[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Yohimbic Acid Lactone. Conversion of Yohimbine to β-Yohimbine

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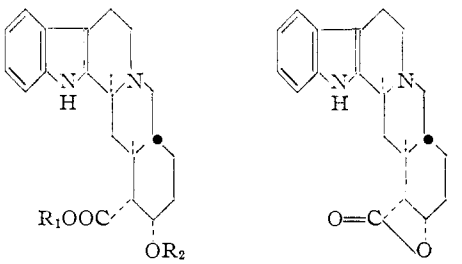
The reaction of yohimbic acid and ethyl chloroformate in pyridine gives yohimbic acid lactone, which constitutes a new method for the preparation of β-lactones. The mechanism of the reaction is discussed. Yohimbine has been converted to β-yohimbine.

The recent interest in the tranquilizing and hypotensive activity of some Rauwolfia alkaloids such as reserpine and deserpidine has led us to prepare derivatives of other Rauwolfia alkaloids containing the same pentacyclic system, such as yohimbine (I). In connection with these studies we had occasion to treat yohimbic acid (II) with an excess of ethyl chloroformate in pyridine at room temperature. The product, isolated in 35% yield, proved to be yohimbic acid lactone (III) on the basis of the following evidence: The empirical formula was $C_{20}H_{22}O_2N_2$ as shown by elemental analysis, saponification equivalent and neutral equivalent when titrated with perchloric acid in glacial acetic acid. The compound was no longer amphoteric but possessed only basic properties. The infrared spectrum had a band at 5.55 μ typical[1] of a carbonyl group in a four-membered ring containing oxygen (oxetanone) and showed no absorption in the hydroxyl region of the spectrum. That N-acylation had not occurred was shown by the ultraviolet spectrum which had only the characteristic indole absorption.[2] Mild alkaline hydrolysis of III regenerated yohimbic acid.

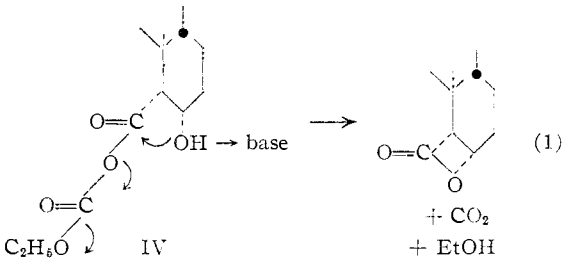


I, $R_1 = CH_3$, $R_2 = H$
II, $R_1 = H$, $R_2 = H$
V, $R_1 = H$, $R_2 = COCH_3$

III

The formation of yohimbic acid lactone corroborates the proposed[3] *cis*-stereochemical relationship of the carbomethoxyl and hydroxyl groups of yohimbine. That inversion of either of these groups could have occurred in lactone formation seems unlikely since on mild alkaline hydrolysis the lactone reverts to yohimbic acid.

Janot and Goutarel have shown[3] that the carbomethoxyl group of yohimbine is equatorial. Thus, the *cis*-C_{17}-hydroxyl must be axial and this fact aids in an understanding of the mechanism of β-lactone formation. Fieser, *et al.*,[4] have demonstrated that axial hydroxyl groups of steroids cannot be cathylated (carbethoxylated) by treatment of the steroid with ethyl chloroformate in pyridine. That this selectivity applies also to alkaloids is evident since reaction of yohimbine with ethyl chloroformate failed to produce O-carbethoxyyohimbine whereas methyl reserpate (C_{18}-hydroxyl equatorial) readily gave an O-cathylate.[5] Thus, the mechanism of formation of the β-lactone, as shown in reaction 1 probably involves initial formation of the mixed anhydride IV followed by attack of the unacylated and sterically favorable hydroxyl group on the carbonyl group attached to C-16 which is now more polarized due to anhydride formation. Electronic rearrangement with concomitant loss of carbon dioxide and ethanol complete the reaction.



IV

(1)

It is interesting to note that reaction of yohimbic acid with acetic anhydride, an acylating agent capable of acetylating axial hydroxyl groups, gives O-acetylyohimbic acid (V).[6] Lactone formation in this case is prevented due to acylation of the hydroxyl group.

