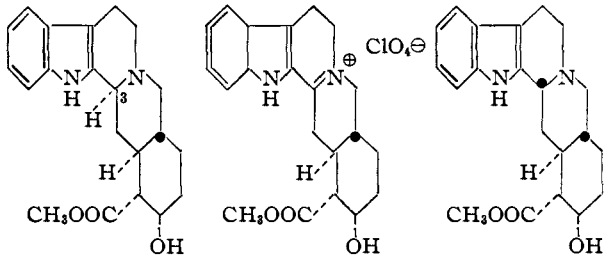
In 1927 Schomer[3] observed that yohimbine (I) was oxidized by mercuric acetate to give a colored material which was not characterized but which could be reduced with zinc and hydrochloric acid to an isomer of yohimbine of unknown structure. In our hands the oxidation of yohimbine with mercuric acetate 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).

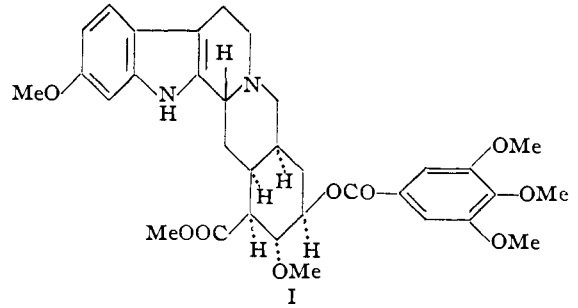
THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
NEW BRUNSWICK, NEW JERSEY
FRANK L. WEISENBORN
PATRICK A. DIASSI

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.

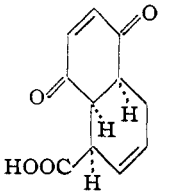


I

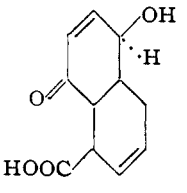
(1) J. M. Müller, E. Schlittler and H. J. Bein, *Experientia*, **8**, 338 (1952).

(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. Dylion and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955).

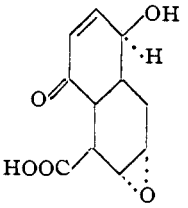
The adduct (II)[3] (m.p. 220–225° (dec.), found: C, 63.91; H, 5.00), from *p*-benzoquinone and vinylacrylic acid, was reduced by sodium borohydride to the alcohol (III) (m.p. 179–180°, found: C, 63.47; H, 6.08), which was converted by perbenzoic acid in benzene-dioxane to the oxide (IV) (m.p. 160–161°, found: C, 58.86; H, 5.64). The corresponding lactone (V) (m.p. 177–177.5°, found: C, 64.13; H, 4.95), obtained from (IV) by the



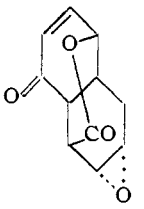
II



III

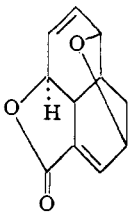


IV

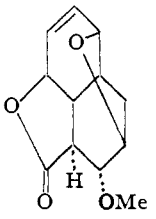


V

action of acetic anhydride and sodium acetate in benzene, was transformed by aluminum isopropoxide in hot isopropylalcohol into the ether (VI) (m.p. 124–126°, found: C, 69.34; H, 5.41), and thence, by the action of sodium methoxide in methanol, to the methoxy-ether (VII) (m.p. 105°, found: C, 65.11; H, 6.46; OMe, 13.86). The bromohydrin (VIII) (m.p. 146–148°, found: C, 45.24;

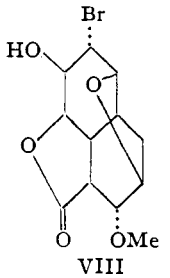


VI

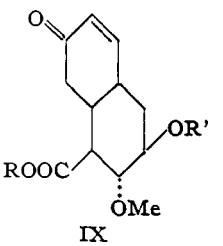


VII

H, 4.86; Br, 25.13), obtained by the action of N-bromosuccinimide on (VII) in warm aqueous solution in the presence of sulfuric acid, was oxidized by chromium trioxide in acetic acid to the corresponding ketone (m.p. 165–166°, found: C, 45.45; H, 4.32; Br, 25.35), which was transformed by short

