pension of 3-hydroxy-4-carbethoxy-5-methylpyrrole (0.7 g. in 50 cc. of ethanol). The hydroxypyrrole went into solution, which turned orange, then deep red. After 15 minutes it was neutralized with aqueous sodium bicarbonate and allowed to stand overnight in the ice-box. The crude product (1.2 g.) was crystallized twice as orange plates from hexane and benzene; m.p. 214–216° dec., λ_{max} 4150 Å., and ϵ 1.72 × 10^4. When crystallized very slowly, yellow needles were obtained. This product had λ_{max} 4150 Å. and ϵ 1.78 × 10^4. *Anal.* Calcd. for $C_{19}H_{24}O_6N_2$: C, 63.32; H, 6.71. Found: orange plates, C, 63.31; H, 6.88; yellow needles, C, 63.50; H, 6.90. This N-methyldipyrrylmethene thus appears to have two crystal forms.

Condensation of 3,5,4′-Tricarbethoxy-4,3′,5′-trimethyldipyrrylmethene with 3-Hydroxy-4-carbethoxy-5-methylpyrrole.—The dipyrrylmethene (0.50 g.) and α-free pyrrole (0.21 g.) were added to 25 cc. of purified dioxane. The addition of a pinch of powdered $KHSO_4$, with shaking, caused the color to change from red to yellow almost instantly. In 15 minutes, 25 cc. of water was added slowly to precipitate the product, which, after drying, melted over a wide range in the vicinity of 140°. The presence of about 10% 3,5,4′-tricarbethoxy-4,5′-dimethyl-3′-hydroxydipyrrylmethene (VIII) was indicated by the absorption spectra, which showed two bands of about equal intensities at *ca.* 3700 and 4430 Å. A drop of *N* HCl in the absorption cell caused almost quantitative cleavage to VIII over a period of several hours. This dipyrrylmethene presumably is formed by the cleavage of a tripyrrylmethane intermediate X, which has not been analyzed because of purification difficulties.

Attempted Condensation of 3,5,4′-Tricarbethoxy-4,5′-dimethyl-3′-hydroxydipyrrylmethene (VIII) with 3,5-Dimethyl-4-carbethoxypyrrole (VI).—A solution which was 0.001 and 0.02 *M*, respectively, with respect to VIII and VI showed no decrease in light absorption at 4430 or 3700 A. in 40 hours at room temperature.

3,5,4′-Tricarbethoxy-4,3′,5′-trimethyldipyrrylmethene (III).—The hydrochloride was prepared by the method of Corwin and Quattlebaum.[14] The free base[3b] was prepared by shaking the hydrochloride with a suspension of calcium hydroxide in benzene, filtering, precipitating in hexane and recrystallizing twice from hexane–benzene, and from anhydrous acetone.

3,5,4′-Trimethyl-4,3′-dicarbethoxy-5′-chlorodipyrrylmethene (I).—The hydrochloride was prepared in 45% yield by the method of Fischer, Sturm and Friedrich,[16] except that benzene was used as solvent. The free base was prepared as described above, and recrystallized twice from acetone; m.p. 145–146°.

3,5,4′-Trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene (II).—The hydrobromide was prepared by the method of Corwin and Viohl.[17] The free base was prepared as above and recrystallized twice from a 2:1 mixture of acetone and hexane.

3,5,3′-Trimethyl-4,4′-dicarbethoxy-5′-bromodipyrrylmethene (V).—This was also prepared by the method of Corwin and Viohl.[17]

3,4,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethene (IV).—This was prepared by the method of Piloty, Krannich and Will.[18] The free base[3a] was prepared as above and was recrystallized twice from hexane–benzene, and from acetone.

Synthesis of 3,5,4′,3″,5″-Pentamethyl-4,3′,4″-tricarbethoxy-5′-chloro-2,2′,2″-tripyrrylmethane.—3,5,4′-Trimethyl-4,3′-dicarbethoxy-5′-chlorodipyrrylmethene (0.30 g.) and an equivalent amount of 3,5-dimethyl-4-carbethoxypyrrole are dissolved in 25 cc. of absolute ethanol containing one drop lactic acid. The methane precipitated overnight in the ice-box. It was filtered, washed with ether and recrystallized from absolute methanol by very slowly cooling with Dry Ice; yield 0.30 g., m.p. 231–232° dec.

