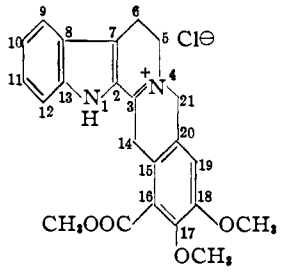
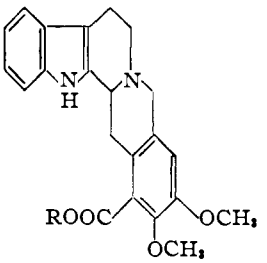
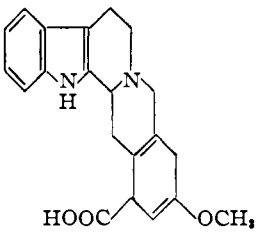
11.12). Condensation of this chloromethyl derivative with tryptamine in tetrahydrofuran at room temperature yielded N-(2-(3-indolyl)-ethyl)-3-oxo-5-carbomethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, m. p. 168–169° (found: C, 67.71; H, 5.73; N, 6.84). Cyclization of this lactam with phosphorous oxychloride at 100° furnished the unsaturated base (I), isolated as the hydrochloride, m. p. 245–247° (found: C, 65.13; H, 5.73; Cl, 8.38). The salt (I) was subsequently reduced with platinum in methanol to the saturated base (IIa), m.p. 205–207° (found: C, 70.55; H, 6.13; N, 7.07; eq. wt. (perchloric acid), 398). Hydrolysis of IIa with aqueous ethanolic potassium hydroxide gave the corresponding acid (IIb) (hydrochloride, m.p. 255–256°; found: C, 63.89; H, 5.58; N, 6.92; Cl, 8.20). Reduction of the acid with sodium in liquid ammonia in the presence of isopropylalcohol resulted in loss of the C-17 methoxyl group and further reduction to the enol ether (III) (m. p. 230–232°; found: C, 71.82; H, 6.35; λ_{max}^{Nujol} 5.85 μ, 6.00 μ)



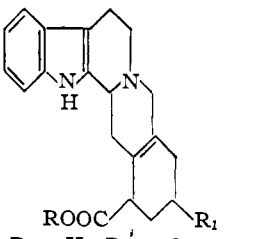
I



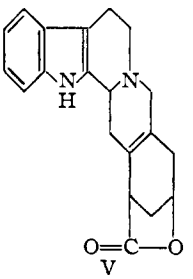
IIa, R = CH_3
IIb, R = H



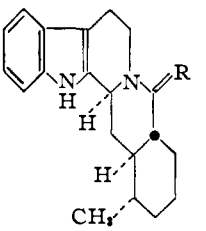
III



IVa, R = H; R_1 = O
IVb, R = H; R_1 = 
IVc, R = CH_3; R_1 = 

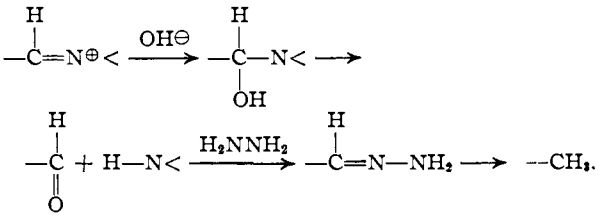


V



VIa, R = O
VIb, R = H_2

which on hydrolysis with dilute hydrochloric acid produced the unsaturated ketoacid (IVa), isolated as the hydrochloride, m. p. 251–254° ($C_{20}H_{20}O_3N_2 \cdot HCl \cdot 2H_2O$; found: C, 58.48; H, 6.44; N, 6.82; Cl, 8.68). The infrared spectrum of IVa showed carbonyl absorption at 5.84 μ but no absorption at 6.0 μ indicative of an α,β-unsaturated ketone. The double bond present in this ketoacid, therefore, must have remained in the unconjugated position between C_{15} and C_{20}. When IVa was reduced by the Wolff-Kishner method, a neutral lactam (VIa) ($C_{20}H_{24}ON_2$; m. p. 277–279°; found: C, 78.22, H, 7.60; N, 8.75; C—CH_3, 3.51; λ_{max}^{Nujol} 6.22 μ) was obtained. The formation of VIa is compatible with the presence of a C_{15}-C_{20} double bond since, presumably, the lactam is formed by migration of a double bond to the C_{21}-N_4 position followed by the reactions



