**Benzylidene Derivative of 3-Amino-4(3H)pteridinone (V).**—A mixture of 2.0 g. of the benzylidene derivative of 2-aminopyrazine-3-carboxyhydrazide, 15 ml. of ethyl orthoformate and 15 ml. of acetic anhydride was heated under reflux for 2 hours, diluted with 50 ml. of ethanol and cooled to give 2.07 g. (quantitative) of light tan fluffy needles, m.p. 202–203°, with preliminary softening at 199°. Recrystallization from ethanol yielded colorless needles, m.p. 203–204°.

*Anal.* Calcd. for $C_{13}H_9N_5O$: C, 62.1; H, 3.6; N, 27.9. Found: C, 62.3; H, 3.9; N, 27.9.

**3-Amino-4(3H)pteridinone (VI).**—To a solution of 3.0 g. of the isopropylidene derivative of 3-amino-4(3*H*)pteridinone in 50 ml. of water at room temperature was added, with shaking, 5 ml. of 0.1 *N* hydrochloric acid. The reaction mixture was allowed to stand for 2 minutes and was then diluted with 300 ml. of ethanol and chilled to 0°. Filtration after 1 hour yielded 2.0 g. (83%) of white needles, m.p. 240–245°. Recrystallization from aqueous ethanol raised the melting point to 242–245°; $\lambda_{max}^{EtOH}$ 240, 311 mμ; log ε 3.94, 3.73; $\lambda_{max}^{H_2O}$ 238, 311 mμ; log ε 4.00, 3.78; $\lambda_{max}^{0.1\ N\ HCl}$ 239, 311 mμ; log ε 3.98, 3.75; $\lambda_{max}^{0.1\ N\ NaOH}$ 272, 338 mμ; log ε 4.19, 3.74.

*Anal.* Calcd. for $C_6H_5N_5O$: C, 44.2; H, 3.1; N, 42.9. Found: C, 44.5; H, 3.1; N, 42.4.

The same compound could be obtained in much lower yield by hydrolysis of the benzylidene derivative of VI as follows: A suspension of 0.5 g. of V in 40 ml. of ethanol containing 10 ml. of 0.5 *N* hydrochloric acid was stirred at room temperature for 10 minutes, by which time complete solution of the starting material had taken place. The resulting pale yellow solution was diluted with 200 ml. of ether and chilled to give 0.05 g. (15%) of white needles, m.p. 240–245°, identical with the product obtained by hydrolysis of the isopropylidene derivative as described above.

Solutions of 3-amino-4(3*H*)pteridinone in dilute acid or dilute alkali upon warming rapidly turned bright yellow. Cooling then yielded 2-aminopyrazine-3-carboxyhydrazide in good yield.

PRINCETON, N. J.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF CIBA PHARMACEUTICAL PRODUCTS, INC., THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, AND THE DEPARTMENTS OF CHEMISTRY OF IOWA STATE COLLEGE AND THE UNIVERSITY OF WISCONSIN]

# The Stereochemistry of Reserpine, Deserpidine and Related Alkaloids[1,2]

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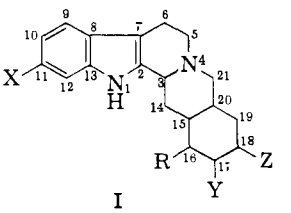
Chemical and physical data are presented which allow the rigorous assignment of stereoformulas XXXIc and XXXIb to the alkaloids reserpine and deserpidine, respectively. The stereochemistry of related natural products is discussed in light of these data.

By early 1955, intensive structure studies on reserpine and deserpidine, two important hypotensive and sedative alkaloids of the Rauwolfia species, by Schlittler and his co-workers[7] had led to structures Ia and Ib, respectively, for these medicinally valuable natural products. The task of elucidating the relative spatial configuration of the six asymmetric centers C-3, 15, 16, 17, 18 and 20 in both compounds remained, although the accumulated evidence[7] already pointed to certain definite stereochemical features. Both alkaloids had been shown to possess a thermodynamically unstable environment at C-3 and a *cis* relationship of the C-16 and -18 substituents, while deserpidine, whose chemical reactivity paralleled in every respect that of reserpine, had been interrelated with rauwolscine (α-yohimbine) (Ic) and 3-epi-α-yohimbine (Ic), whose stereochemistry had been assigned only partially. It appeared that a critical study of the basic ring systems and of the behavior of the individual skeletal substituents present in the alkaloids would lead to the information necessary for complete stereochemical assignment.



I

a, R = $CO_2Me$, X = Y = OMe, Z = $OCOC_6H_2(OMe)_3$
b, R = $CO_2Me$, X = H, Y = OMe, Z = $OCOC_6H_2(OMe)_3$
c, R = $CO_2Me$, X = Z = H, Y = OH
d, R = $CO_2Me$, X = Y = OMe, Z = $OSO_2C_7H_7$
e, R = $CH_2OH$, X = Y = OMe, Z = H
f, R = $CH_2OH$, X = Z = H, Y = OMe
g, R = $CO_2Me$, X = Z = H, Y = $OSO_2C_7H_7$
h, R = $CO_2Me$, X = Y = OMe, Z = Br
i, R = $CO_2Me$, X = Y = OMe, Z = OH
j, R = $CO_2H$, X = Y = OMe, Z = OH

(1) The work contained herein, representing the independent efforts of four laboratories, was written as a joint publication at the suggestion of the Editor. Presented in part by E. W. to the 7th Summer Seminar in the Chemistry of Natural Products, University of New Brunswick, Fredericton, Canada, August 16–20, 1955.

(2) For preliminary accounts of part of this work *cf.*; (a) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, THIS JOURNAL, **77**, 2028 (1955); (b) E. E. van Tamelen, P. D. Hance, K. V. Siebrasse and P. E. Aldrich, *ibid.*, **77**, 3930 (1955); (c) C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia*, **11**, 303 (1955); (d) E. Wenkert and L. H. Liu, *ibid.*, **11**, 302 (1955); (e) C. F. Huebner and E. Wenkert, THIS JOURNAL, **77**, 4180 (1955); (f) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); (g) E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955); (h) C. F. Huebner, M. E. Kuehne, B. Korzun and E. Schlittler, *Experientia*, **12**, 249 (1956); (i) C. F. Huebner and D. F. Dickel, *ibid.*, **12**, 250 (1956); (j) E. Wenkert, E. W. Robb and N. V. Bringi, THIS JOURNAL, **79**, 6570 (1957).

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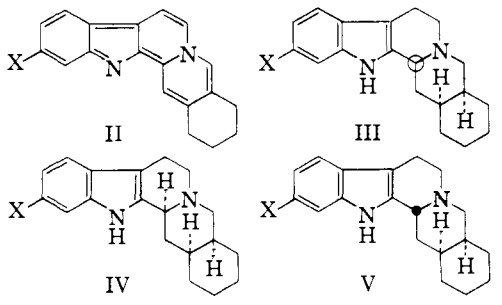
(6) Department of Chemistry, Iowa State College.

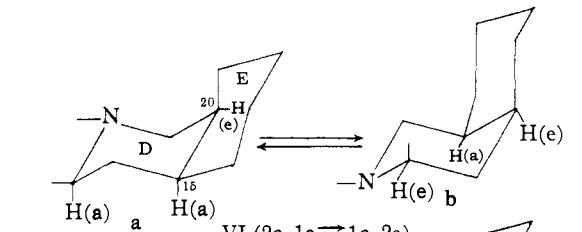
(7) (a) H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. André, THIS JOURNAL, **77**, 1071 (1955), and preceding papers. For the full articles pertaining to this communication *cf.*: (b) H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and P. R. Ulshafer, *ibid.*, **77**, 4335 (1955); (c) C. F. Huebner, A. F. St. André, E. Schlittler and A. Uffer, *ibid.*, **77**, 5725 (1955).

In view of the close relationship of deserpidine with 3-epi-$\alpha$-yohimbine[7a,8] the former appeared to have an epialloyohimbane skeleton, whose D/E ring juncture was unambiguously *cis*, as suggested by Janot's conversion of sempervirine (IIa) to *d,l*-alloyohimbane (IIIa) by catalytic hydrogenation[9] and corroborated by stereospecific syntheses of *d,l*-epialloyohimbane (IIIa) and its diastereomers.[10,11] However the configuration at C-3 was by no means as clear. The sempervirine reduction[9] unfortunately was of little diagnostic value on this point because of the uncertainty of the stereochemistry of catalytic hydrogenation in alkaline medium, and became less so when it was discovered that a large-scale reduction led not only to the allo compound but also to some *d,l*-epialloyohimbane.[1d] Whereas the production of the allo derivative by hydrogenation of *d,l*-$\Delta^3$-alloyohimbene in the last step of a total synthesis[10a] suggested a *syn-cis* configuration (IVa) for alloyohimbane and hence an *anti-cis* structure (Va) for epialloyohimbane, the scantiness of evidence pertaining to so vital a stereochemical question invited further experimentation.[12]

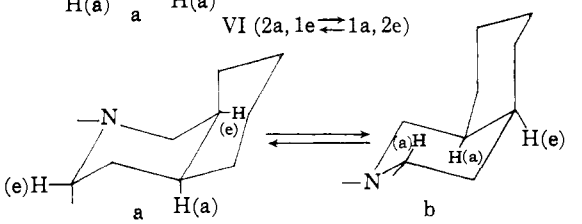



a, X = H; b, X = OMe

Comparison of conformational part structures of alloyohimbane, whose more stable of two possible low-energy forms (VIa and b) is VIa, and epialloyohimbane, best represented by VIIb, revealed enough of a difference in the C-3 and $N_b$ environment to allow for a difference in reactivity at those positions.[13] Thus $N_b$ quaternization was expected to proceed with unequal ease with the two substances, on the reasonable assumption that the nitrogen atom would orient itself during this process in such a way as to produce the more stable C/D *trans* ring juncture. It was considered that both kinetically and thermodynamically controlled processes would prefer quaternization of the nitrogen on the side of the ring system *syn* to the C-15 and 20 hydrogen atoms; in case of the former process because of less steric hindrance toward approach of reagent, and in case of the latter because of the formation of a more stable ammonium ion, *i.e.*, one containing fewer unfavorable 1,3-diaxial nonbonded interactions. Thus it was expected that epialloyohimbane (VIIb) would react faster than its 3-epimer VIa, and that in an equilibrium reaction VIIb would be more of an ammonium salt than VIa. These predictions were substantiated when it was shown that hydrogen peroxide treatment of alloyohimbane and epialloyohimbane under identical conditions of reaction and work-up led to starting material in the former case and epialloyohimbane oxide in the latter, and that alloyohimbane was distinctly less basic ($pK'_a$ 7.13) than its epiallo isomer ($pK'_a$ 7.50).[1d]




VI (2a, 1e⇄1a, 2e)




VII (1a, 2e⇄2a, 1e)

A more rigorous test of the C-3 stereochemistry appeared to be catalytic ring C dehydrogenation since this oxidation, being dependent on substrate adsorption on the catalyst's surface prior to hydrogen abstraction at C-3, 5 and 6, was expected to be subject to steric control. It was felt that catalyst approach at C-3 on the side of the ring skeleton *syn* to the C-15 and 20 hydrogens would be much more favorable than interaction on the *anti* side. When alloyohimbane and epialloyohimbane were exposed to catalytic oxidation by palladium in aqueous maleic acid solution[14] under identical conditions, the former reacted at an appreciably faster rate than the latter.[1d]

While the above data strengthened the case for an *anti-cis* configuration (Va) for epialloyohimbane, and hence also for 3-epi-$\alpha$-yohimbine and deserpidine, three different and independent pieces of evidence led to a similar assignment for the ring skeleton of reserpine.

During initial degradation studies on reserpine it was observed that attempted collidine detosylation of methyl reserpate tosylate (Id) yielded a very polar isomer as the major product.[1a] It was recognized readily to be a quaternary ammonium tosylate on the basis of the following facts. In contrast to Id it could not be titrated as a base with perchloric acid in acetic acid, nor did it take up sodium hydroxide in 67% dimethylformamide

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

(9) A. LeHir, R. Goutarel and M.-M. Janot, *Bull. soc. chim., France*, **19**, 1091 (1952).