Anal. Calcd. for $C_{27}H_{34}O_6N_3Cl$: C, 60.98; H, 6.61. Found: C, 60.92; H, 6.45.

(16) H. Fischer, E. Sturm and H. Friedrich, *Ann.*, **461**, 267 (1928).
(17) A. H. Corwin and P. Viohl, THIS JOURNAL, **66**, 1137 (1944).
(18) O. Piloty, W. Krannich and H. Will, *Ber.*, **47**, 2544 (1914).

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Rauwolfia Alkaloids. XIV. Derivatives of Yohimbé Alkaloids

BY CHARLES F. HUEBNER, R. LUCAS, H. B. MACPHILLAMY AND HYLA AMES TROXELL

RECEIVED JULY 15, 1954

A series of esters of yohimbine, corynanthine and α-yohimbine have been prepared for pharmacological testing as reserpine substitutes. The amide of yohimbic acid was obtained by the action of sodium amide on yohimbine in liquid ammonia. The synthesis of N-methylyohimbine and yohimbhydrazide is reported.

Reserpine, a sedative and hypotensive alkaloid from *Rauwolfia serpentina Benth*, has been shown to be an ester of 3,4,5-trimethoxybenzoic acid. Since methyl reserpate, the alcoholic portion of this ester, has been postulated to have the pentacyclic ring system found in the yohimbé alkaloids,[1] and since methyl reserpate does not show the characteristic physiological activity of reserpine, it seemed pertinent to prepare esters of certain of the yohimbé alkaloids. Yohimbine and two of its stereoisomers, corynanthine and α-yohimbine,[2] were included in this study. In addition some new derivatives of yohimbine, involving transformations of the carbomethoxyl and imino functions, have been synthesized.

Esterification of these hydroxyl-bearing alkaloids was accomplished by reaction with excess acid chloride in pyridine at room temperature. O-Benzoyl, -anisoyl, -veratroyl, and -3,4,5-trimethoxybenzoylyohimbine, O-3,4,5-trimethoxybenzoylcorynanthine and O-3,4,5-trimethoxybenzoyl-α-yohimbine were prepared by this method. With acetic anhydride as the acylating agent, yohimbine gave crystalline O-acetylyohimbine of m.p. 215–220°. Schomer[3] has described what is presumably this compound as an amorphous material of m.p. 133°. That O- rather than N-acylation has occurred, is demonstrated by the typical indole ultraviolet absorption spectra of the products. Janot and Goutarel[4] have shown that N-acetylation, as exemplified by O,N-diacetylyohimbine, shifts the shortest of the two characteristic indole maxima

(1) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

(2) Our sample of α-yohimbine was isolated from *Rauwolfia Canesens* L. The alkaloid obtained from this source previously has been known as "rauwolscine" until its recent identification as α-yohimbine by A. Chatterjee, A. Bose and S. Pakrashi, *Chem. and Ind.*, 491 (1954).

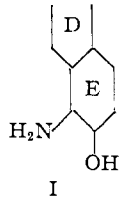
(3) (a) A. Schomer, *Arch. d. Pharm.*, **265**, 509 (1927); (b) M. M. Janot and R. Goutarel, *Bull. soc. chim.*, [5] **10**, 383 (1943).

(4) (a) M. M. Janot and R. Goutarel, *Compt. rend.*, **229**, 360 (1949); (b) M. M. Janot and R. Goutarel, *Ann. pharm. franc.*, **1**, 552 (1949).

from 226 mμ to 244 mμ. Further, we have established that the amide carbonyl infrared absorption at 1698 cm.$^{-1}$, exhibited by the latter compound, is lacking in the O-acyl derivatives reported here. Because of the supposed axial conformation of the hydroxyl group in yohimbine and corynanthine,[5] one might expect esterification to proceed with some difficulty.[6] Yields in the esterification varied from 58% for the benzoate of yohimbine to 5–10% for the three 3,4,5-trimethoxybenzoates. This variation is probably due to differences in the method and in the ease of isolation of the ester. In all cases, a considerable amount of dark, tarry by-products was encountered.