The reaction of a β-hydroxy acid with ethyl chloroformate constitutes a new method for the preparation of a β-lactone, the usual methods requiring reaction of a β-halogen acid with base or reaction of a ketene with a carbonyl compound.[7] From the mechanism of the reaction, however, it would seem that this method is applicable only to alicyclic *cis*-β-hydroxy acids having an axial hydroxyl group, and perhaps to aliphatic β-hydroxy acids.

The rather unique property of β-lactones to cleave at the alkyl–oxygen bond as well as at the carbonyl–oxygen bond when treated with nucleo-

(1) (a) D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946); (b) P. D. Bartlett and P. N. Rylander, THIS JOURNAL, **73**, 4275 (1951); (c) G. B. Hoen, D. O. Dean and C. T. Lester, *ibid.*, **77**, 391 (1955); (d) B. L. Murr, G. B. Hoey and C. T. Lester, *ibid.*, **77**, 4430 (1955); (e) J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *ibid.*, **78**, 4812 (1956); (f) R. Hirschman, *et al.*, *ibid.*, **78**, 4814 (1956).

(2) N-Acylation of indoles causes a shift of the shorter of the two characteristic indole maxima from 226 to 244 mμ; M. M. Janot and R. Goutarel, *Compt. rend.*, **229**, 360 (1949); *Ann. pharm. franc.*, **1**, 552 (1949).

(3) (a) M. M. Janot, R. Goutarel, A. LeHir, M. Amin and V. Prelog, *Bull. soc. chim.*, **12**, 1085 (1952); (b) R. C. Cookson, *Chemistry & Industry*, 337 (1953).

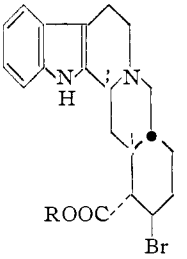
(4) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, THIS JOURNAL, **74**, 3309 (1952).

(5) J. Szmuszkovicz, U. S. Patent 2,763,655.

(6) C. F. Huebner, R. Lucas, H. B. MacPhillamy and Hyla Ames Troxell, THIS JOURNAL, **77**, 469 (1955).

(7) For a review of the preparation and properties of β-lactones see H. E. Zaugg, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 305–363.

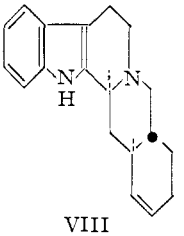
philic reagents[7] suggested yohimbic acid lactone as an attractive starting material for the preparation of 17-substituted derivatives of yohimbine. Our first attempt in this direction was to introduce a methoxy group at C-17. Gresham, *et al.*,[8] have reported that alcoholysis of β-propiolactone in neutral or mildly acidic solution gives β-alkoxypropionic acids, whereas in alkaline medium β-hydroxypropionic esters are obtained. Yohimbic acid lactone therefore was treated with methanol, methanolic hydrogen chloride and dilute sodium methoxide in methanol; however in each case we were able to isolate only yohimbine.



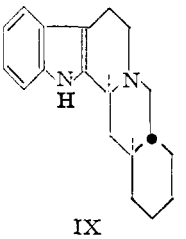
VI, R = H
VII, R = CH_3

Reaction of III with lithium bromide in acetone, however, caused cleavage of the alkyl–oxygen bond to give 17β-bromo-17-desoxyyohimbic acid (VI) which was converted to 17β-bromo-17-desoxyyohimbine (VII) by treatment with diazomethane. The bromide is most likely formed with inversion of configuration at C-17 and the bromine is therefore beta[9] and equatorial.