(10) (a) G. Stork and R. K. Hill, THIS JOURNAL, **76**, 949 (1954); **79**, 495 (1957); (b) E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 950 (1954); E. E. van Tamelen, M. Shamma and P. Aldrich, *ibid.*, **78**, 4628 (1956).

(11) *Cf.* also R. T. Rapala, E. R. Lavagnino, E. R. Shepard and E. Farkas, *ibid.*, **79**, 3770 (1957).

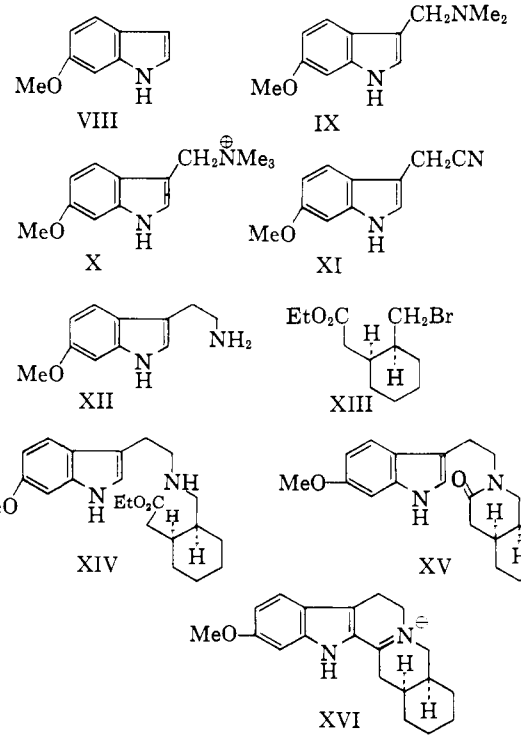
(12) It is of interest that the lack of further C-3 data caused M.-M. Janot, R. Goutarel, A. LeHir, G. Tsatsas and V. Prelog [*Helv. Chim. Acta*, **38**, 1073 (1955)] to reassign incorrectly the stereostructures of alloyohimbane, epialloyohimbane and reserpine.

(13) For a previous discussion of the conformation of D/E *cis* indole alkaloids, *cf.* A. Chatterjee, A. K. Bose and S. Pakrashi, *Chemistry & Industry*, 491 (1954); for corrections of erroneous arguments, contained therein, *cf.* ref. 1d.

(14) R. Majima and S. Murahashi, *Proc. Imp. Acad. (Tokyo)*, **10**, 341 (1934).

as did the *p*-toluenesulfonic acid salt of methyl reserpate. When treated with sodium iodide in acetonitrile, it gave an instantaneous precipitate of sodium *p*-toluenesulfonate and was converted to an iodide which likewise was a neutral salt. The infrared spectrum of the new tosylate confirmed its quaternary character since it showed four bands, at 8.56, 8.95, 9.71 and 9.94 $\mu$, characteristic of the *p*-toluenesulfonate ion[15] and lacked absorption (3.8-4.0 $\mu$) characteristic for an $NH^+$ group. While the exact position of the $N_b$ attachment in ring E will require further interpretation, the very existence and easy formation of the quaternary salt necessitated the assignment of a D/E *cis* configuration for reserpine.[1a] The production of such a salt in a *trans* compound would have been a steric impossibility.

Identical conclusions regarding the D/E ring juncture and new data pertaining to the C-3 configuration were obtained *via* syntheses of the basic reserpine ring skeleton.[1b,7c] One synthesis was similar in reaction sequence to the synthesis of sempervirine[7c,16] while the other followed the pathway previously outlined for the construction of normal, allo and epiallo yohimbanes.[10] 6-Methoxytryptamine (XII) was prepared from 6-methoxyindole (VIII)[17] by conversion of the latter




to 6-methoxygramine (IX) by action of formaldehyde and dimethylamine in dioxane–acetic acid, formation of 6-methoxygramine methosulfate (X), cyanide displacement of trimethylamine with the production of 6-methoxy-3-indoleacetonitrile (XI) and Raney nickel-catalyzed hydrogenation of the latter.[1b] The substituted tryptamine XII was alkylated with the *cis*-bromoester XIII[10a] by heating the two reactants in refluxing dimethylformamide, the process yielding the *cis*-lactam XV after chromatography. The product presumably results through simple alkylation to yield the aminoester XIV, which subsequently eliminates ethanol in a simple ring closure operation. The lactam XV was crystallized and analyzed as a benzene solvate (m.p. 72.5–74°), which displayed the infrared band at 6.2 $\mu$ characteristic of N-alkyl-$\alpha$-piperidones.[10,18] Heating a benzene solution of the lactam with phosphorus oxychloride yielded the $\Delta^3$-product, probably XVI. The unsaturated salt was not purified, but hydrogenated directly over platinum to the desired *d,l*-11-methoxyalloyohimbane (IIIb), a colorless crystalline solid (m.p. 209–210°) isolated by chromatography and purified by crystallization from methanol. A chloroform solution of the synthetic base displayed an infrared spectrum which, possessing a generous number of absorption bands, was indistinguishable from that given by a chloroform solution of authentic 3-isoreserpane (IIIb).

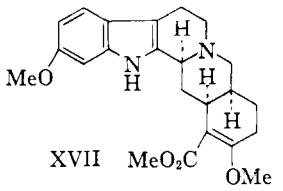
Both syntheses of 3-isoreserpane (IIIb) confirmed the *cis* nature of the D/E ring juncture in reserpine and permitted the assignment of an allo configuration (IVb) to 3-isoreserpane and an epiallo structure (Vb) to reserpane[7c] on the basis of arguments identical with those presented above for their 11-demethoxy analogs. Unfortunately none of these data distinguished rigorously between an allo and epiallo form for reserpine itself, although previous tangential evidence made the epiallo framework more attractive.[1c,7b,c]

When the above stereochemical preference for deserpidine and reserpine was accepted provisorily, a rational, albeit not definitive, interpretation of the orientation of the C-16 and 18 substituents could be made. The acid-induced conversions of deserpidine, reserpine and their derivatives to 3-iso compounds[7] implied that the epiallo form in these systems was less stable than the allo configuration. The interconversion of reserpine and 3-isoreserpine depended somewhat on experimental conditions, although it always produced the 3-iso system in preponderance: (a) refluxing acetic anhydride transformed reserpine exclusively to its 3-epimer[7b] (less than 0.01% reserpine detected by paper chromatography), while (b) refluxing acetic acid converted 3-isoreserpine to a mixture of 3-epimers, containing 15% reserpine.[1h] In view of the comparable energy content of a bare epialloand alloyohimbane,[13] the presence of the ring E substituents must be responsible for the C-3 instability of the epiallo form. This interpretation was placed especially sharply into focus when it was shown that an acid-catalyzed C-3 epimerization is an equilibrium process and that acid treatment of either *d,l*-alloyohimbane or *d,l*-epialloyohimbane led to a 74 ± 5% yield of a mixture consisting of a 3.6:1 ratio of products in favor of the epiallo compound.[1d] In similar fashion, the acid hydrolysis of methyl anhydroreserpate (XVII) to a 3:2 mixture of reserpone (XVIIIa) and 3-isoreserpone (XIX), respectively,[7c] stressed the fact that equilibration

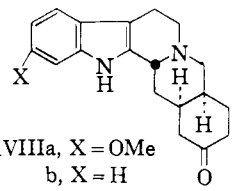
(15) F. L. Weisenborn and D. Burn, THIS JOURNAL, **75**, 259 (1953).
(16) R. B. Woodward and W. M. McLamore, *ibid.*, **71**, 379 (1949).
(17) S. Akabori and K. Saito, *Ber.*, **63B**, 2245 (1930).

(18) The alkylation reaction was complex, leading to products among which there was identified $N_b$-formyl-6-methoxytryptamine, undoubtedly arising from interaction with the solvent.

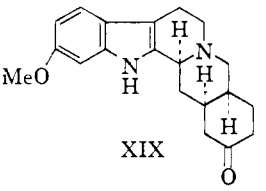
of compounds lacking conformationally important ring E substituents leads preponderantly to the epiallo system. As an interesting sidelight, alkaline C-3 isomerization, a procedure used in the past as a stereochemical diagnostic tool in the D/E *trans*-yohimbine series,[19] was found not to be an equilibrium process.[1d] Base treatment of *d,l*-alloyohimbane as well as *d,l*-epialloyohimbane under Huang-Minlon conditions yielded 78% of a mixture containing merely 4% of isomerized amine. While inducing more epimerization, enhanced stringency of conditions caused greater destruction of compounds.



XVII

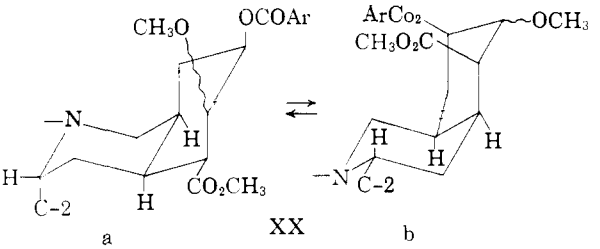


XVIIIa, X = OMe
b, X = H

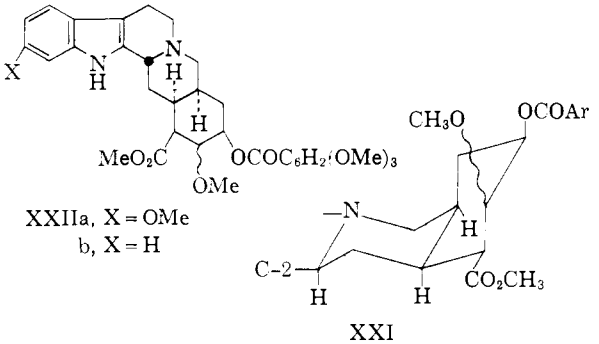


XIX

The above data could be summarized in conformational representation by XX wherein the relative instability of deserpidine and reserpine is ascribed to either the unfavorable environment at C-3 (XXa) or the axial orientation of the C-16 and 18 substituents (XXb). Inversion of C-3 yields the most stable configuration at all three centers, C-3, 16 and 18, as illustrated by the part structure XXI for a 3-iso compound. Thus, XXIIa and b were favored in portraying most of the stereochemistry of reserpine and deserpidine, respectively.



a XX b

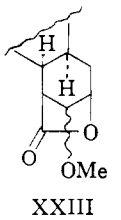


XXIIa, X = OMe
b, X = H

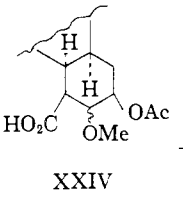
XXI

(19) R. C. Cookson, *Chemistry & Industry*, 337 (1953).

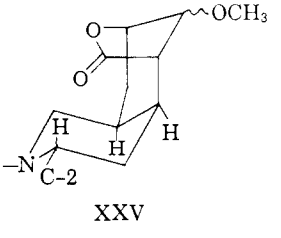
Such interpretation was in agreement with the results obtained from attempted lactonizations of reserpic and 3-iso-reserpic acids (Ij). While the former yielded reserpic acid lactone (XXIII) with ease under the influence of acetic anhydride,[20] the latter formed merely an O-acetyl amino acid (XXIV).[1c] Furthermore, under conditions of C-3 equilibration 3-iso-reserpic acid (Ij) could be dehydrated to reserpic acid lactone (XXIII).[1h] Inspection of XX reveals that in one conformation (XXb) reserpic acid would have its C-16 and 18 substituents in 1,3-diaxial proximity, ready to interact with the production of lactone XXV. However, the 3-iso counterpart to XXb would be incapable of existence, because of the steric interference of C-2 and the C-16 substituent. Hence the preferred formation of an 18-acetate as a consequence of the inability of 3-iso-reserpic acid to form a lactone in a stable C-D di-chair conformation was not unexpected.