Efforts to obtain the amide of yohimbic acid by the usual methods, which included reaction of yohimbine with ammonia under various conditions and synthesis from O-acetylyohimbic acid *via* the acid chloride or the carbonic acid anhydride, failed. Reaction of yohimbine with a large excess of sodium amide in liquid ammonia successfully led to the desired amide. So far as we are aware, this is a new method of preparing amides from esters which react with difficulty. We have also prepared reserpamide by this method.[7]

The hydrazide of yohimbic acid was obtained by prolonged reaction of yohimbine with hydrazine. Yohimbine does not react under the usual conditions of hydrazide formation. The amino alcohol I derived from yohimbhydrazide by the Curtius degradation would be of interest in corroborating the recently proposed stereochemical relationship of the 16-carbomethoxyl and 17-hydroxyl in yohimbine.[5] There was obtained by this degradation a compound still containing the carbonyl function which can be best formulated as an oxazolone II.



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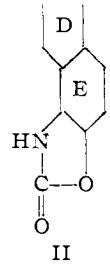


II

II proved to be resistant to acid hydrolysis and to cleavage by lithium aluminum hydride.

The final derivative to be reported is N-methylyohimbine. Its synthesis from yohimbine in high yield was accomplished by treatment with potassium amide and then methyl iodide in liquid ammonia solution according to the method previously described for the preparation of N-methyl methyl reserpate.[7]

Pharmacological studies carried out on these compounds under the direction of Dr. A. Plummer of these laboratories indicated that the esters do not exhibit any of the characteristic sedative properties of reserpine. These esters as well as the other yohimbine derivatives reported here do have, however, the adrenolytic and hypotensive activity of yohimbine in greater or lesser degree. Certain of the compounds have these desirable characteristics with less toxicity (central stimulation, convulsions, etc.) than yohimbine.

We wish to thank Mr. Louis Dorfman and staff for the physical measurements and microanalysis. Samples of corynanthine and α-yohimbine were made available to us by Drs. C. R. Scholz and A. F. St. André. It is a pleasure to acknowledge the help of Dr. E. Schlittler who suggested this problem.

Experimental[8]

O-Acetylyohimbine.—A solution of 1.7 g. of yohimbine (m.p. 234–235°, $[\alpha]_D$ +62.0° (*c* 1, ethanol)), prepared from the yohimbine hydrochloride of commerce by one recrystallization of the base from ethanol–water, in 20 ml. of anhydrous pyridine and 10 ml. of acetic anhydride is allowed to stand overnight at room temperature. The sirupy residue resulting from distillation *in vacuo* to a small volume is dissolved in water and made basic with ammonia. The solid ester is filtered and recrystallized twice from ethanol to yield 0.9 g. of O-acetylyohimbine; m.p. 215–220°, $[\alpha]_D$ +16.7° (*c* 1, ethanol). A mixture of this substance and yohimbine melts at 190–195°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.63; H, 7.15; N, 7.15.

Ultraviolet absorption in ethanol indicates maxima at 226 mμ (log ε 4.53), 282 mμ, (log ε 3.89) and 290 mμ (log ε 3.85) and infrared absorption in a Nujol mull shows only one band in the NH–OH region at 3343 cm.$^{-1}$ (yohimbine shows both the NH and OH bands at 5545 and 3345 cm.$^{-1}$) and a carbonyl band at 1723 cm.$^{-1}$. O,N-Diacetylyohimbine[2] shows maxima at 244 mμ, (log ε 4.20), 266 mμ, (log ε 3.04), 290 mμ, (log ε 3.75) and 300 mμ, (log ε 3.71) and no infrared absorption is present in the NH–OH region while three carbonyl bands appear at 1732, 1715 and 1698 cm.$^{-1}$. The hydrochloride of O-acetylyohimbine is amorphous, but the thiocyanate may be recrystallized from water, m.p. 242–248°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot HCNS$: N, 9.23. Found: N, 9.40.

O-Acetylyohimbic Acid.—A solution of 3 g. of yohimbic acid in 20 ml. of pyridine and 10 ml. of acetic anhydride is allowed to stand overnight at room temperature. The solution is concentrated to a small volume *in vacuo* and diluted with 50 ml. of water. After the solution is made alkaline with dilute sodium hydroxide and then adjusted to *p*H 6 with acetic acid, a slow crystallization of the product occurs. The crude O-acetylyohimbic acid (2.8 g.) can be recrystallized from water or from methanol diluted with water to yield a substance of m.p. 226–228° dec., $[\alpha]_D$ +69.5° (*c* 1, methanol). The m.p. of a mixture with yohimbic acid is 200–240°.

The recrystallization of this ester from methanol results in progressive lowering of the melting point and a widening of the range. This presumably is due to partial methanolysis at the new ester linkage. No such tendency was noted when ethanol was the recrystallization solvent.