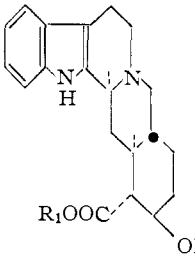
Acetolysis of yohimbic acid lactone by sodium acetate in acetic acid gave two products. One was the basic compound, apocorynanthol (VIII) formed by decarboxylation of the β-lactone. Catalytic hydrogenation of VIII over platinum oxide gave yohimbane (IX).[10]



VIII



IX



X, R_1 = H, R_2 = $COCH_3$
XI, R_1 = CH_3, R_2 = H
XII, R_1 = CH_3, R_2 = $COCH_3$

The other product was an amphoteric compound, $C_{22}H_{26}O_4N_2$ (X), isolated as the hydrochloride, which was proved to be O-acetyl-β-yohimbic acid hydrochloride since treatment with methanolic hydrogen chloride converted it to β-yohimbine[11] (XI) identical in all respects with an authentic sample of this alkaloid.[12]

Reaction of X with diazomethane gave O-acetyl-β-yohimbine (XII).

Pharmacological studies conducted under the direction of Dr. B. Rubin of these laboratories have shown that yohimbic acid lactone does not exhibit any of the characteristic sedative activity of reserpine or deserpidine but does possess the adrenolytic and transient hypotensive activity in anesthetized dogs typical of yohimbine.

Experimental

Yohimbic Acid Lactone (III).—To a cold solution of 500 mg. (1.47 millimoles) yohimbic acid in 7.5 ml. of dry pyridine there was added dropwise 0.42 ml. (4.41 millimoles) of ethyl chloroformate. The solution immediately turned orange-red and gassing was evident during the addition. A reddish gum separated which slowly redissolved as the mixture was allowed to come up to room temperature. After standing overnight, the solution was poured into 25 ml. of water whereupon needle-like crystals slowly separated. These were filtered, washed with water and recrystallized from ethanol; yield 175 mg. (37% theoretical), m.p. 173–175°, $[\alpha]^{22}D$ +11.6° (chf.). The ultraviolet spectrum in methanol exhibited maxima at 226 mμ (log ε 4.52), 282 mμ (log ε 3.89) and 290 mμ (log ε 3.85). The infrared absorption in Nujol mull showed one band in the carbonyl stretching region at 5.55 μ.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$ (322.40): C, 74.50; H, 6.88; N, 8.69. Found: C, 74.35; H, 6.88; N, 8.59; equiv. wt. (perchloric acid titration), 321.

Hydrolysis of Yohimbic Acid Lactone.—To 25 ml. of 2 *N* potassium hydroxide in methanol–water (1:1, v.:v.) there was added 209 mg. (0.615 millimole) of yohimbic acid lactone and the mixture refluxed for one hour. The reflux condenser was then removed and the methanol evaporated by heating on a steam-bath; 10 ml. of water was added and the *p*H adjusted to 6.6 with acetic acid. On standing crystals formed. They were filtered, washed with water, dried and recrystallized from absolute ethanol, yield 130 mg., m.p. 294–296°, $[\alpha]^{22}D$ +128° (pyridine). A mixture melting point with an authentic sample of yohimbic acid showed no depression. The infrared spectrum taken in Nujol was identical with a similar spectrum of yohimbic acid.

Methanolysis of Yohimbic Acid Lactone. (a) **Neutral Methanol.**—A solution of 520 mg. (1.66 millimoles) of yohimbic acid lactone in 55 ml. of absolute methanol was refluxed under nitrogen for 24 hours. The solution was then concentrated *in vacuo* to approximately 5 ml., whereupon crystallization occurred. The crystals were filtered, washed with methanol and dried, wt. 378 mg., m.p. 235.5–237°, $[\alpha]^{22}D$ +101° (pyridine). Mixture melting point with an authentic sample of yohimbine showed no depression. The infrared and ultraviolet spectra were also identical to that of yohimbine.

(b) **Methanolic Hydrogen Chloride.**—A solution of 502 mg. (1.56 millimoles) of yohimbic acid lactone in 25 ml. of absolute methanol was saturated with dry hydrogen chloride. After 2 hours at room temperature the crystals which separated were filtered, washed with water and dried, wt. 440 mg., m.p. 295–298°. Mixture melting point and infrared spectrum comparison with authentic yohimbine hydrochloride showed the compounds to be identical.