XXIII



XXIV



XXV

Molecular rotation studies also were in accord with the stereoconfiguration XXII. Application of Klyne's extension of Hudson's lactone rule[21] to reserpine showed that the change in molecular rotation from reserpic acid, $[M]_D$ − 692° (pyridine), to reserpic acid lactone, $[M]_D$ +300° (pyridine), was +992°.[1a] The molecular rotation difference for deserpidine was +641°.[1c,7b] These values indicated that the C-18 asymmetry is related to D-glyceraldehyde and that XXI also expresses the absolute configuration of the two rauwolfia alkaloids. Molecular rotation differences between various allo compounds and their ring C tetradehydro derivatives[1c,22] suggested a β-orientation for the hydrogen atom at C-3, in conformity with XXII. Infrared spectral evidence has recently yielded the same results.[23a,b]

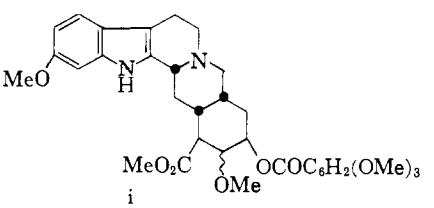
However, unambiguous final proof of XXII only came when the proximity of the C-16 carboxyl carbon and $N_b$, a relationship most apparent in

(20) L. Dorfman, A. Furlenmeyer, C. F. Huebner, R. A. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1953).

(21) W. Klyne, *Chemistry & Industry*, 1198 (1954).

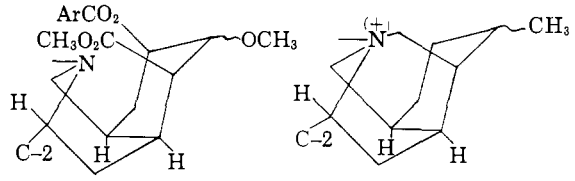
(22) Reference in footnote 12.

(23) (a) E. Wenkert and D. K. Roychaudhuri, THIS JOURNAL, **78**, 6417 (1956); **80**, 1613 (1958). (b) In the absence of an exact assignment of the epiallo configuration to reserpine no distinction regarding the stereochemistry of this alkaloid could yet be made between XXIIa and the structure i.



i

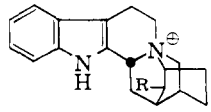
part structure XXVI, suggested a potential chemical interaction of the two atoms. When, indeed, reserpinol (Ie), 3-isoreserpinol (Ie) and deserpidinol (If) were treated with *p*-toluenesulfonyl chloride in pyridine, crystalline products of part structure XXVII were obtained whose quaternary ammonium salt moiety could be checked by criteria described above and to which configurations XXVIIIa, XXIX and XXVIIIb, respectively, could be assigned.[1e,f,g] *These results were proof of the all-*cis *nature of the C-15, 16-and 20-hydrogen atoms, and thus afforded rigorous chemical evidence of the stereochemistry of five of the six asymmetric centers in reserpine (XXIIa) and deserpidine (XXIIb).*



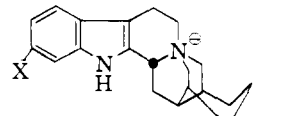
XXVI



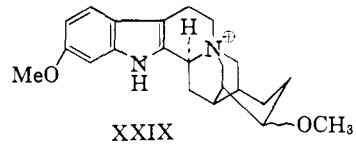
XXVII



XXXa, R = $CO_2Me$
b, R = H



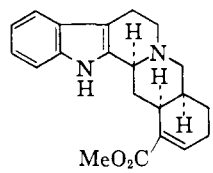
XXVIIIa, X = OMe
b, X = H



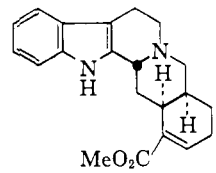
XXIX

Assignment of the configuration of the remaining asymmetric carbon atom, C-17, proved to be a major obstacle. In deserpidine (XXIIb) it finally evolved from the chemistry of rauwolscine (α-yohimbine) (Ic) and 3-epi-α-yohimbine (Ic). Previous investigations[8] had indicated that the stereochemistry of all three alkaloids at C-15, 16, 17 and 20 was identical. In view of this fact and in view of the above-illustrated ease of intramolecular $N_b$ interaction with the carbonyl carbon atom, it became of diagnostic interest to study similar quaternizations involving C-17, especially since the latter's spatial disposition to $N_b$ is equivalent to that of the carbomethoxy carbonyl carbon.

Both rauwolscine (Ic) and 3-epi-α-yohimbine (Ic) were converted to their 17-toxyloxy derivatives (Ig) on mild treatment with tosyl chloride in pyridine. While the rauwolscine product was quite stable, the 3-epi-α-yohimbine derivative was most labile and, in fact, could not be isolated unless the reaction mixture was worked up rapidly and the temperature was not permitted to rise above 20°. At 60° and a five-minute reaction time a 73% yield of the quaternary salt XXXa was obtained. Refluxing of the ester tosylates Ig in collidine or dimethylformamide solution, however, led to their corresponding apo derivatives, apo-rauwolscine (XXXI) and apo-3-epi-α-yohimbine (XXXII).[1i,5]



XXXI



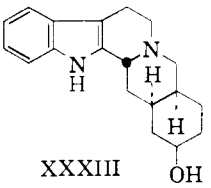
XXXII

These results were explicable on the following basis. The ready quaternization of 3-epi-α-yohimbine tosylate under relatively non-ionizing conditions pointed to a direct intramolecular displacement of the covalent tosylate by $N_b$, hence an α-orientation of the C-17 substituent. The lack of quaternization of rauwolscine tosylate must be ascribed to the energetically unfavorable steric repulsion of the bulky carbomethoxy group by the indole ring during the formation of the quinuclidine system. Finally, the production of the apo derivatives in collidine merely represents an ordinary base-catalyzed β-elimination, while that in dimethylformamide is probably a solvolytic elimination.[5]

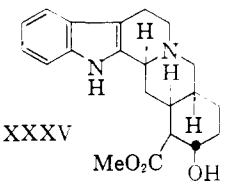
Confirmatory evidence for the above interpretation came from a study of the reduction products of 3-epi-α-yohimbone (XVIIIb). Sodium borohydride treatment of the latter unfortunately yielded a mixture of alcohols.[24] Without separation of the C-17 epimers the mixture was tosylated and the predominant ester obtained in a pure state by chromatography. Refluxing of the product in dimethylformamide converted it to the quaternary salt XXXb, but pyridine treatment at 60° for one hour merely yielded the latter to the extent of 10%, 90% of unchanged ester being recovered. The vast difference in rates of quaternization of the alcohol tosylate and 3-epi-α-yohimbine tosylate (Ig) in pyridine at 60° pointed up the opposite orientation of their tosyloxy groups. The slow reaction rate of the alcohol sulfonate in a concerted displacement suggested a β-constitution of the hydroxyl group in the alcohol XXXIII, while the fast rate of quaternary salt formation of the 3-epi-α-yohimbine ester confirmed the aforementioned α-configuration of the C-17 substituent in the alkaloid XXXIVa. The stereochemistry of the alcohol XXXIII was in agreement with the expected preponderant formation of an equatorial alcohol from the borohydride reduction of the ketone XVIIIb, the latter being assumed to exist in the conformation VIIb. Furthermore, the behavior of the alcohol tosylate in dimethylformamide was in line with the known high ionizing power of the solvent. Thus *formulas XXXIVa,b and XXXV represent the complete stereochemical structures of 3-epi-α-yohimbine, deserpidine and rauwolscine (α-yohimbine).*[5,25]

(24) The same mixture appears to have been obtained more recently by C. Vamvacas, W. v. Phillipsborn, E. Schlittler, H. Schmid and P. Karrer [*Helv. Chim. Acta*, **40**, 1793 (1957)]. It was separated by conversion into two $N_b$-methyl derivatives.

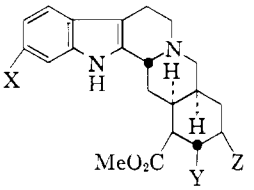
(25) In contrast to the impression created in a recent review on rauwolfia alkaloids (A. Chatterjee, S. C. Pakrashi and G. Werner, in L. Zechmeister, "Progress in the Chemistry of Organic Natural Products," Springer Verlag, Vienna, 1956, Vol. XIII, p. 346) the above constitutes the first rigorous stereochemical analysis of rauwolscine (α-yohimbine). References to previous work on the alkaloid are cited in 8, and the first suggestion of stereoformula XXXV can be found in 1d.



XXXIII



XXXV

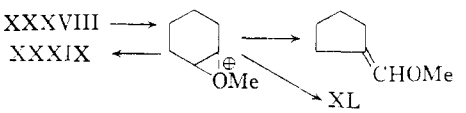


XXXIVa, X = Z = H, Y = OH

b, X = H, Y = OMe, Z = $OCOC_6H_2(OMe)_3$

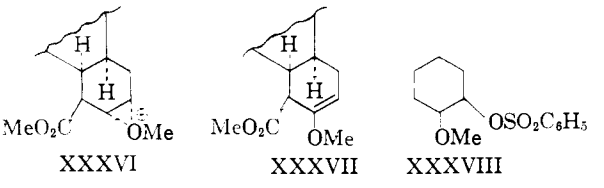
c, X = Y = OMe, Z = $OCOC_6H_2(OMe)_3$

Assignment of the configuration of C-17 in reserpine was attempted also by interpretation of quaternization reactions. As already stressed in the above discussion, methyl reserpate tosylate (Id) led to a mixture of methyl anhydroreserpate (XVII) and a quaternary ammonium salt on collidine treatment.[1a] Similar dimethylformamide treatment led to the same compounds as well as an unidentified $C_{23}H_{30}O_5N_2$ product.[5] If again the assumption is made that in collidine, a solvent of low dielectric constant, only concerted (backside) displacements and (*trans*) eliminations proceed rapidly, then a direct $N_b$–$C_{18}$ interaction in the formation of the quaternary ammonium system is precluded because of the $\beta$-orientation of the 18-tosyloxy group. However, such intramolecular displacement becomes permissible if the C-18 configuration becomes inverted by prior participation of a *trans*-17-methoxy group in the extrusion of tosylate ion. Such rationale would require reserpine to possess a structure as depicted in XXIVc, would suggest that XXXVI be the intermediate in both displacement and elimination processes and in the latter would point to a *trans* path leading to XXXVII and thence by prototropic shift to the more stable methyl anhydroreserpate (XVII).[1d,g] Results from the study of a model compound tended to confirm the participation mechanism. When *trans*-2-methoxycyclohexyl benzenesulfonate (XXXVIII) was subjected to the action of refluxing collidine, 1-methoxycyclohexene (XXXIX), the model counterpart of XXXVII, was isolated and, through hydrolysis of the crude reaction product, identified by formation of cyclohexanone dinitrophenylhydrazone.[26] On the

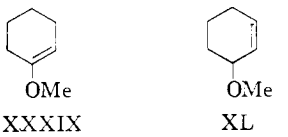


other hand, elimination of benzenesulfonic acid from XXXVIII through the use of potassium *t*-butoxide in *t*-butyl alcohol resulted in 3-methoxycyclohexene (XL) as the only isolable product.[1g]

(26) There was also obtained evidence for the presence of 3-methoxycyclohexene (XL) and cyclopentylcarboxaldehyde in the acid hydrolysate. Collidine-induced elimination of the sulfonate XXXVIII may then be formulated tentatively along the lines

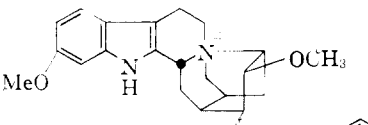


XXXVI XXXVII XXXVIII

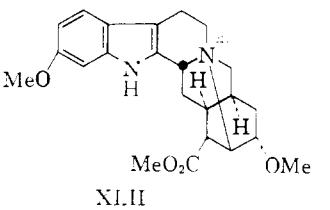


XXXIX XL

The structure of the quaternary ammonium compound became questionable when XXXVI was assumed to be its precursor. Since $N_b$ could now interact at both C-17 and -18, *a priori* either XLI or XLII could be considered as its structure. However, the former was much more acceptable, since the latter, in analogy with the chemical behavior of XXXa, would be expected to be base-sensitive. Confirmation of this view was forthcoming, when the salt proved itself to be completely stable to aqueous potassium hydroxide, collidine, Hofmann and potassium *t*-butoxide treatments.[5]