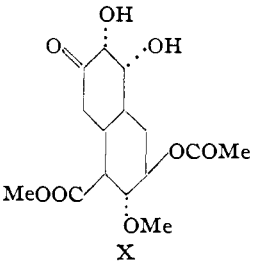


VIII

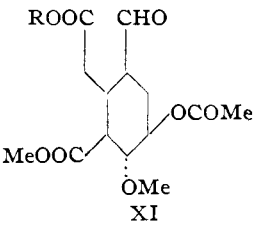


IX

treatment with zinc in cold glacial acetic acid to the hydroxy-acid (IX, R = R′ = H) (m.p. 204–206°, found: C, 59.96; H, 6.93; OMe, 12.88). The methyl ester (IX, R = Me, R′ = H) (m.p. 139–140°, found: C, 61.53; H, 7.54; OMe, 24.65), prepared from (IX, R = R′ = H) with diazomethane in dioxane, was converted to the acetate (IX, R = Me, R′ = COMe) (m.p. 137–138°, found: C, 60.58; H, 7.00; OMe, 20.43) by acetic anhydride in warm pyridine, and thence to the diol (X) (m.p. 174–175°, found: C, 54.72; H, 6.82) by treatment with aqueous osmium tetroxide, followed

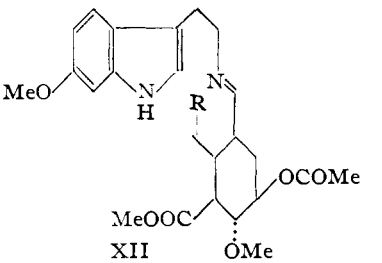


X

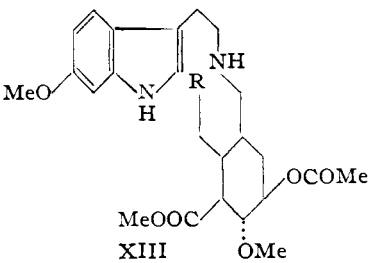


XI

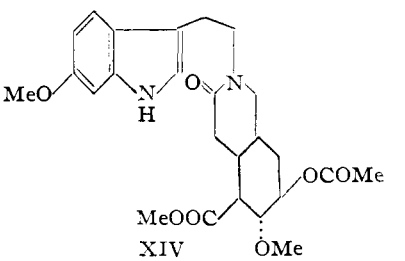
by potassium chlorate. The diol (X) was transformed directly in high yield, without isolation of the labile intermediates (XI, R = H), (XI: R = Me) (IR: 3.68 μ), (XII: R = COOMe) (IR, 6.00 μ) and (XIII, R = COOMe), to the lactam (XIV) (m.p. 239–240° (vac.), found: C, 63.18;



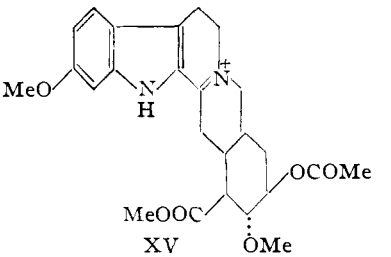
XII



XIII



XIV



XV

(3) We should like to express our appreciation to Dr. Peter Bladon for his participation in the preparation of the adduct (II).

H, 6.94; N, 5.91), through successive treatments with aqueous periodic acid and ethereal diazomethane, condensation with 6-methoxytryptamine[4] (new synthesis) in benzene, and reduction with sodium borohydride in methanol. Boiling phosphorus oxychloride converted the lactam (XIV) into the quaternary cation (XV), which was reduced directly with aqueous methanolic sodium borohydride to *dl*-methyl O-acetyl*iso*reserpate (m.p. 267–268° (vac.), found: C, 65.60; H, 7.11; N, 6.17); the infrared spectrum of the racemic ester was rich in detail, and identical in every respect with that of *l*-methyl O-acetyl*iso*reserpate (m.p. 284.5–285° (vac.), $[\alpha]_D = -133°$ [c = 1.04 ($CHCl_3$)]), prepared from reserpine[5]. The *racemic* ester gave with di-*p*-toluyl-*l*-tartaric acid a sparingly soluble *salt* (m.p. 153–155° (vac.)), from which on decomposition *l*-methyl O-acetyl*iso*reserpate (m.p. 287.5–288° (vac.), m.m.p. 285.5–286.5° (vac.), $[\alpha]_D = -134°$ [c = 1.06 ($CHCl_3$)]) was obtained. When *iso*reserpic acid hydrochloride (m.p. 278–279° (vac.)), obtained from the O-acetyl ester by hydrolysis with methanolic potash, followed by treatment with hydrochloric acid, was warmed briefly in pyridine with N,N′-dicyclohexylcarbodiimide, it was smoothly transformed into *iso*reserpic acid lactone (m.p. 222–224° (vac.), $[\alpha]_D = -138°$ [c = 1.05 ($CHCl_3$)], found: C, 69.17; H, 6.59; N, 7.30), which was substantially quantitatively isomerized by pivalic acid in boiling xylene to reserpic acid lactone[2a] (m.p. 319–321° (vac.)), identical in all respects with an authentic sample. The methanolysis of reserpic acid lactone to methyl reserpate, and the transformation of the latter by 3,4,5-trimethoxybenzoyl chloride in pyridine to reserpine (I), follow well-trodden paths.[2a]

(4) S. Akabori and K. Saito, *Ber.*, **63**, 2245 (1930).