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot {}^1/_2H_2O$: C, 67.52; H, 6.91; N, 7.16. Found: C, 67.27; H, 6.91; N, 7.06.

Treatment of an ethanolic solution of O-acetylyohimbic acid with an excess of ethereal diazomethane gave a material identical to the O-acetylyohimbine prepared by direct acetylation of yohimbine as shown by determination of the melting point of the mixture and the identity of the infrared absorption curves.

O-Benzoylyohimbine.—Freshly distilled benzoyl chloride (7 ml., (3 molar equivalents)) is added dropwise to a cooled solution of 7 g. of yohimbine in 70 ml. of pyridine. The solution is allowed to warm to room temperature and kept at that temperature overnight. After distillation *in vacuo* of about 50 ml. of the pyridine, 100 ml. of ice-water and 300

(5) (a) M. M. Janot, R. Goutarel, A. le Hir, M. Amin and V. Prelog, *Bull. soc. chim.*, **12**, 1085 (1952); (b) R. C. Cookson, *Chem. and Ind.*, 337 (1953).

(6) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(7) C. F. Huebner, THIS JOURNAL, **77**, 472 (1955).

(8) All melting points are uncorrected. Analytical samples were dried at 100° and 15 mm. over phosphorus pentoxide for 12 hours. The water of solvation, often encountered with these compounds, could not be removed despite more vigorous drying conditions.

ml. of ethyl acetate are added. A 5% aqueous potassium hydroxide solution is added slowly to the mixture with good shaking till the aqueous phase is permanently basic. The ethyl acetate phase is shaken with 5% aqueous hydrochloric acid, causing the separation at the interface of a brown, amorphous, insoluble O-benzoylyohimbine hydrochloride. This is filtered and converted to the free base by trituration with excess 5% alkali (*p*H 9) in the presence of ethyl acetate. The ethyl acetate solution is washed with water, dried and distilled to dryness *in vacuo*. The brown gummy residue is dissolved in hot ethanol, water added to turbidity and crystalline O-benzoylyohimbine (5.2 g.) separates on cooling. The crude ester (m.p. 150–161°) can be purified by recrystallization from ethanol–water, m.p. 166–167°.

Anal. Calcd. for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.16; H, 6.65; N, 6.11.

Ultraviolet absorption in ethanol indicates maxima at 224 mμ (log ε 4.62), 274 mμ (log ε 3.85) and 282 mμ (log ε 3.86), and infrared absorption shows the NH band at 3310 cm.$^{-1}$ and two carbonyl bands at 1738 and 1722 cm.$^{-1}$.

O-Anisoylyohimbine.—Substituting anisoyl chloride for benzoyl chloride and proceeding as described above, the desired ester is obtained in a 16% yield, m.p. 247–250°. Acetone–water is used as a crystallization medium.

Anal. Calcd. for $C_{29}H_{32}N_2O_5 \cdot {}^1/_2H_2O$: C, 70.02; H, 6.91; N, 5.84. Found: C, 69.92; H, 6.66; N, 5.76.

O-Veratroylyohimbine.—During the concentration of the final ethyl acetate solution containing the crude ester obtained as described above, O-veratroylyohimbine separates in crystalline form (17% yield). It is recrystallized from ethyl acetate; m.p. 227–230°.

Anal. Calcd. for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.84; H, 6.75; N, 5.48.

O-3,4,5-Trimethoxybenzoylyohimbine.—A solution of 2 g. of yohimbine and 1.57 g. of 3,4,5-trimethoxybenzoyl chloride in 20 ml. of anhydrous pyridine is allowed to stand at room temperature for two hours. During this time a crystalline material separates from the mixture. It is filtered, washed with benzene and triturated with excess 5% aqueous alkali (*p*H 9) in the presence of ethyl acetate. The ethyl acetate solution is washed with water, dried and evaporated to dryness *in vacuo*. The residue is taken up in 15 ml. of 95% ethanol. On cooling, 250 mg. of the desired ester separates. After recrystallization from 95% ethanol the m.p. is 246–250°.

Anal. Calcd. for $C_{31}H_{36}N_2O_7 \cdot H_2O$: C, 65.71; H, 6.76; N, 4.94. Found: C, 65.76; H, 6.81; N, 5.03.