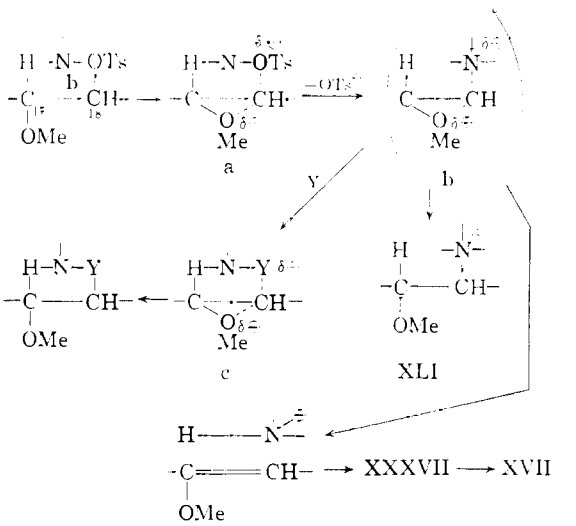


XLI



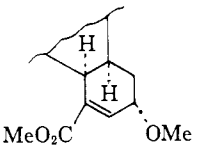
XLII

While the collidine-induced intramolecular removal of an 18-$\beta$-tosylate is in agreement with the assignment of an $\alpha$-orientation to the vicinal 17-methoxy group, the lack of formation of XLII



and/or *via* it or by way of XXXVI an apo product, *e.g.*, XLIII, spoke against a weakening of the $C_{17}$–O bond in the transition state and, hence, against XXXVI as a realistic intermediate in the above

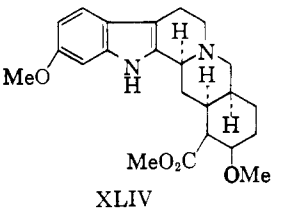
processes. Instead, all C-18 reactions can be pictured to proceed through several ion pairs, which in most cases are internally solvated by $N_b$ and the 17-methoxy function, in close analogy with the recently proposed mechanism for merged substitution and elimination reactions,[27] as shown. Such mechanistic portrayal suggests that the C-18 reactivity would be a function of the ability of $N_b$ to come close to the reaction site (*cf.* b) and that attack by external nucleophiles most probably results in 18$\beta$-products (*cf.* c) because of the easier replacement of the looser $C_{18}$–$N_b$ bond than the $C_{18}$–O linkage in b.[28] Further studies on 18-tosylates tended to corroborate these suggestions.



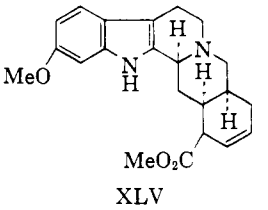

XLIII

Quaternization could not be realized from any 3-iso derivatives.[5] Since steric interference between the 16-carbomethoxy group and the indole ring would prevent $N_b$ from close interaction with C-18, this experimental result was not unexpected. Methyl 3-iso-reserpate tosylate (Id) was converted only to a $C_{23}H_{32-4}O_6N_2$ compound and methyl 3-iso-reserpate formate on refluxing in dimethylformamide. In model experiments a similar reaction with cyclohexyl, androsterone and epiandrosterone tosylates in the presence or absence of one mole of tertiary base led only to olefins. Collidine treatment of methyl-3-iso-reserpate bromide (Ih) gave back starting materials.

Refluxing in dimethylformamide in the presence of sodium acetate caused a conversion of methyl reserpate tosylate into methyl reserpate acetate.[5] This clear-cut example of retention of the C-18 configuration in a displacement reaction as well as the creation of only one epimer in each of the productions of 18-halo compounds from methyl reserpate tosylate (Id) and its C-3 isomer intimated that the halides also possessed an 18$\beta$-orientation.[5] Four halides were obtained by treatment of the tosylates with sodium iodide or lithium bromide in acetonitrile and were interrelated by conversion of methyl reserpate bromide (Ih) to iodide with sodium iodide in acetonitrile, and to methyl 3-iso-reserpate bromide (Ih) by refluxing in acetic acid or by ring C lead tetraacetate oxidation and sodium borohydride reduction.[5] Reduction of all halides by either zinc and acetic acid or Raney nickel and base gave methyl 18-desoxy-3-iso-reserpate (XLIV) as major product.[5] The $C_3$–H $\alpha$-orientation of the latter was proved by ring C oxidation and reduction.[5,29] A slightly different result was obtained from a zinc reduction of the reaction mixture of the lithium bromide–acetic acid treatment of methyl reserpate mesylate.[4] The products consisted of C-3 epimerized starting material, XLIV and XLV.[4] Exposure of the mesylate to lithium bromide and acetic acid alone yielded methyl 3-iso reserpate bromide (Ih), which could be reduced to XLIV by hydrogenation with platinum in base.[4]



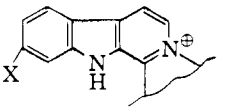

XLIV



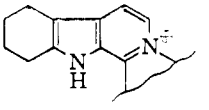

XLV

Both methyl reserpate bromide (Ih) and iodide were stable to collidine[4,5] and the former also to sodium acetate in refluxing ethanol for four days.[5] While a three-hour treatment with sodium hydroxide, followed by diazomethane, did not affect methyl reserpate bromide, a similar ten-hour reaction led to a small amount of methyl reserpate (Ii).[5] Dimethylformamide refluxing of the 18-iodo compound after fifteen minutes gave a small yield of the quaternary salt XLI.[5] While none of the reactions of the 18-halo compounds pinned down rigorously the stereochemistry at C-18, they are most readily explicable on the basis of a $\beta$-halogen orientation.

All chemical evidence now substantiated stereostructures XXXIVb and c for deserpidine and reserpine and was supported by arguments based on molecular rotation differences.[1i,30] Two recent pieces of chemical data gave further confirmation of the structural assignments: (a) a stereospecific total synthesis of reserpine,[31] and (b) the following conversion of reserpine and deserpidine to a common system.[1j] Palladium–maleic acid dehydrogenation of reserpine and deserpidine gave their tetradehydro products, XLVIa and b, respectively. Catalytic hydrogenation of the products in acid medium[32] led to the identical tetradehydrotetrahydro derivative XLVII.




XLVIa, X = OMe
b, X = H




XLVII

**Acknowledgment.**—P. E. A., P. D. H. and E. E. v. T. wish to express their gratitude to the Department of Health, Education and Welfare for financial support (Grant No. G-3892), to S. B. Penick and Co. for gifts of reserpine and deserpidine, and

(27) S. Winstein, D. Darwish and N. J. Holness, THIS JOURNAL, **78**, 2915 (1956).

(28) Should bond formation be quite important, in the transition state of the production of a $C_{18}$–Y compound the stability of the product would determine the orientation of the C-18 substituent. Thus, on this basis also an 18$\beta$-configuration might be predicted.

(29) While the C-3 isomerization in the zinc reduction is a consequence of the presence of acid, its occurrence in the nickel reduction must be catalyst-induced and coupled with halogen removal. Another C-3 epimerization, caused by platinum, has been observed recently on a similar substrate [F. L. Weisenborn, THIS JOURNAL, **79**, 4818 (1957)].

(30) E. Schlittler, in "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957, p. 94.

(31) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, THIS JOURNAL, **78**, 2023, 2657 (1956); *Tetrahedron*, **2**, 1 (1958).

(32) For a comparable reduction of ring A in serpentine *cf.* H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

to H. Boaz of the Lilly Research Laboratories for the titration data. L. H. L., E. W. R., D. K. R. and E. W. are most grateful to CIBA Pharmaceutical Products, Inc., for a supply of alkaloids and for generous financial support.

## Experimental

**Hydrogenation of Sempervirine (IIa).**[6]—A mixture of 5.50 g. of sempervirine (IIa), 600 mg. of $PtO_2$ and 0.1 ml. of 2 *N* alcoholic KOH in 120 ml. of methanol was hydrogenated under 48 lb. of pressure for 24 hr. Some white precipitate had separated at the end of the reaction. The suspension was filtered and the residue digested with hot methanol. Partial concentration of the combined extract and filtrate, and cooling led to 2.00 g. of crystalline material, m.p. 146–148°. Several crystallizations from methanol gave *d,l*-alloyohimbane (IVa), m.p. 149–150°, no depression on admixture with an authentic sample[10,33]; $pK'_a$ (in 80% methyl Cellosolve) 7.12, 7.13. Further concentration of the filtrate yielded 1.10 g. of a mixture, m.p. 120–135°, followed by a final crop of 600 mg., m.p. 120–135°. Alumina chromatography of the last two crops of products and petroleum ether–ether elution yielded first 1.40 g. of more *d,l*-alloyohimbane, followed by 300 mg. of crystals, m.p. 167–171°. Several crystallizations from methanol afforded *d,l*-epialloyohimbane (Va), m.p. 187–188°, same m.m.p. with an authentic specimen[10,33]; $pK'_a$ (80% methyl Cellosolve) 7.48, 7.51. Many runs with varying amounts of starting material gave a range of yields of 55–66% IVa and 2–6% Va.

***d,l*-Epialloyohimbane Oxide.**[6]—A 30% hydrogen peroxide solution (2.5 ml.) was added to a solution of 200 mg. of *d,l*-epialloyohimbane (Va) in 10 ml. of methanol. The white precipitate, which separated immediately, was dissolved by the addition of more methanol and the warming of the solution on the steam-bath. When the solution was left standing at room temperature for 18 hr., white needles deposited, which proved to be the N-oxide, 75 mg. (35%), m.p. 238–239°.

*Anal.* Calcd. for $C_{19}H_{24}ON_2$: C, 76.98; H, 8.16; N, 9.45. Found: C, 76.81; H, 8.76; N, 9.43.

When this oxidation was carried out on *d,l*-alloyohimbane (IVa) under identical conditions, only starting material could be recovered.

**Dehydrogenations of the Alloyohimbanes.**[6]—The palladium–maleic acid oxidation of *d,l*-alloyohimbane (IVa) was described earlier.[23] Dehydrogenation of *d,l*-epialloyohimbane (Va) under identical conditions led to no appreciable tetradehydro product.

**Preparation of Quaternary Tosylate Salt XLI.**[4]—A solution of methyl reserpate tosylate[20] (3.18 g.) in 25 ml. of collidine was refluxed under nitrogen for three hours. To the cooled mixture water was added and most of the collidine was removed by azeotropic distillation, *in vacuo*. Chloroform (50 ml.) was added to the residue and the insoluble material was filtered, washed with chloroform and crystallized from acetone–methanol to give 311 mg. of the quaternary salt XLI, m.p. 290–291°, $[\alpha]^{23}D$ +88.5° (*c* 0.75, HOAc).

*Anal.* Calcd. for $C_{30}H_{36}O_7N_2S$: C, 63.36; H, 6.38; N, 4.93; S, 5.63; 3MeO–, 16.36. Found: C, 63.27; H, 6.23; N, 4.93; S, 5.54; MeO–, 16.2.

The chloroform solution was washed with 10% ammonium hydroxide and water, dried over sodium sulfate and evaporated to dryness, *in vacuo*. The residue (2.0 g.) was dissolved in acetone–benzene (1:1) and chromatographed on 40 g. of Merck acid-washed alumina. Elution with the same solvent gave 300 mg. of methyl anhydroreserpate.[20] Elution with acetone–methanol (20:1) gave an additional 600 mg. of the quaternary tosylate salt XLI.

**Conversion of XLI to its Quaternary Iodide.**[4]—To a solution of 243 mg. of XLI in 45 ml. of hot acetonitrile there was added a solution of 700 mg. of sodium iodide in 5 ml. of acetonitrile. The precipitated sodium *p*-toluenesulfonate was filtered and dried, weight 70.3 mg.

The filtrate was evaporated to dryness *in vacuo* and crystallized from methanol; yield 139.3 mg. of XLI (63%), m.p. 238–240°, $[\alpha]^{23}D$ +93° (*c* 0.71, MeOH).

*Anal.* Calcd. for $C_{23}H_{29}O_4N_2I \cdot 2H_2O$: C, 49.29; H, 5.94; N, 5.00; I, 22.64. Found: C, 49.99; H, 5.90; N, 4.96; I, 22.31.