The filtrate was evaporated to dryness and distributed between chloroform (20 ml.) and 10% ammonium hydroxide (20 ml.). The chloroform extract was separated, washed with water and evaporated to dryness *in vacuo*. The residue (99 mg.) was crystallized from methanol to give yohimbine.

Acidification of the alkaline extract gave no precipitate.

(c) **Dilute Sodium Methoxide.**—Yohimbic acid lactone (105 mg., 0.326 millimole) was dissolved in a solution of 20

(8) T. L. Gresham, *et al.*, THIS JOURNAL, **70**, 1004 (1948).

(9) The nomenclature used here is the same as is commonly applied to the steroids (*cf.* C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. Andre, *Experientia*, **11**, 303 (1955), and E. E. van Tamelen, M. Shamma and P. Aldrich, THIS JOURNAL, **78**, 4628 (1956)).

(10) M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 509 (1949).

(11) Since the completion of this work the conversion of yohimbine to β-yohimbine by another route has been reported also by W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **11**, 1013 (1957).

(12) A sample of β-yohimbine for comparison was very kindly furnished by Dr. A. Hofmann, Pharmaceutical Chemical Laboratory, Sandoz, Basel, Switzerland.

mg. of sodium in 15 ml. of absolute methanol and the mixture refluxed under nitrogen for 1 hour. After cooling, the solution was acidified with concentrated hydrochloric acid and then concentrated *in vacuo*. The crystals which separated were filtered, washed with water and dried, wt. 82 mg., m.p. 298–301°.

The crystals were shown to be yohimbine hydrochloride by mixture melting point with an authentic sample of the alkaloid salt and comparison of ultraviolet and infrared spectrum.

Reaction of Yohimbic Acid Lactone with Lithium Bromide.—To a solution of 539 mg. (6.2 millimoles) of lithium bromide in 20 ml. of acetone, 500 mg. (1.55 millimoles) of yohimbic acid lactone was added and the mixture refluxed under nitrogen. During the first 15 minutes of heating, the lactone slowly went into solution and a short time later a precipitate began to separate. The mixture was refluxed for two hours, cooled and the precipitate filtered and washed with acetone. The 17β-bromo-17-desoxyyohimbic acid was converted to the hydrobromide salt by dissolving it in 15 ml. of water and adding a few drops of 48% hydrobromic acid. It was crystallized from methanol–water, yield 490 mg. (63%), m.p. 283–286°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2Br_2 \cdot H_2O$ (502.27): C, 47.82; H, 5.22; N, 5.58; Br, 31.82. Found: C, 48.10; H, 5.35; N, 5.50; Br, 31.30; neut. equiv., 482 ($HClO_4$ titration).

A portion (274 mg.) of the 17β-bromo-17-desoxyyohimbic acid hydrobromide was suspended in 20 ml. of methanol and treated with an excess of ethereal diazomethane. The precipitate dissolved and after standing at room temperature for 1 hour the solution was evaporated to dryness *in vacuo* and the residue crystallized from methanol–water, yield 182 mg., m.p. 298–300°, $[\alpha]^{24}D$ +74.1° (pyridine).

Anal. Calcd. for $C_{21}H_{25}O_2N_2Br$ (417.25): C, 60.43; H, 6.04; N, 6.71; Br, 19.15. Found: C, 60.59; H, 5.89; N, 6.17; Br, 18.96; neut. equiv., 416 ($HClO_4$ titration).

Acetolysis of Yohimbic Acid Lactone.—A solution of 2.0 g. (6.1 millimoles) of yohimbic acid lactone and 2.0 g. (24.4 millimoles) of anhydrous sodium acetate dissolved in 40 ml. of glacial acetic acid was refluxed under nitrogen for 2.5 hours and then left at room temperature overnight. The acetic acid was removed *in vacuo*, 75 ml. of water was added to the residue and the solution made alkaline with ammonium hydroxide. The base-insoluble precipitate was filtered, washed with water and crystallized from methanol to give 134 g. (8%) of apocorynanthol, m.p. 170–172°, $[\alpha]^{23}D$ +158° (chlf.), +183° (abs. ethanol).