O-3,4,5-Trimethoxybenzoylcorynanthine.—Corynanthine (0.5 g., m.p. 221–225°, $[\alpha]_D$ −124° (*c* 1, ethanol)) is added to a solution of 1.5 g. of 3,4,5-trimethoxybenzoyl chloride in 15 ml. of anhydrous pyridine and allowed to stand at room temperature for 5 days. To the reaction mixture is added 20 g. of ice and a small amount of 3,4,5-trimethoxybenzoic anhydride (m.p. 156–159°) is filtered off. The solution is evaporated to dryness under nitrogen *in vacuo* and the residue dissolved in 50 ml. of chloroform. The chloroform solution is washed in succession with 50 ml. of 2% hydrochloric acid, 50 ml. of 2% potassium hydroxide, 50 ml. of 2% hydrochloric acid and 50 ml. of water. After drying over sodium sulfate, the chloroform is evaporated to dryness and 15 ml. of benzene added to the residue. A benzene-insoluble portion is obtained and after recrystallization from acetone yields 125 mg. of O-3,4,5-trimethoxybenzoylcorynanthine hydrochloride, m.p. 235–237°.

Anal. Calcd. for $C_{31}H_{36}N_2O_7 \cdot HCl \cdot {}^1/_2H_2O$: C, 62.67; H, 6.45, N, 4.72; Cl, 5.97. Found: C, 62.21; H, 6.07; N, 4.52; Cl, 6.27.

Infrared absorption shows the NH band at 3078 cm.$^{-1}$ and two carbonyl bands at 1729 and 1717 cm.$^{-1}$.

O-3,4,5-Trimethoxybenzoyl-α-yohimbine.—α-Yohimbine (0.5 g.) is treated with 3,4,5-trimethoxybenzoyl chloride as described in the preceding example. The reaction mixture is worked up similarly to the point of obtaining a chloroform solution of the crude reaction mixture. This solution is washed with dilute ammonia and then with water until neutral. The chloroform solution is dried and the solvent removed. The residue is taken up in methanol and on dilution with water a yellow precipitate forms which is filtered, washed with water and dried (900 mg.). This is dissolved in benzene and the benzene solution chromatographed on neutral alumina (activity II–III). The fraction eluted with benzene (500 mg.) is recrystallized from acetone–water to yield 108 mg. of the product, m.p. 237–239°.

Anal. Calcd. for $C_{31}H_{36}O_7N_2$: C, 67.86; H, 6.61; N, 5.11. Found: C, 67.28; H, 6.34; N, 4.95.

Yohimbamide.—Yohimbine (2 g.) is stirred with a suspension of sodium amide (freshly prepared from 2 g. of sodium) in 30 ml. of liquid ammonia. The reaction mixture is cooled in a dry ice–alcohol mixture. After one hour the ammonia is allowed to evaporate. Fifty grams of ice-water is added with stirring and the crystalline suspension of the amide filtered. It is dissolved in 30 ml. of hot ethanol and filtered through Filter-cel to remove the iron oxide originally introduced to catalyze the formation of sodium amide. Water is added to the hot solution till turbidity and the crystals separating on cooling are recrystallized from the same solvent mixtures; yield 1.7 g., m.p. 165–170° with softening beginning at 160° and the evolution of bubbles at the melting point, $[\alpha]_D$ −12.3° (*c* 1, ethanol).

Anal. Calcd. for $C_{20}H_{25}N_3O_2 \cdot {}^1/_2H_2O$: C, 68.74; H, 7.79; N, 12.03. Found: C, 68.50; H, 7.68; N, 11.98.

Infrared absorption shows a strong broad NH band at 3315 cm.$^{-1}$ and an amide carbonyl at 1659 cm.$^{-1}$.

Yohimbhydrazide.—Five grams of yohimbine is refluxed with 5 ml. of anhydrous hydrazine in 25 ml. of methanol for four days. Samples removed after one and two days showed the presence of large amounts of unreacted yohimbine. The methanol solution is diluted with water to give the crude product, which yields 3.2 g. of purified hydrazide on recrystallization from ethanol–water. It melts at 175–180° with previous softening at 170° in a manner similar to yohimbamide, which also crystallizes as a hydrate, $[\alpha]_D$ +5.3° (*c* **1**, chloroform).

Anal. Calcd. for $C_{20}H_{26}N_4O_2 \cdot H_2O$: C, 64.49; H, 7.58; N, 15.04. Found: C, 64.40; H, 7.38; N, 14.61.