**6-Methoxygramine (IX).**[3]—The procedure of Ek and Witkop was followed.[34] Three grams of 6-methoxyindole (VIII) dissolved in 20 ml. of pure dioxane was added slowly to an iced, stirred solution of 20 ml. of dioxane, 20 ml. of acetic acid, 1.65 g. of 37% formaldehyde solution and 1.5 ml. of 25% dimethylamine solution. After two hours at ice temperature, the reaction stood overnight at room temperature. After the addition of 250 ml. of water, the solution was filtered with charcoal and extracted with chloroform, after basification with aqueous sodium hydroxide. The chloroform was evaporated and the residue was crystallized from benzene–hexane to yield 3.1 g. (74%) of 6-methoxygramine, m.p. 92–96°. An analytical sample obtained by chromatography on silicic acid melted at 93.5–95.0°.

*Anal.* Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90. Found: C, 70.59; H, 7.71.

**6-Methoxy-3-indolylacetonitrile (XI).**[3]—The chloroform extract of 6-methoxygramine (4.2 g.) was evaporated, and the residue was taken up in 25 ml. of dry tetrahydrofuran. The solution was added slowly to a cooled (10–15°) solution of 0.6 ml. of acetic acid, 13 g. of dimethyl sulfate and 12 ml. of dry tetrahydrofuran. After being allowed to stand in the dark for three hours, the reaction mixture was taken down under reduced pressure, and the residue was washed with 15 ml. of ether. The quaternary salt was dissolved in 40 ml. of water, and, after the addition of 3 g. of potassium cyanide, the solution was heated on the steam-bath for 40–50 minutes. The reaction mixture was allowed to stand overnight; it was then chilled, and the solid nitrile collected by filtration. The crude product was purified by dissolving in benzene and passage over an alumina column (eluted with benzene). The isolated product was crystallized twice from benzene, after which it melted at 111.0–112.0° (lit.[17] m.p. 113–114°) and weighed 2.0 g. (52%).

**6-Methoxytryptamine (XII).**[3]—6-Methoxyindolylacetonitrile (1.5 g.) was hydrogenated in 50 ml. of pure methanol (saturated at 0° with ammonia) over 1 g. of Raney nickel at room temperature and 100 atmospheres and in a *glass liner*. Hydrogen uptake was complete in about 1.5 hours; shaking was continued for another 0.5 hr. After filtration, the solution was evaporated down under reduced pressure while the temperature was not allowed to rise above that of the room. After crystallization from aqueous methanol, the tryptamine, m.p. 138–142°, weighed 1.22 g. (80%). A single crystallization from benzene raised the melting point to 141–143° (lit.[17] 142.5–143.5°).

**Lactam of N[β-(6-Methoxy-3-indolyl)-ethyl]-*cis*-2-aminomethylhexahydrophenylacetic Acid (XV).**[3]—6-Methoxytryptamine (285 mg.) and ethyl *cis*-2-bromomethylhexahydrophenylacetate (394 mg.) were heated for 24 hr. with 100 mg. of sodium iodide and 100 mg. of potassium carbonate in 5 ml. of refluxing dimethylformamide. The cooled reaction mixture was poured into water and extracted with chloroform; the extract was washed thoroughly with water, dried and evaporated down. Chromatography of the residue on silicic acid yielded, on elution with chloroform, unchanged bromoester. The band which was eluted by chloroform–2% methanol was crystallized from ethyl acetate–benzene to give 80 mg. (24%) of N-formyl-6-methoxytryptamine, m.p. 96.5–98.0°.

*Anal.* Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47. Found: C, 66.21; H, 6.49.

The mother liquors from the crystallization of the $N_b$-formyl-6-methoxyltryptamine were rechromatographed on Woelm alumina. The column, after initial elution with benzene, was eluted with 1:1 benzene–chloroform followed by chloroform. The resulting material was crystallized twice from ethyl acetate–benzene, after which there was obtained 85 mg. (14%) of material, m.p. 72.5–74.0°, whose analysis indicated it to be a benzene solvate. Attempts to obtain a crystalline non-solvated lactam were unsuccessful.

*Anal.* Calcd. for $C_{20}H_{26}N_2O_2 \cdot C_6H_6$: C, 77.19; H, 7.97. Found: C, 77.02; H, 7.96.

**11-Methoxyalloyohimbane (IIIb).**[3]—One hundred and sixty milligrams of lactam XII was heated for 2.5 hr. in a refluxing solution of 0.3 ml. of phosphorus oxychloride and 5 ml. of benzene. The brown reaction mixture was stripped

(33) L. H. L., E. W. R., D. K. R. and E. W.[6] are most grateful to Professor G. Stork for sending them a sample of this substance.

(34) A. Ek and B. Witkop, THIS JOURNAL, **76**, 5579 (1954).

down under reduced pressure, 10 ml. of benzene was added and the solvent was again removed under reduced pressure. The dark residue was dissolved in 95% ethanol and hydrogenated over platinum (from 15 mg. of platinum oxide). The reduction was stopped when approximately the theoretical amount of hydrogen had been taken up. After filtration and concentration, the reaction mixture was made basic with ammonia and extracted with chloroform. The residue remaining after removal of the solvent was chromatographed on alumina. After preliminary benzene elution, 1:1 and 2:1 ether–benzene cuts gave crystalline material melting at about 210°. A single methanol crystallization of this material afforded 90 mg. (68% of V, m.p. 206–208.5°. Three recrystallizations from the same solvent raised the melting point to 209–210°.

*Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 76.65; H, 8.25.

The chloroform solution of this base displayed an infrared spectrum identical with that of authentic 11-methoxyalloyohimbane obtained by degradation from reserpine.[35]

**Conversion of 3-Isoreserpine to Reserpine.**[5]—One gram of paper chromatographically pure 3-isoreserpine in 35 ml. of acetic acid was refluxed under nitrogen for 24 hours. Most of the acetic acid was distilled off *in vacuo*, the residue diluted with water, made basic with ammonia and extracted with chloroform. Paper chromatography of a sample of this alkaloid mixture showed it to be a mixture of 25% reserpine and 75% 3-isoreserpine. The system used was formamide–methanol (7:3) impregnated Whatman No. 1 paper with benzene–cyclohexane as the mobile phase. Reserpine has an $R_f$ value of 0.32 and 3-isoreserpine of 0.82. Evaporation of the chloroform extract gave a sirup which crystallized on rubbing with a few ml. of ethanol. The mixture of reserpine and 3-isoreserpine was stirred for 5 min. with 7 ml. of ethyl acetate, filtered and washed with 2 ml. of ethyl acetate. (Reserpine is only slightly soluble in ethyl acetate whereas 3-isoreserpine is exceedingly soluble.) The material insoluble in ethyl acetate was recrystallized from chloroform–methanol to give 150 mg. of reserpine, m.p. 265–268°. The identity of the sample was established by the infrared spectrum.

*Anal.* Calcd. for $C_{33}H_{40}N_2O_9$: C, 65.11; H, 6.62; N, 4.60. Found: C, 65.29; H, 6.88; N, 4.63; $[\alpha]^{25}D$ −118° (chloroform).

An additional 50 mg. of reserpine could be separated from the ethyl acetate-soluble fraction by chromatography on a cellulose column impregnated with formamide using benzene–cyclohexane (1:1) as the eluting agent.

**C-3 Epimerizations of the Alloyohimbanes. (a) Acid-catalyzed Processes.**[6]—A mixture of 1.00 g. of *d,l*-alloyohimbane (IVa), 10 ml. of 48% hydrobromic acid and 10 ml. of glacial acetic acid was refluxed under nitrogen for 6 hr. The acids were removed by distillation under vacuum. Addition of water, basification with ammonium hydroxide, extraction with ether, washing of the extract with water and saturated NaCl solution, drying over sodium sulfate, and evaporation of the solvent led to a residue which yielded 535 mg. of *d,l*-epialloyohimbane (Va), m.p. 184–185°, on crystallization from 30 ml. of methanol. The mother liquor was concentrated to dryness and chromatographed on 19 g. of alumina. Petroleum ether–ether (1:1) elution yielded 162 mg. of starting material, m.p. 147–149°, in the first eight fractions, and 55 mg. of more Va, m.p. 185–186°. Several similar runs produced yields averaging 74 ± 5% of mixtures containing 78 ± 1% of *d,l*-epialloyohimbane (Va). Identical runs carried out on Va as starting compounds led to the same results.

(b) **Base-catalyzed Processes.**[6]—A mixture of 300–500 mg. of either IVa or Va, and 500 mg. of KOH in 10 ml. of ethylene glycol was heated under nitrogen at 200° for 6 hr. The reaction mixture then was poured into 10 ml. of water and extracted with chloroform. The organic solution was washed, dried over sodium sulfate and concentrated to dryness. The residue was crystallized from methanol, while the crystallization mother liquor was chromatographed on 8 g. of alumina and eluted with 1:1 petroleum ether–ether. Several such runs, with both the allo (IVa) and epiallo (Va) compounds serving as starting materials, led to 78% yields of mixtures containing only 4% isomerized amine.

(35) P. E. A., P. D. H. and E. E. v. T.[3] are grateful to Drs. Schlittler and St. André for their coöperation in identifying these substances.

**Conversion of 3-Isoreserpic Acid to Reserpic Acid Lactone (XXIII) 3-Isoreserpic Acid Hydrochloride.**[5]—A solution of 1.0 g. of methyl 3-isoreserpate in 60 ml. of methanol containing 4.0 g. of potassium hydroxide was refluxed under a nitrogen atmosphere for 3.5 hr. The methanol was then removed at room temperature, *in vacuo* and the residue dissolved in 50 ml. of water. After extraction of the aqueous solution with four 25-ml. portions of chloroform, the water was removed *in vacuo* at room temperature and the residue taken up in 60 ml. of methanol. The solution was acidified with 7 *N* hydrochloric acid and the precipitated potassium chloride filtered off. The salt was washed with 20 ml. of a 4:1 mixture of chloroform–methanol and the combined filtrates evaporated to dryness *in vacuo*. The residue from evaporation was triturated with 50 ml. of a 4:3 chloroform–methanol mixture and further potassium chloride filtered off. After vacuum concentration of the filtrate, the crude product was dissolved in 20 ml. of methanol and crystallized by slow addition of 200 ml. of anhydrous ether; 1.05 g. of a white, crystalline material, m.p. 267–269° (98% yield), was obtained. A sample purified by recrystallization from the same solvent mixture gave a m.p. 277–279° after drying at 50° under reduced pressure.

*Anal.* Calcd. for $C_{22}H_{28}O_5N_2.HCl.{}^1/_2H_2O$: C, 59.24; H, 6.78; N, 6.28. Found: C, 59.13; H, 6.85; N, 6.28.

**Reserpic Acid Lactone (XXIII).**[5]—(a)-3-Isoreserpic acid hydrochloride, 0.50 g., of practical purity, m.p. 267–269°, was refluxed for 50 min. under nitrogen with 25 ml. of acetic anhydride and 2 drops of glacial acetic acid. The reaction mixture was then concentrated to dryness *in vacuo* at 60° and the residue taken up in water. The aqueous solution was acidified with a few drops of 10% hydrochloric acid and extracted six times with 30-ml. portions of chloroform. The combined organic washings were extracted eight times with 20-ml. portions of water containing a few drops of hydrochloric acid. All aqueous solutions were then combined, adjusted to *p*H 8 with ammonium hydroxide and extracted four times with 40-ml. portions of chloroform. After washing of the organic extracts with a saturated sodium chloride solution, concentration *in vacuo* and crystallization of the residue from acetone gave 0.075 g. of product (17% yield), m.p. 307–314°; recrystallized once from chloroform, m.p. 310–314°.

A sample of reserpic acid lactone obtained from reserpic acid showed an identical melting point and no depression was observed in a mixed melting point. The infrared spectra of the two samples were identical.

(b) To a solution of 0.60 g. of 3-isoreserpic acid hydrochloride (practical purity, m.p. 267–269°) in 20 ml. of collidine, 1.0 g. of phosphorus pentoxide and 0.15 g. of *p*-toluenesulfonic acid was added. The mixture was refluxed for five hours under nitrogen and the solvent then removed *in vacuo*. The residue was taken up in 50 ml. of water, the *p*H adjusted to 8 with ammonium hydroxide and the solution extracted well with chloroform. After washing once with saturated sodium chloride solution, the chloroform was evaporated *in vacuo* and the crude residue triturated with acetone to give 0.15 g. of product (29% yield), m.p. 310–314°.