Anal. Calcd. for $C_{19}H_{22}N_2$ (279.38): C, 81.97; H, 7.96; N, 10.06. Found: C, 81.90; H, 7.54; N, 9.89.

The basic filtrate was made strongly acidic with hydrochloric acid whereupon crystals separated. These were filtered and recrystallized from water containing a few drops of hydrochloric acid to give 635 mg. (25%) of β-yohimbic acid-17-acetate hydrochloride, m.p. 286–288°, $[\alpha]^{23}D$ +99° (pyridine).

Anal. Calcd. for $C_{22}H_{26}O_4N_2 \cdot HCl$ (418.91): C, 63.08; H, 6.50; Cl, 8.46. Found: C, 63.02; H, 6.65; Cl, 9.19. equiv. wt. (perchloric acid titration), 391.

Hydrogenation of Apocorynanthol.[9]—A solution of 52.8 mg. (0.188 millimole) of apocorynanthol in 25 ml. of absolute ethanol with 60 mg. of platinum oxide catalyst was hydrogenated at room temperature and atmospheric pressure for 20 hours. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was crystallized from methanol to give 45 mg. of yohimbane, m.p. 204–206°, $[\alpha]D$ −63° (absolute ethanol), −107° (pyridine).

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.78; H, 8.26; N, 9.99.

β-Yohimbine.—A solution of 530 mg. (1.26 millimoles) of β-yohimbic acid 17-acetate hydrochloride in 50 ml. of absolute methanol was saturated with hydrogen chloride and left at room temperature for 3 hours. The methanol was then removed *in vacuo* and the residue distributed between chloroform and 10% ammonium hydroxide. The chloroform phase was washed twice with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was crystallized from methanol to give 173 mg. of β-yohimbine, m.p. 234–236°, $[\alpha]^{24}D$ −16.2° (abs. ethanol), −44.7° (pyridine). The ultraviolet spectrum in ethanol showed maxima at 226 mμ (log ε 4.55), 283 mμ (log ε 3.88) and 290 mμ (log ε 3.81). The infrared spectrum in Nujol was identical to the spectrum of β-yohimbine.

Anal. Calcd. for $C_{21}H_{26}O_3N_2$ (354.44): C, 71.16; H, 7.39; N, 7.90. Found: C, 71.58; H, 7.28; N, 7.10; equiv. wt. (perchloric acid titration), 349.

β-Yohimbine 17-Acetate.—A solution of 228 mg. (0.545 millimole) of β-yohimbic acid 17-acetate hydrochloride in 20 ml. of methanol was treated with 15 ml. of an ethereal solution of diazomethane (approximate concentration 3 millimoles/ml.). After 1 hour the solution was evaporated nearly to dryness whereupon crystals were formed. They were filtered and recrystallized from methanol to give β-yohimbine 17-acetate, 175 mg. (81%), m.p. 189–191°, $[\alpha]^{22}D$ +21° (pyridine), +17° (abs. ethanol). The ultraviolet spectrum taken in ethanol showed maxima at 225 mμ (log ε 4.61), 283 mμ (log ε 3.88), 291 mμ (log ε 382) and a shoulder at 277 mμ (log ε 3.87).

Anal. Calcd. for $C_{23}H_{28}O_4N_2$ (396.47): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.70; H, 6.85; N, 6.91.

Methyl Reserpate O-Cathylate.—The procedure was essentially that described by Szmuszkovicz.[5] Crystallization of the product from methanol gave methyl reserpate O-cathylate, m.p. 238–240°, $[\alpha]^{23}D$ −97° (*c* 0.66, chloroform); λ_{max}^{Nujol} 2.95, 6.72–6.80, 6.13 and 6.36 μ.

Anal. Calcd. for $C_{26}H_{34}O_7N_2$ (486.52): C, 64.18; H, 7.04; N, 5.76. Found: C, 64.24; H, 6.92; N, 5.96; neut. equiv. ($HClO_4$), 475.

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