Lactamization of the newly formed amine would then lead to VIa. The structure of the latter compound was proved by reduction with lithium aluminum hydride in tetrahydrofuran to give a basic compound (VIb), m. p. 191–193° ($C_{20}H_{26}N_2$; found: C, 81.75; H, 9.11; eq. wt. (perchloric acid), 292) which was shown to be *dl*-16-methylyohimbane by the identity of its infrared spectrum in carbon disulfide with that of anthentic 16-methylyohimbane (m. p. 193–195°) prepared by the method of Karrer and Saemann.[2]

Reduction of IVa with sodium borohydride gave a hydroxy acid (IVb), m. p. 255–256° (found: C, 71.02; H, 6.54) which formed a γ-lactone (V), m. p. 284–286° (found: C, 75.19; H, 6.37; λ_{max}^{Nujol} 5.65 μ) on treatment with pyridine and acetic anhydride. Since reduction of the aromatic carboxylic acid (IIb) by sodium in liquid ammonia should lead to the equatorially oriented carboxyl group, the formation of a γ-lactone indicates that the hydroxyl group at C_{18} in IVb is also equatorial as well as *cis* to the C_{16} carboxyl group. Treatment of the lactone (V) with sodium methoxide in methanol gave 18-hydroxy-16-carbomethoxy-$\Delta^{15(20)}$-yohimbene (IVc), m. p. 214–216° (found: C, 71.57; H, 6.74).

The pharmacological properties of these compounds will be reported elsewhere.

(2) P. Karrer and R. Saemann, *Helv. Chim. Acta*, **35**, 1932 (1952).

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
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RECEIVED APRIL 2, 1956

THE REACTION OF RAUWOLFIA ALKALOIDS WITH MERCURIC ACETATE. CONVERSION OF 3-ISORESERPINE TO RESERPINE

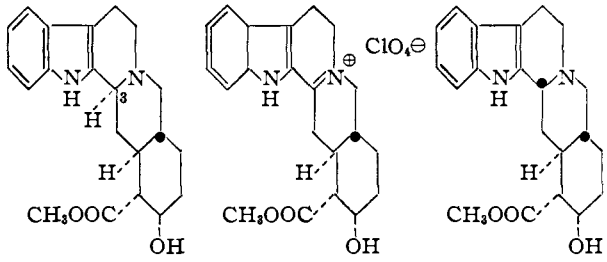
Sir:

In conjunction with our work on the total synthesis of compounds related to reserpine,[1] a method was needed for converting an α-oriented C_3-hydrogen to the generally less stable β-oriented form.[2] We now wish to report a method by which this transformation may be accomplished.

(1) F. L. Weisenborn and H. E. Applegate, to be published.

(2) (a) E. Wenkert and L. H. Liu, *Experientia*, **11**, 302 (1955); (b) C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *ibid.*, **11**, 303 (1955).

In 1927 Schomer[3] observed that yohimbine (I) was oxidized by mercuric acetate to give a colored material which was not characterized but which could be reduced with zinc and hydrochloric acid to an isomer of yohimbine of unknown structure. In our hands the oxidation of yohimbine with mercuric acetate in acetic acid at 60° for two hours gave, after removal of the mercurous acetate by filtration and precipitation of the excess mercuric ion with hydrogen sulfide, an 85% yield of crystalline perchlorate, m.p. 205–206°, by the addition of an equimolar amount of perchloric acid to the acetic acid solution. This substance is formulated as the salt of the unsaturated base (II) ($C_{21}H_{25}O_7N_2Cl$, Found: C, 55.69; H, 5.63; Cl, 7.85); λ_{max}^{EtOH} 246 mμ (10,500), 352 mμ (21,400). Reduction of the dehydroyohimbine perchlorate (II) with zinc and hydrochloric acid at room temperature during one-half hour followed by fractional crystallization of the product yielded a base, m.p. 277–278°, $[\alpha]_D$ +28° (pyridine), which was identified as pseudoyohimbine (III)[4] by comparison of its infrared spectrum in nujol with that of an authentic sample. Reduction of 3-dehydroyohimbine with hydrogen and platinum in methanol gave only yohimbine.



I II III

α-Yohimbine[5] was oxidized in the same manner to give 3-dehydro-α-yohimbine perchlorate, m.p. 211–212° ($C_{21}H_{25}O_7N_2Cl$; Found: C, 55.85; H, 5.53). Reduction of the salt with zinc and hydrochloric acid at room temperature followed by chromatography of the product gave epi-α-yohimbine,[6] identified by optical rotation, $[\alpha]_D$ −81° (chloroform), and infrared spectrum in chloroform.