**Quaternary Salts Related to Reserpinol (Ie).**[5]—A solution of 0.2 g. of reserpinol and 0.4 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was allowed to stand in the ice-box for one week. The solid material separating was filtered, dissolved in 10 ml. of hot water and treated with 0.2 g. of sodium iodide in 5 ml. of water. The crystalline iodide salt separating immediately (0.12 g.) was recrystallized from methanol to yield purified XXVIIIa iodide, m.p. 345–350°, $[\alpha]D^{25}$ + 122° (2% in dimethylformamide).

*Anal.* Calcd. for $C_{22}H_{29}N_2O_2I$: C, 54.98; H, 6.10; N, 5.83. Found: C, 54.99; H, 6.30; N, 5.93.

**Quaternary Salts Related to 3-Isoreserpinol (Ie).**[5]—A solution of 0.3 g. of 3-isoreserpinol and 0.6 g. of *p*-toluenesulfonyl chloride in 4 ml. of pyridine was allowed to stand in the ice-box for three days. The crystalline solid separating (0.27 g.) could be crystallized from an ethanol–water mixture, m.p. 320–330°. Analysis indicated it to be a mixed tosylate–chloride salt.

*Anal.* Calcd. for $C_{22}H_{29}N_2O_2\oplus\cdot 0.6SO_3C_6H_7\ominus\cdot 0.4Cl\ominus$: C, 66.86; H, 7.09; N, 5.96; S, 4.09; Cl, 3.02. Found: C, 66.64; H, 7.10; N, 6.02; S, 3.89; Cl, 2.87.

The iodide salt was prepared as described in the previous example. After recrystallization from methanol, XXIX

iodide melted at 360–365°, $[\alpha]^{25}D$ −95° (2% in dimethylformamide).

*Anal.* Calcd. for $C_{22}H_{29}N_2O_2I$: C, 54.98; H, 6.10; N, 5.86; I, 26.42. Found: C, 55.33; H, 6.17; N, 6.06; I, 25.93.

**Intramolecular Quaternization of Reserpinol (Ic).**[4]—To a cold solution of 1.0 g. (2.70 mmoles) of reserpinol[20] in 35 ml. of dry pyridine there was added dropwise with swirling a solution of 1.15 g. (6.0 mmoles) of *p*-toluenesulfonyl chloride in 4 ml. of dry pyridine. The solution was kept in an ice-bath overnight, during which time a crystalline precipitate separated. The precipitate was filtered and crystallized from methanol to give 500 mg. of the quaternary chloride (XXVIIIa, m.p. 352–353°, $[\alpha]^{23}D$ +73.6° (*c* 0.71 in water).

*Anal.* Calcd. for $C_{22}H_{29}N_2O_2Cl$: C, 67.94; H, 7.52; N, 7.20; Cl, 9.12. Found: C, 67.92; H, 7.53; N, 7.17; Cl, 8.90.

The pyridine filtrate was evaporated to dryness and the residue dissolved in 20 ml.. of chloroform. The chloroform solution was washed successively with 10% $NH_4OH$ and water, dried over sodium sulfate and evaporated to dryness. The residue (450 mg.) was crystallized from methanol to give 190 mg. of the tosylate salt XXVIIIa, m.p. 310–312°.

*Anal.* Calcd. for $C_{29}H_{36}N_2O_5S$: C, 66.38; H, 6.92; N, 5.34; S, 6.11. Found: C, 65.91; H, 6.51; N, 5.35; S, 5.59.

**Intramolecular Quaternization of Deserpidinol (If).**[4]—Deserpidinol[8] (1.00 g., 2.94 mmoles) was dissolved in 35 ml. of cold dry pyridine. To this was added dropwise a solution of 1.15 g. (6.02 mmoles) of *p*-toluenesulfonyl chloride in 4 ml. of pyridine. The reaction was kept in an ice-bath for two hours and then left at room temperature for 60 hours. During this time a precipitate separated. It was filtered and crystallized from acetone–methanol to give 375 mg. of the quaternary chloride XXVIIIb, m.p. 349.5–351°, $[\alpha]^{25}D$ +48.3° (*c* 0.77, $H_2O$).

*Anal.* Calcd. for $C_{21}H_{27}N_2OCl \cdot {}^1/_2H_2O$: C, 68.55; H, 7.67; N, 7.61; Cl, 9.64. Found: C, 68.42; H, 7.49; N, 7.64; Cl, 9.51.

The pyridine mother liquors were evaporated to dryness *in vacuo*. The residue was dissolved in 25 ml. of acetone and on standing an additional 200 mg. of XXVIIIb crystallized. This compound consumed no base upon titration with 0.01 *N* sodium hydroxide.

**Quaternized Reserpinol Tosylate (XXVIIIa).**[3]—Reserpinol (200 mg.) was allowed to stand with 400 mg. of pure *p*-toluenesulfonyl chloride in 7 ml. of dry pyridine and 5 ml. of ethyl acetate for four days at room temperature. The deposited crystals (80 mg.) were filtered off and gave a m.p. 350° after two crystallizations from methanol–chloroform. This material appeared to be quaternized reserpinol chloride.

The original filtrate was diluted with water and extracted with chloroform; the extract was washed, dried, filtered, and concentrated. Two crystallizations from methanol–acetone gave 60 mg. (21%) of reserpinol quaternary tosylate, m.p. 330–333° dec.

*Anal.* Calcd. for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92. Found: C, 66.18; H, 6.88.

Titration in aqueous dimethylformamide showed no basic or acidic groups between *p*H 3 and 13. A sample was dissolved in methanol, made basic to phenolphthalein, and evaporated under nitrogen. On addition of water, product crystallized, and was recrystallized from methanol–acetone to give only starting material.

In another quaternization experiment, the reaction was run exactly as above but worked up directly by dilution with water and extraction with chloroform. The extracts were washed, dried and filtered, and the solvent was removed under reduced pressure. The residue was twice crystallized from methanol-acetone to give 110 mg. (38%) of quaternary tosylate, m.p. 331–334°, whose infrared spectrum was identical with that of the above sample.

**Quaternized Deserpidinol Tosylate (XXVIIIb).**[3]—Deserpidinol (200 mg., vacuum-dried) was added to 4 ml. of dry pyridine and 300 mg. of *p*-toluenesulfonic anhydride. The reaction was allowed to stand 12 hours at room temperature, warmed at about 60° for 0.5 hr.; after standing overnight, white crystals had deposited. Solvent was stripped under reduced pressure and the residue warmed with acetone. After chilling, filtering, washing with acetone and then water, the product was crystallized twice from methanol–acetone to give 180 mg. (62%) of quaternary salt, m.p. 344–347° dec.

*Anal.* Calcd. for $C_{28}H_{34}N_2O_4S$: C, 67.99; H, 6.93. Found: C, 67.93; H, 6.95.

**Rauwolscine Tosylate (Ig).**[5]—A solution of 3.0 g. of rauwolscine and 5.0 g. of *p*-toluenesulfonyl chloride in 50 ml. of dry pyridine was allowed to stand in the refrigerator for 3 days and then at room temperature for one day. The solution was poured slowly into ice and water and the resulting precipitate filtered, washed with water and recrystallized from acetone; yield 1.61 g., m.p. 212–214°. This material was apparently the tosyl salt of the tosylate and was therefore treated with dilute sodium hydroxide and chloroform. The chloroform solution was washed with water, dried and solvent removed. The product, 843 mg., was recrystallized from acetone and yielded 644 mg. of substance, m.p. 130–133°. Analytical data showed this material to contain one mole of solvent of crystallization. It was, therefore, recrystallized from methanol, m.p. 158.5–160.5°.

*Anal.* Calcd. for $C_{28}H_{32}N_2O_5S$: C, 66.19; H, 6.31; N, 5.52; S, 6.3. Found: C, 66.41; H, 6.11; N, 5.57; S, 6.43.

**Aporauwolscine (XXXI) from Rauwolscine Tosylate.**[5] (a).—A solution of 1.82 g. of rauwolscine tosylate in 12.5 ml. of collidine was refluxed for 3 hours in a nitrogen atmosphere. The solvent was removed by distillation with water *in vacuo* using four portions of water in all. The residue was dissolved in chloroform and dilute sodium hydroxide and the chloroform layer washed with water, dried and the solvent removed. The residue (1.11 g.) was dissolved in a small amount of benzene and chromatographed on 25 g. of alumina. The fractions eluted immediately with benzene gave 890 mg. of crystals, m.p. 202–205°. These were recrystallized from methanol and yielded 600 mg. of aporauwolscine (XXXI), m.p. 204–207°.

*Anal.* Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.29; N, 8.33. Found: C, 75.03; H, 6.94; N, 8.38.

(b).—Rauwolscine tosylate (200 mg.) was refluxed with 1 ml. of dimethylformamide for two hours. The product was worked up as described for XXXa to yield 60 mg. of aporauwolscine (XXXI), m.p. 204–205°. The melting point of a mixture with authentic XXXI was not depressed and the infrared spectra were identical.

**3-Epi-α-yohimbine Tosylate and its Conversion to the Quaternary Tosylate XXXa.**[5]—One gram of *p*-toluenesulfonyl chloride was added slowly with cooling to a solution of 0.5 g. of 3-epi-α-yohimbine in 4 ml. of pyridine. After standing in the ice-box for two weeks (shorter reaction time gave incomplete esterification), a mixture of 10 g. of ice-water and 2 ml. of concd. ammonium hydroxide was added. After 10 min. the mixture was extracted with 50 ml. of chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo* as rapidly as possible, care being taken that the temperature did not rise above 20°. The remainder of the pyridine is best removed at the high vacuum oil-pump. A tan colored froth of the ester tosylate resulted. It could not be obtained crystalline and in view of its labile nature could not be purified further.

*Anal.* Calcd. for $C_{28}H_{32}N_2O_5S$: N, 5.51; S, 6.30. Found: N, 5.35; S, 5.91.

Paper chromatography of this material on formamide impregnated Whatman No. 1 paper with benzene–cyclohexane (1:1) as the mobile phase indicated the ester tosylate to have an $R_f$ value of 0.15. A trace (*ca.* 2%) of the quaternary tosylate was noted.

Two hundred and sixty mg. of this ester tosylate was dissolved in 5 ml. of pyridine and heated at 60° for 5 min. The crystalline quaternary tosylate XXXa after filtering off and washing with acetone weighed 190 mg. (73%), m.p. 162–165°. Paper chromatography of the mother liquor showed the presence of about 35 mg. of additional quaternary tosylate together with some unchanged ester tosylate. On recrystallization from acetone the melting point was raised to 167–170°. The identity of the product was established by its melting point with a mixture of authentic quaternary tosylate[11,8] and by its infrared absorption spectrum.

**Apo-3-epi-α-yohimbine (XXXII) from the Quaternary Tosylate (XXXa).**[5] (a).—A solution of 1 g. of the quater-

nary tosylate XXXa in 7 ml. of 2,4,6-collidine was refluxed for three hours under nitrogen. The reaction mixture was evaporated to dryness and the residue was dried *in vacuo* over phosphorus pentoxide. The product was dissolved in chloroform, washed with 2 *N* aq. sodium hydroxide and finally with water. The chloroform solution was dried with sodium sulfate and evaporated, giving 0.56 g. of amorphous material. A benzene solution of the crude product was chromatographed on 18 g. of neutral alumina (Activity I). Benzene and benzene–ether mixtures eluted 0.41 g. of a substance that still failed to crystallize. Addition of methanolic hydrogen chloride yielded crystalline anhydro-3-epi-α-yohimbine hydrochloride, m.p. 264–268°. For analysis the compound was recrystallized from methanol, m.p. 274–276°; ultraviolet absorption: max., 224 mμ (43,850), 281 mμ (8,200), 289 mμ (6,700); min., 248 mμ (3500), 288 mμ (6,600). The conjugated carbonyl system is indicated by the infrared absorption.

*Anal.* Calcd. for $C_{21}H_{24}N_2O_2$.HCl: C, 67.64; H, 6.76; N, 7.51; Cl, 9.51. Found: C, 67.65; H, 7.12; N, 7.47; Cl, 9.65.