Infrared absorption shows an amide carbonyl at 1649 cm.$^{-1}$.

Yohimbcarbamylhydrazide.—Two grams of yohimbhydrazide is dissolved in 50 ml. of water containing 1 ml. of concd. hydrochloric acid. One gram of potassium cyanate is added portionwise over 15 minutes. After another 15 minutes the solution is made basic with ammonia to yield the carbamylhydrazide (1.7 g.); on recrystallization from methanol–water it melts at 200–210° dec.

Anal. Calcd. for $C_{21}H_{27}N_5O_3 \cdot H_2O$: N, 16.89. Found: N, 16.93.

Curtius Degradation of Yohimbhydrazide (II).—To a solution of 1 g. of yohimbhydrazide in 13 ml. of 1 *N* hydrochloric acid cooled to 5° is added dropwise 0.2 g. of sodium nitrite in 10 ml. of water. A positive starch iodide test is obtained toward the end of the addition. After 10 minutes at 5°, the yellow solution is heated to 65° and held at this temperature for one-half hour, by which time nitrogen evolution has ceased. After cooling in the ice-box overnight, a mixture of crystalline and gummy material separates. Recrystallization from water slightly acidified with hydrochloric acid gives 0.2 g. of the hydrochloride of the Curtius degradation product II, m.p. 310° dec.

Anal. Calcd. for $C_{20}H_{23}N_3O_2 \cdot HCl \cdot H_2O$: C, 61.25; H, 6.69; N, 10.72; Cl, 9.06. Found: C, 61.66; H, 6.64; N, 10.86; Cl, 9.36.

Infrared absorption shows a series of bands in the NH–OH region at 3506, 3348 and 3196 cm.$^{-1}$ and a carbonyl band at 1728 cm.$^{-1}$. II was recovered unchanged after refluxing in concd. hydrochloric acid for two hours or treatment of the base with lithium aluminum hydride.

N-Methylyohimbine.—Six grams of yohimbine is added with stirring to a solution of freshly prepared potassium amide (from 0.85 g. of potassium) in 50 ml. of liquid ammonia in a cooling-bath. After 5 minutes, a solution of 1.3 ml. of methyl iodide in 20 ml. of anhydrous ether is added dropwise, a precipitate appearing soon after the addition is complete. After one-half hour the ammonia is allowed to evaporate, and ice-water is added to the residue. Filtration yields N-methylyohimbine in a rather high state of purity, m.p. 255–258°. In contrast to yohimbine it is very poorly soluble in ethanol or acetone. The small amount of iron oxide may be removed from the preparation by dissolving it in chloroform and filtering through Filter-cel. Evapora-

tion to dryness gives a gum which is transformed to a crystalline powder (5 g.) by stirring with hot ethanol while recrystallization may be accomplished from a large volume of ethanol diluted with water (m.p. 240–245°, $[\alpha]_D$ +3.1° (*c* 1, chloroform)), a wholly satisfactory solvent for the recrystallization of this substance could not be found.

Anal. Calcd. for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.95; H, 7.44; N, 7.82.

Infrared absorption shows a weak band in the NH-OH region at 3183 cm.$^{-1}$ and a carbonyl band at 1734 cm.$^{-1}$.

SUMMIT, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

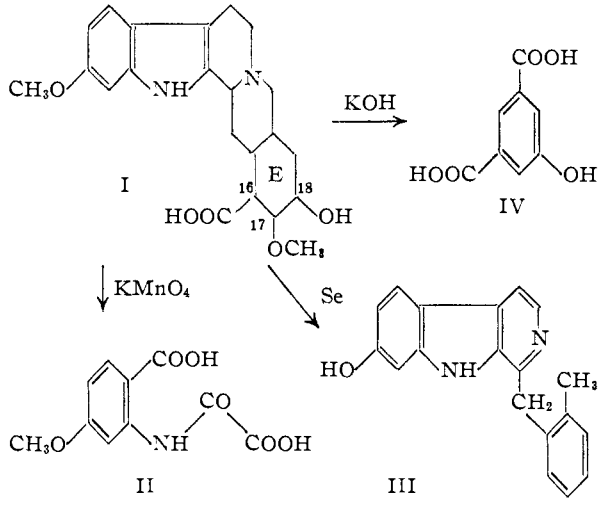
Rauwolfia Alkaloids. XV. The Constitution of Reserpic Acid: Position of Substituents in Ring E