No reaction took place when pseudoyohimbine, reserpine, methyl reserpate[7], and deserpidine[8] were treated under the same conditions with mercuric acetate. 3-Isoreserpine[8], methyl 3-isoreserpate[8] and methyl 3-isoreserpate 18-acetate[8] reacted normally to give 3-dehydroreserpine (nitrate, m.p. 160–170°, $C_{33}H_{39}O_{12}N_3 \cdot H_2O$; Found: C, 57.82; H, 6.03; λ_{max}^{EtOH} 215 mμ (58,800), 265 mμ (17,500), 387 mμ (23,000)), methyl 3-dehydroreserpate (amorphous perchlorate, λ_{max}^{EtOH} 218 mμ (19,100), 263 mμ (5900), 387 mμ (23,800)), methyl 3-dehydroreserpate 18-acetate (perchlorate, m.p. 234–237°, $C_{25}H_{31}O_{10}N_2Cl \cdot 0.5H_2O$; Found: C, 53.48; H, 5.75; λ_{max}^{MeOH} 218 mμ (21,100), 262 mμ (6600), 387 mμ (21,200)), respectively. Reduction of these dehydro compounds with zinc and 50% aqueous acetic acid at room temperature for twenty-four hours gave reserpine,[7] methyl reserpate[7] and methyl reserpate 18-acetate[7] identified by mixed melting point and comparison of infrared spectra with authentic samples.[9]

It appears then that only compounds containing an axial hydrogen at C_3 will react with mercuric acetate. Thus, the mechanism proposed by Leonard[10] for this reaction requires a coplanar (diaxial) attack of mercuric acetate and acetate ion at the reacting centers. It is worthwhile to note that this reaction may be used as a diagnostic tool to determine the presence of an axial or equatorial hydrogen adjacent to a tertiary nitrogen atom, the formation of a precipitate of mercurous acetate being taken as a sign of reaction. It may also be useful in the determinations of configurations of other alkaloids.

(3) A. Schomer, *Archiv. Pharmazie*, **265**, 509 (1927).

(4) M.-M. Janot, R. Goutarel, A. Le Hir, M. Amin and V. Prelog, *Bull. Soc. Chim.*, **19**, 1085 (1952).

(5) A. Le Hir, M. M. Janot and R. Goutarel, *ibid.*, **20**, 1027 (1953).

(6) F. E. Bader, D. F. Dickel, C. F. Huebner, R. A. Lucas and E. Schlittler, THIS JOURNAL, **77**, 3547 (1955).

(7) 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).

(8) H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and P. R. Ulshafer, THIS JOURNAL, **77**, 4335 (1955).

(9) Professor R. B. Woodward has informed us (private communication) that the total synthesis of reserpine recently completed in his laboratory (THIS JOURNAL, **78**, 2023 (1956)) proceeds through *d,l*-methyl 3-dehydroreserpate 18-acetate. It is clear that the application of our reduction method would form the basis for an alternative path from that key intermediate to reserpine.

(10) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *ibid.*, **77**, 439 (1955).

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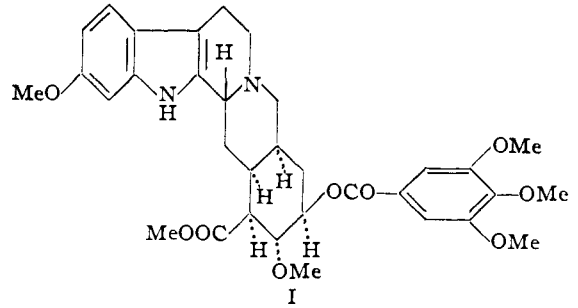
PATRICK A. DIASSI

RECEIVED APRIL 5, 1956

THE TOTAL SYNTHESIS OF RESERPINE

Sir:

Reserpine was first isolated in 1952.[1] The remarkable physiological properties of the alkaloid rapidly won for it an important place in the treatment of hypertensive, nervous and mental disorders. Extensive degradative and analytical studies culminated in 1955 in the proposal of the structure (I).[2] We now wish to record the total synthesis of reserpine.



I

(1) J. M. Müller, E. Schlittler and H. J. Bein, *Experientia*, **8**, 338 (1952).

(2) 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); C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia*, **11**, 303 (1955); E. Wenkert and L. H. Liu, *ibid.*, **11**, 302 (1955); C. F. Huebner and E. Wenkert, THIS JOURNAL, **77**, 4180 (1955); P. A. Diassi, F. L. Weisenborn, C. M. Dyiion and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955).