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

R. B. WOODWARD
CONVERSE MEMORIAL LABORATORY F. E. BADER
HARVARD UNIVERSITY H. BICKEL
CAMBRIDGE 38, MASSACHUSETTS A. J. FREY
R. W. KIERSTEAD

RECEIVED APRIL 10, 1956

BOOK REVIEWS

Symposia of the Society for Experimental Biology. Number IX. Fibrous Proteins and their Biological Significance. Edited by R. BROWN AND J. F. DANIELLI. Academic Press, Inc., Publishers, 125 East 23rd Street, New York 10, N. Y. 1955. vii + 370 pp. 16 × 25 cm. Price, $8.00.

The papers in this volume were read at a Symposium for Experimental Biology at Leeds in September, 1954. Following an introductory review by Astbury there is a general paper by Sanger giving an elegant discussion of the analytical techniques developed for the determination of amino-acid sequences. Chargaff writing on the Deoxypentose Nucleoproteins and their Prosthetic Groups considers some of the detailed chemical requirements which may impose modifications on the current structural model for deoxypentose nucleic acid.

About a half of the remaining papers are on Collagen. These are:

The Distribution of Collagen and Chitin by K. M. Rudall
Metabolism of Collagen under Normal Conditions by A. Neuberger
The Influence of Collagen on the Organization of Apatite Crystallites in Bone by D. Carlström, A. Engström and J. B. Finean
Fibrogenesis of Connective and Skeletal Tissues in the Embryonic Fowl by S. Fitton Jackson and R. H. Smith
Configuration of Collagen and Gelatin Molecules in Condensed and Dispersed States by Richard S. Bear
X-Ray Diffraction Studies of Collagen Fibres by Pauline M. Cowan, A. C. T. North and J. T. Randall
Observations on Native and Precipitated Collagen by J. T. Randall, F. Booth, R. E. Burge, S. Fitton Jackson and F. C. Kelly
States of Aggregation of Collagen, by Francis O. Schmitt, Jerome Gross and John H. Highberger
Collagen Diseases by J. H. Kellgren

Each chapter presents an account of the recent research findings and current viewpoint of one outstanding group of investigators. Many of the papers in this group are very closely related. Most of the authors however avoid comment on the controversial aspects of their own conclusions. The papers read as the lucid and thoughtful preliminaries to vigorous discussion and debate. Unfortunately there is no account of the discussions between Symposium participants. Thus, the over-all impression is analytic—each paper expands a thesis. But there is no synthesis. The reader must work out his own comparative study and draw his own conclusions both about the areas of agreement and of dispute. Once this limitation is properly recognized the importance of these papers may be happily acknowledged. Recent advances in our knowledge of collagen structure, and collagen fiber organization have been very rapid, and it has not been easy to follow these in the literature.

There are five papers dealing with muscle:

The Proteins of the Myofibril by Kenneth Bailey
The Components of the Myofibril and their Relation to its Structure and Function by S. V. Perry
The Structural Basis of Contraction in Striated Muscle by Jean Hanson and H. E. Huxley
Some Observations on the Infra-red Spectrum of Muscle by B. R. Malcolm
The Link between Metabolism and Motility of Cells and Muscles by H. H. Weber

Here, as elsewhere, a report of the discussions between participants would have been most welcome. But the papers themselves are of prime importance—clear and vigorous expositions of recent studies.

The remaining papers in the volume are:

The Chemistry of Keratinous Structures by J. B. Speakman
The Structure of Bacterial Flagella by W. T. Astbury, E. Beighton and C. Weibull
Fibre Patterns in Animal Flagella and Cilia by J. R. G. Bradfield
The Organization of the Mitotic Apparatus by Daniel Mazia
Problems of Structure and Function in the Amphibian Oocyte Nucleus by Joseph G. Gall

Many of the papers in the symposium are nicely organized and excellently presented. This volume is not, however, a textbook, nor a series of review articles. If the style is indeed the man, then the reader must accept the former,