalin and 150 ml. of concentrated hydrochloric acid, the mixture was heated for three hours. It was chilled and the solid

separated by filtration. The filter cake was dissolved in 1000 ml. of hot water and 2000 ml. of hot ethanol was added. While still hot, the solution was neutralized to congo red with 10% ammonium hydroxide solution. After cooling, the crystalline mass was filtered, washed with ethanol and dried. The acid, 49.5 g. (61%), melted at 326°, dec. One recrystallization from aqueous ethanol gave glistening plates which melted at 335°, dec.[13]

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.51; H, 6.15.

3-*n*-Butyrylisoquinoline.—A solution of *n*-propyllithium in 190 ml. of anhydrous ether was prepared from 3.3 g. of lithium and 30.0 g. of *n*-propyl bromide. An aliquot of the ethereal solution when titrated with standard acid indicated that the total solution contained 8.0 g. of *n*-propyllithium. Six grams of 3-carboxy-1,2,3,4-tetrahydroisoquinoline was added to the alkyllithium solution. This mixture was stirred for fifteen hours, decomposed with ice and extracted with ether. The water-washed, dried ethereal solution was concentrated to 5.5 g. of a red-brown, viscous oil. This oil was distilled at 7×10^{-3} mm. and the fraction, 2.9 g., distilling at 126° was collected. Higher boiling materials were present. The 2.9 g. of pale yellow sirup was redistilled at 5×10^{-3} mm. The fraction distilling at 115° amounted to 2.6 g. Efforts to obtain a pure compound from this material either through fractional distillation or fractional crystallization of the picrate were unsuccessful. From analytical data this material appeared to be, essentially, a mixture of 3-*n*-butyryl-1,2,3,4-tetrahydroisoquinoline and 3-*n*-butyrylisoquinoline. This was further substantiated by dehydrogenation. A 100-mg. sample of the mixture was heated with 100 mg. of palladium black at 160–170° (20 mm.) for fifteen minutes. The product was then distilled from the reaction mixture at 140° (0.5 mm.); yield practically quantitative of crystalline material, m. p. 62–65°. One recrystallization from petroleum ether (b. p. 35–60°) gave cream-colored needles of 3-*n*-butyrylisoquinoline melting at 72–73°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.02. Found: C, 78.21; H, 6.66; N, 6.81.

The picrate of this ketone, fine yellow prisms, melted at 161–163° (sintering at 151°) after several recrystallizations from methanol.

Anal. Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.28; H, 3.77. Found: C, 53.43; H, 4.02.

2-(3-Isoquinolyl)-3-ethylindole.—A 2.7-g. sample of the mixture of 3-*n*-butyrylisoquinoline and 3-*n*-butyryl-1,2,3,4-tetrahydroisoquinoline was treated with 1.56 g. of phenylhydrazine at steam-bath temperature for thirty minutes. The liberated water was then removed *in vacuo* (water loss, 180 mg.). The residual material was taken up in 85 ml. of anhydrous ethanol and while chilled in an ice-bath saturated with dry hydrogen chloride. The mixture was allowed to stand at room temperature for thirty minutes and then refluxed for one and one-half hours. The crystalline material which formed on chilling was separated and the filtrate was concentrated *in vacuo* to the point of crystallization. After cautious dilution with ether, the hydrochloride was filtered and washed with ether–ethanol. This material weighed 0.7 g. and melted at 220–225°. Recrystallization of a small sample from ethanol raised the melting point to 233–235°. The bulk of the material was hydrolyzed with 5% sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried and concentrated. The residue was crystallized from ethanol. A total of 0.3 g. of tan crystals, m. p. 126–129°, was obtained in two crops. Purification by sublimation (8×10^{-3} mm.) and recrystallization from aqueous methanol gave fine needles melting at 132°. This gave no depression with an authentic sample of 2-(3-isoquinolyl)-3-ethylindole prepared from tetrahydroyobyrine by palladium dehydrogenation.[3] Furthermore, the absorption spectrum is practically identical with that described by Witkop and Pruckner[14] for the isoquinolyl-indole.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.93. Found: C, 83.44; H, 5.41.

The picrate of 2-(3-isoquinolyl)-3-ethylindole melted at 208° dec., after crystallization from methanol.

Anal. Calcd. for $C_{25}H_{19}N_5O_7$: C, 59.88; H, 3.82. Found: C, 59.71; H, 3.82.

Some effort was made to isolate from the residual material the indole corresponding to the 3-(1,2,3,4-tetrahydroisoquinolyl) ketone. However, to date, resolution of this material has been unsuccessful. This phase is under further investigation.

Summary

1. Yobyrine, a degradation product of the alkaloid yohimbine, has been synthesized by condensation of tryptamine with *o*-tolylacetic acid, followed by ring closure and dehydrogenation. Its structure is therefore completely elucidated and yobyrine is shown to be 3-*o*-xylyl-4-carboline.

2. The preparation of yobyrone by air oxidation of dihydroyobyrine is reported.

3. The first synthesis of so-called "tetrahydroyobyrine" is herewith recorded and confirms its structure as 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole.

CHICAGO, ILLINOIS RECEIVED[15] JULY 21, 1947

(13) Pictet and Spengler[5] reported a melting point of 311° for this acid.

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

(15) Original manuscript received September 9, 1946.