BY C. F. HUEBNER, H. B. MACPHILLAMY, A. F. ST. ANDRÉ and E. SCHLITTLER

RECEIVED JULY 29, 1954

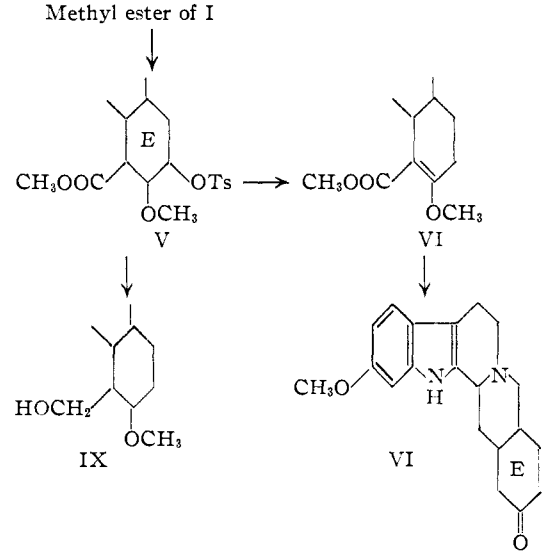
In consonance with the proposed formulation of methyl anhydroreserpate (VI) as the enol ether of a β-keto ester, it was hydrolyzed and decarboxylated by acid to the ketone VII. The carboxyl in reserpic acid has been placed in the 16-position by the sequence: reduction of the carboxyl to hydroxymethyl followed by selenium dehydrogenation of the resulting alcohol to 1-(2,6-dimethylbenzyl)-7-hydroxy-9H-pyrid[3,4-b]indole (VIII). The structure of VIII was established by synthesis of its methyl ether XIV from harmine and 2,6-dimethylcyclohexanone.

The alkaloid reserpine, the trimethoxybenzoyl ester of methyl reserpate, has acquired some importance in the therapy of hypertension[1] and more recently in psychiatric use.[2] The constitution of reserpic acid has been formulated as I. This postulate is supported by the following degradative reactions: permanganate oxidation of reserpic acid yields N-(carboxyformyl)-4-methoxyanthranilic acid (II), selenium dehydrogenation gives 7-hydroxyyobyrine (7-hydroxy-1-(2-methylbenzyl)-9H-pyrid[3,4-b]indole (III)) and by a potash fusion 5-hydroxyisophthalic acid (IV) is obtained.[3]



Since no ketoyobyrine type compound was isolated from the selenium dehydrogenation of reserpic acid, the position of the carboxyl group was not located. For biogenetic reasons, it was assumed that the carboxyl occupies the same 16-position (numbered according to Barger and Scholz[4]) as it does in yohimbine. Since reserpic acid easily lactonizes, it appeared likely that the hydroxyl group of reserpic acid is in the 18-position. Also infrared spectral evidence spoke in favor of a γ-lactone. The methoxyl group was conditionally attributed to position 17 as indicated in formula I.

Evidence for the validity of the assumption that all three substituents in ring E are on adjoining carbon atoms has been described briefly.[5] The experimental details of this degradation are given in the present paper. The tosyl ester of methyl reserpate (V) was subjected to detosylation with collidine yielding methyl anhydroreserpate (VI). Its strong infrared absorption bands at 1613 and 1709 cm.$^{-1}$ are known to be characteristic for the grouping ROOC—C=C—OR.[6] Further proof that VI is the enol ether of a β-keto acid was offered by its acid hydrolysis and simultaneous decarboxylation to the ketone reserpone[7] (VII).



Although these reactions indicated with some degree of certainty the relative positions of the

(1) R. W. Wilkins, *Ann. N. Y. Acad. Sci.*, **59**, 36 (1954).

(2) N. S. Kline, *ibid.*, **59**, 107 (1954).

(3) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

(4) G. Barger and C. Scholz, *ibid.*, **16**, 1343 (1933).

(5) E. Schlittler, H. B. MacPhillamy, L. Dorfman, H. Furlenmeier, C. F. Huebner, R. Lucas, J. M. Mueller, R. Schwyzer and A. F. St. André, *Ann. N. Y. Acad. Sci.*, **59**, 1 (1954).

(6) F. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).

(7) Trivial names are proposed for these compounds until their complete stereochemistry is certain. At that time systematic names may be assigned. See W. Klyne, *Chem. and Ind.*, 1032 (1953).