(b).—Compound XXXa (200 mg.) was refluxed in 1 ml. of dimethylformamide for two hours. Ether was added to precipitate the crude tosylate salt which was collected by filtration and converted to the base by shaking with chloroform and excess 1% sodium hydroxide. The material remaining after evaporation of the chloroform was dissolved in a small amount of ethanol and made acid with 6 *N* ethanolic hydrogen chloride; 70 mg. of XXXa hydrochloride was collected, m.p. 265–270°. Identity with the sample obtained above was established by the infrared spectrum and the m.p. of a mixture.

**3-Epi-α-yohimbol Tosylate and its Quaternary Salt (XXXb).**[5]—A mixture of 200 mg. of 3-epi-α-yohimbone and 50 mg. of sodium borohydride in 20 ml. of ethanol was refluxed for 15 min. The ethanol was largely removed by distillation, the residue diluted with water and extracted with chloroform. A crystalline mixture of alcohols remained after evaporation of the chloroform. No practical method for their separation could be found. The mixture was therefore tosylated by allowing it to react with 400 mg. of *p*-toluenesulfonylchloride in 3 ml. of pyridine at 5° for 3 days. After the addition of ice and an excess of ammonia, the mixture was extracted with chloroform. Evaporation of the chloroform gave a crystalline mixture of tosylates. This mixture was dissolved in 2 ml. of ethanol-free chloroform and placed on a chromatography column of 10 g. of aluminum oxide (Woelm II). It was developed first with benzene and then benzene containing increasing amounts of acetone. The major fraction was eluted with 2% acetone in benzene. This material was recrystallized from acetone–water to yield 120 mg. of 3-epi-α-yohimbol tosylate, m.p. 157–160°.

*Anal.* Calcd. for $C_{26}H_{30}N_2O_3S \cdot H_2O$: C, 66.63; H, 6.90; N, 5.99. Found: C, 67.05; H, 7.20; N, 5.85.

This substance was shown to be homogeneous by paper chromatography on formamide impregnated Whatman No. 1 paper with benzene–cyclohexane (1:1) as the mobile phase ($R_f$ 0.23).

3-Epi-α-yohimbol tosylate (30 mg.) was refluxed in 1 ml. of dimethylformamide for five minutes. Within one minute the insoluble crystalline quaternary tosylate began to separate. The sparingly soluble quaternary salt XXXb was filtered and washed with ethanol; yield 15 mg., m.p. 315–320°. The infrared absorption spectrum in Nujol mull showed tosylate ion bands at 1175, 1120, 1033 and 1007 cm.$^{-1}$ and lacked the $NH^+$ band. Paper chromatography of XXXb on formamide impregnated Whatman No. 1 paper with benzene–cyclohexane (1:1) as the mobile phase showed it to have $R_f$ value of 0.01.

*Anal.* Calcd. for $C_{26}H_{30}N_2O_3S$: C, 69.28; H, 6.71; N, 6.22. Found: C, 69.54; H, 6.59; N, 6.39.

3-Epi-α-yohimbol tosylate (5 mg.) was heated at 60° in 2 ml. of pyridine for one hour. The pyridine was evaporated *in vacuo* and the residue paper chromatographed in the system described above; 5–10% of a material of $R_f$ 0.01 (XXXb) and 90–95% of a material of $R_f$ 0.23 (3-epi-α-yohimbol tosylate) was indicated.

**Transformations of Methyl Reserpate Tosylate (Id) in Dimethylformamide.**[5]—Five grams of methyl reserpate tosylate was refluxed in 5 ml. of dimethylformamide for two hours. After cooling, 1 g. of the quaternary ammonium tosylate (XLI) was collected, m.p. 285–290°. Its identity was established by the melting point of a mixture with an authentic sample and by the infrared spectrum. The dimethylformamide filtrate was diluted with 75 ml. of water and the gum which precipitated was filtered and dissolved in chloroform. The chloroform was washed with 1 *N* sodium hydroxide, water and dried over sodium sulfate. This extract was then evaporated to a few ml. and chromatographed on 50 g. of Woelm alumina (Activity II). With benzene there was eluted 80 mg. (after recrystallization from acetone) of methyl anhydroreserpate, m.p. 268–271°, whose identity was established by the usual criteria. Increasing amounts of acetone were added to the benzene as elution was continued. The bulk of the material was eluted with benzene–acetone (5:1). After recrystallization from methanol–water, 1.5 g. of a material of m.p. 164–165° was obtained. Its precise empirical formula was difficult to establish because of its retention of various amounts of solvent of crystallization.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_5 \cdot {}^1/_2H_2O$: C, 65.20; H, 7.39; N, 6.61. Found: C, 65.51; H, 7.39; N, 6.56.

The exact nature of this material was not established, but a free hydroxyl group is apparently present since acetylation with acetic anhydride–pyridine at room temperature gave a new substance (infrared spectral evidence and m.p.). The m.p. after recrystallization from methanol–water was 220–225°.

*Anal.* Calcd. for $C_{25}H_{32}N_2O_6 \cdot 1\text{-}{}^1/_2H_2O$: C, 62.07; H, 7.30; N, 5.80; $30CH_3$, 19.24. Found: C, 62.22; H, 7.17; N, 6.11; $OCH_3$, 19.29.

***trans*-2-Methoxycyclohexyl Benzenesulfonate (XXXVIII).**[3]—Ten grams of *trans*-2-methoxycyclohexanol and 21 g. of benzenesulfonyl chloride in 25 ml. of pyridine was allowed to stand at 0° for 2.5 days. The reaction mixture was added to ice-water and the product isolated by chloroform extraction. Crystallization of the product from benzene–hexane gave 19.55 g. (94%) of the sulfonate, m.p. 53.5–55.0°.

*Anal.* Calcd. for $C_{13}H_{18}O_4S$: C, 57.77; H, 6.71. Found: C, 8.03; H, 6.48.

**Elimination Reactions of XXXVIII.** (a) **Collidine.**[3]—The above benzenesulfonate (10.0 g.) was heated with 35 ml. of redistilled 2,4,6-collidine in the pot of a 2.5 foot Podbielniak-type column. Product distilling over a range of 139–155° was collected over a period of 2.0 hr. This product was allowed to stand overnight at room temperature with 10 ml. of methanol, 4 ml. of water and hydrochloric acid (acid to congo red paper). The reaction mixture was diluted with ice-water and extracted with ether; the extracts were washed with base, water and then were dried. Fractionation gave incomplete separation of at least three products. The first cut, b.p. 136–139°, had bands in the infrared indicating some 3-methoxycyclohexene and possibly cyclopentyl aldehyde. This fraction gave a strong Tollens test, further supporting the occurrence of the aldehyde in this fraction.

A fourth cut, b.p. 152–156° (0.26 g., 7%), was cyclohexanone (lit. b.p. 157°); the infrared spectrum was identical with a comparison sample, and gave a semicarbazone, m.p. 164.4–165.3° (lit. °66°).

To an aliquot of the hydrolysate of the crude elimination product was added, in order to remove aldehyde, with stirring, an aqueous solution of permanganate until a pink color persisted. The reaction mixture was filtered, the cake washed thoroughly, and the filtrate made basic and extracted with chloroform. The residue after removal of the solvent gave 30% of DNP, m.p. 155–159° after one crystallization. Two more crystallizations from ethyl acetate–alcohol gave 25% of cyclohexanone 2,4-DNP, m.p. 160.0 162.0°, m.m.p. 161.0–162.0° with an authentic sample.

(b) **Potassium *t*-Butoxide.**—Ten grams of *trans*-2-methoxycyclohexyl benzenesulfonate was refluxed 10 hours in a solution of 2.4 g. of potassium dissolved in 50 ml. of dry *t*-butyl alcohol. About half of the alcohol was carefully fractionated off through an efficient column. The residue was cooled, poured into water and extracted with ether. An aliquot of this extract gave no DNP. The product was fractionated, giving 2.0 g. (48%) of 3-methoxycyclohexene, b.p. 130–136° (the compound is very volatile, notwithstanding its boiling point, and there was not enough to give a good boiling point in the column head). The product was redistilled from potassium metal, $n^{25}D$ 1.4523.

Comparison was made with 3-methoxycyclohexene prepared by reaction of 3-bromocyclohexene and sodium methoxide in absolute methanol. The product obtained in this fashion had a boiling point of 133–136° and $n^{25}D$ 1.4533. The infrared spectrum was identical with that of the product described as resulting from XXXVIII by the action of *t*-butoxide and, in part, collidine.

**Reactions of Quaternary Salt XLI Derived from Methyl Reserpate Tosylate (Id).**[5] **(a).**—A solution of 0.5 g. of the quaternary salt XLI and 2 g. of potassium hydroxide in 30 ml. of water was refluxed for 12 hours. The solution was made slightly acid with acetic acid and concentrated to dryness *in vacuo*. The mixture of salts was suspended in 100 ml. of ethanol and allowed to stand overnight with an excess of etherial diazomethane. This solution was treated with a small amount of acetic acid and concentrated to dryness *in vacuo*. The residue was dissolved in the minimum of hot water and treated with 0.5 g. of potassium iodide. The solid separating on cooling was recrystallized from methanol–water to yield 0.3 g. of the iodide of XLI, m.p. 235–240°. The identity was established by the melting point of a mixture with an authentic sample prepared according to Diassi, *et al.*,[1a] and by the infrared spectrum.

(b).—A solution of 0.3 g. of XLI and 0.5 g. of potassium in 15 ml. of *t*-butyl alcohol was refluxed for 12 hours. The *t*-butyl alcohol was removed *in vacuo*, water added and the mixture worked up in the manner described above; 0.2 g. of the iodide of XLI, which was identified by the usual criteria, resulted.

(c).—A suspension of 0.5 g. of XLI in 10 ml. of collidine was refluxed for 12 hours. The bulk of the XLI remained undissolved. Most of the collidine was distilled off *in vacuo* and the solid collected with ethanol. A total of 0.45 g. of XLI, m.p. 285–290°, was obtained. Its identity was established by the usual criteria.

Compound XLI (0.4 g.) was converted to its iodide salt and the latter shaken with an excess of freshly prepared moist silver oxide in a mixture of 10 ml. of ethanol and 5 ml. of water for ten minutes. The strongly basic solution of the quaternary hydroxide was filtered from the silver salts and evaporated to dryness *in vacuo*. The resinous residue was heated to 100° for 5 min. The residue was dissolved in 5 ml. of hot water and acidified with hydroiodic acid; 0.2 g. of the crystalline iodide of XLI was obtained, m.p. 235–240°. The identity of the compound was established by the melting point of a mixture with an authentic sample and by the infrared spectrum.

**Methyl 3-Isoreserpate Formate from Methyl 3-Isoreserpate Tosylate (Id) in Refluxing Dimethylformamide.**[5]—A solution of 4.5 g. of methyl 3-isoreserpate tosylate in 25 ml. of dimethylformamide was refluxed for two hours. The clear solution was diluted with 100 ml. of water, made basic with sodium hydroxide and extracted twice with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was recrystallized twice from methanol–water to yield 1.1 g. of methyl 3-isoreserpate formate, m.p. 260–263°.

*Anal.* Calcd. for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.00; H, 7.33; N, 6.30.

Its structure was indicated by the reaction: 100 mg. of methyl 3-isoreserpate formate was refluxed in 10 ml. of methanol with 2.0 ml. of 1 *N* aqueous sodium hydroxide for 6 hours. The majority of the solvent was distilled off *in vacuo* and the residue acidified with nitric acid. The crystalline nitrate was filtered and recrystallized from water to yield 60 mg. of 3-isoreserpic acid nitrate, m.p. 276–280°. The product was identified by its melting point with an authentic sample and by an infrared spectrum. The formyl grouping in methyl 3-isoreserpate proved to be completely resistant to the usual base-catalyzed methanolysis.

**Methyl 3-Isoreserpate Bromide (Ih).**[5]—A solution of 2 g. of methyl 3-isoreserpate tosylate and 2 g. of lithium bromide in 50 ml. of acetonitrile was refluxed overnight. The insoluble lithium tosylate was filtered and most of the acetonitrile distilled off *in vacuo*. The residue was diluted with water and extracted with chloroform. After washing the chloroform extract with water and drying over sodium sulfate, the chloroform was evaporated *in vacuo*. The residue was recrystallized twice from ethanol; yield 1.4 g., m.p. 229–230°, $[\alpha]^{25}D$ −22° (chloroform). The infrared absorption spectrum was different from that of methyl reserpate bromide.

*Anal.* Calcd. for $C_{23}H_{29}BrN_2O_4$: C, 57.84; H, 6.12. Found: C, 57.51; H, 6.25.

**Refluxing Collidine on Methyl 3-Isoreserpate Bromide (Ih).**[5]—Two hundred mg. of Ib was refluxed in 5 ml. of collidine for 3 hours. Removal of the collidine by distillation *in vacuo* left a crystalline residue which gave 85 mg. of purified Ib on recrystallization from methanol, m.p. 225°. The identity was established by the usual criteria.

**Methyl 3-Isoreserpate Iodide.**[5]—A solution of 1.5 g. of methyl 3-isoreserpate tosylate and 2 g. of sodium iodide in 20 ml. of acetonitrile was refluxed overnight. The sodium tosylate was filtered off and the filtrate evaporated to dryness *in vacuo*. Water was added and the mixture extracted with chloroform. The residue remaining after removal of the chloroform was recrystallized from acetone–water to yield 0.9 g. of methyl 3-isoreserpate iodide, m.p. 215–220°, $[\alpha]^{25}D$ −54° (chloroform). The infrared absorption spectrum of this substance and methyl reserpate iodide were distinctly different.

*Anal.* Calcd. for $C_{23}H_{29}IN_2O_4.H_2O$: C, 50.90; H, 5.40; N, 5.16. Found: C, 51.26; H, 5.27; N, 5.37.

**Methyl Reserpate Bromide (Ih).**[5]—A solution of 830 mg. of methyl reserpate tosylate and 830 mg. of lithium bromide in 25 ml. of acetonitrile was refluxed for 16 hours and then worked up as described for the above iodide. Recrystallization from methanol yielded 520 mg. of methyl reserpate bromide, m.p. 224–226°.

*Anal.* Calcd. for $C_{23}H_{29}BrN_2O_4$: C, 57.86; H, 6.12; N, 5.87; Br, 16.74. Found: C, 57.54; H, 5.95; N, 5.99; Br, 16.78.

**Methyl Reserpate Iodide.**[5]—A mixture of 1.5 g. of methyl reserpate tosylate and 1.5 g. of sodium iodide in 50 ml. of acetonitrile was refluxed for 15 hours. The insoluble material was removed by filtration and the filtrate was then evaporated to dryness. The residue remaining was dissolved in chloroform–water and the water separated and extracted twice more with chloroform. The chloroform extract was washed with water, dried and the solvent removed leaving 1.24 g. of material. This was recrystallized several times from methanol and yielded 850 mg. of methyl reserpate iodide, m.p. 215–216° dec., $[\alpha]^{25}D$ +47° (chloroform).

*Anal.* Calcd. for $C_{23}H_{29}IN_2O_4$: C, 52.68; H, 5.57; N, 5.34. Found: C, 53.28; H, 5.55; N, 5.13.

**Methyl Reserpate Iodide from Methyl Reserpate Bromide.**[5]—A solution of 0.2 g. of methyl reserpate bromide and 0.4 g. of sodium iodide was refluxed in 5 ml. of acetonitrile overnight. The solution was evaporated to dryness *in vacuo* and shaken with chloroform and water. The residue remaining after removal of the chloroform was recrystallized from methanol to yield 0.1 g. of methyl reserpate iodide, m.p. 215–220°. Its identity was established by the melting point of a mixture with an authentic sample and by the infrared absorption spectrum.

**Conversion of Methyl Reserpate Bromide to Methyl 3-Isoreserpate Bromide.**[5] (a).—To a solution of 0.5 g. of methyl reserpate bromide in 10 ml. of acetic acid held at 50° was added dropwise 44 ml. of 0.05 *M* lead tetraacetate. After about 30 min. when the oxidant was consumed (moist starch–iodide paper), the acetic acid was evaporated to a few ml. *in vacuo*, 100 ml. of chloroform and 10 ml. of water was added. The mixture was shaken and cooled during careful basification with 50% aqueous sodium hydroxide. The chloroform solution was washed with a small amount of water, dried over sodium sulfate and made just acid with ethanolic hydrogen chloride. Evaporation of the chloroform gave the crude resinous tetradehydro derivative. No attempt was made to purify it. It was dissolved in 15 ml. of methanol and 100 mg. of sodium borohydride added portionwise over 10 min. After standing at room temperature for 30 min., the majority of the methanol was distilled off *in vacuo*. After dilution with water, the mixture was extracted with chloroform. The residue remaining after removal of the chloroform was recrystallized from ethanol, m.p. 225–230°. The identity of the material (120 mg.) as methyl 3-isoreserpate bromide was established by the melting point of a mixture with an authentic sample and by infrared spectrum.

(b).—Methyl reserpate bromide (0.2 g.) was refluxed in 10 ml. of acetic acid for 3 days. The acetic acid was distilled off *in vacuo* and the residue shaken with water basified with ammonia and extracted with chloroform. The chloro-

form was removed *in vacuo* and the residue recrystallized from ethanol, m.p. 225–228°. The identity of the sample as methyl 3-isoreserpate bromide was established in the usual way.

**Potassium *t*-Butoxide on Methyl 3-Isoreserpate Tosylate (Id).**[5]—One gram of methyl 3-isoreserpate tosylate was refluxed 18 hours in 50 ml. of *t*-butyl alcohol in which 0.3 g. of potassium had been dissolved. An insoluble crystalline potassium salt separated during the reaction. At the end of the reaction, this was dissolved in a small amount of water, made slightly acid (*p*H 6) and a solid amino acid separated. The latter was suspended in ethanol and esterified with etherial diazomethane. The crude ester was worked up in the usual way and crystallized from acetone–water to yield 0.6 g. of starting material Id, m.p. 225–228°, which was identified by the usual criteria. A search made of various crude fractions for methyl anhydroreserpate by means of its characteristic infrared absorption bands at 1613 and 1709 cm.$^{-1}$ failed to reveal any.

**Sodium Acetate on Methyl Reserpate Tosylate (Id).**[5]—A mixture of 0.5 g. of methyl reserpate tosylate and 1 g. of sodium acetate was refluxed in 2 ml. of dimethylformamide for two hours. The mixture was diluted with water and extracted with chloroform. The residue remaining after distillation of the chloroform crystallized on rubbing with methanol. Recrystallization from ethanol gave 95 mg. of methyl reserpate acetate, m.p. 295–298°. Its identity was established by the melting point of a mixture with an authentic sample and by the infrared absorption spectrum.

**Methyl 18-Desoxy-3-isoreserpate (XLIV).**[5] (a).—To a refluxing solution of 1.8 g. of methyl reserpate iodide in 50 ml. of glacial acetic acid was added 5.0 g. of zinc dust portionwise during 5 hours. Refluxing was continued for an additional 12 hours. The hot solution was filtered and the zinc dust washed twice with acetic acid (10 ml.) and three times with water (10 ml.). The combined filtrates were concentrated to dryness *in vacuo* and the residue dissolved in water. The aqueous solution was made alkaline with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and the solvent removed. The residue crystallized on the addition of methanol. After recrystallization from this solvent 1.25 g. of XLIV was obtained, m.p. 228–230° dec.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.35; H, 7.26; N, 7.04.

(b).—To 0.5 g. of methyl reserpate iodide dissolved in 100 ml. of methanol was added 2 ml. of 2 *N* sodium methoxide and 1 g. of Raney nickel. The mixture was hydrogenated at 40 p.s.i. for 3 hours. The catalyst was removed and the methanol distilled off *in vacuo* to a volume of 10 ml. During the concentration, pure XLIV separated; yield 0.34 g. The identity of the product with that described above was established in the usual way.

In like manner from methyl reserpate bromide, methyl 3-isoreserpate bromide and methyl 3-isoreserpate iodide by both the zinc reduction and the hydrogenation, equivalent yields of XLIV were obtained.

**Oxidation of Methyl 18-Desoxy-3-isoreserpate (XLIV) to its Tetradehydro Derivative and Reduction Back to XLIV.**[5]—To a solution of 0.5 g. of XLIV in 25 ml. of acetic acid held at 50° was added dropwise 55 ml. of 0.0505 *M* lead tetraacetate in acetic acid. The course of the oxidation was followed by checking for excess oxidant by moist starch–iodide paper. After completion of the reaction (*ca.* 30 min.) most of the acetic acid was distilled off *in vacuo*. Chloroform (100 ml.) was added and 50% aqueous potassium hydroxide added dropwise with cooling and shaking till the aqueous phase was basic. The chloroform was washed with water, acidified with ethanolic hydrogen chloride and distilled to dryness. The resinous tetradehydro compound, without any attempt at isolation, was reduced directly. It was dissolved in 25 ml. of methanol and 0.3 g. of sodium borohydride added over 10 min. After standing 30 min. at room temperature, the majority of the methanol was removed by distillation *in vacuo*, water added and the crude product filtered. After recrystallization from methanol, 0.35 g. of XLIV, m.p. 225–230°, was obtained. Its identity was established by the usual criteria.

**Raney Nickel and Alkali on Reserpinediol.**[5]—One gram of reserpinediol was shaken with 3 g. of Raney nickel and 3 ml. of 2 *N* sodium ethoxide in 50 ml. of ethanol for 24 hours. The catalyst was centrifuged off and the supernatant evaporated to dryness. The residue was washed with water and recrystallized from acetone–water to yield 0.7 g. of authentic reserpinediol possessing the characteristic double melting point of 212–214° and 233–235°.

**Methyl Reserpate Methylsulfonate.**[4]—A solution of 148 mg. of methylsulfonyl chloride in 3 ml. of pyridine was added dropwise with stirring to a solution of 400 mg. of methyl reserpate in 7 ml. of pyridine cooled to 0°. After standing overnight at room temperature, the dark-red reaction mixture was diluted slowly with 50 ml. of 2.5% sodium bicarbonate solution. The mesylate crystallized immediately in almost colorless prisms, 412 mg., m.p. 244–246°. Two recrystallizations from chloroform–methanol gave an analytical sample, m.p. 251–251.5°, $[\alpha]_D$ −82° (pyridine).

*Anal.* Calcd. for $C_{24}H_{32}O_7N_2S$: C, 58.52; H, 6.55; N, 5.69. Found: C, 58.69; H, 6.46; N, 5.42.

**Methyl 18-Bromo-18-desoxy-3-isoreserpate (Ih).**[4]—Methyl reserpate methylsulfonate (575 mg.) was dissolved in 5.0 ml. of glacial acetic acid and added to a solution of lithium bromide (716 mg.) in 5.8 ml. of acetic acid. The mixture was heated under reflux for one hour in a nitrogen atmosphere, the acetic acid removed *in vacuo* and the residue taken up in chloroform and 5% sodium bicarbonate solution. The chloroform extract was washed with water, dried over sodium sulfate, concentrated to give 433 mg. of crystalline residue. For analysis a sample was recrystallized from ethanol, m.p. 225–228°, $[\alpha]_D$ −14° (chloroform).

*Anal.* Calcd. for $C_{23}H_{29}O_4N_2Br$: C, 57.86; H, 6.12. Found: C, 57.66; H, 5.91.

**Reduction of the 18-Bromo Derivative Ih with Zinc.**[4]—A mixture of methyl reserpate methylsulfonate (513 mg.), lithium bromide (680 mg.) and 10 ml. of acetic acid was heated under reflux for 1.25 hours. The solution was cooled slightly, 1.5 g. of zinc dust was added, and the mixture heated again for 1.5 hours. The hot solution was filtered, the residue washed with acetic acid and the filtrate evaporated to dryness. The residue was taken up in chloroform and water, the aqueous layer extracted with chloroform then made basic with 5% sodium bicarbonate solution and again extracted with chloroform. The combined chloroform extracts were washed with bicarbonate solution, water, dried over sodium sulfate, concentrated and the residue fractionally crystallized from ether–hexane. The first crop weighed 98 mg. and after recrystallization from methanol–methylene chloride had m.p. 244–244.5°, $[\alpha]_D$ −64° (pyridine), and analyzed for a mesylate, presumably methyl 3-isoreserpate mesylate.

*Anal.* Calcd. for $C_{24}H_{32}O_7N_2S$: C, 58.52; H, 6.55; 3MeO, 18.85. Found: C, 58.37; H, 6.65; MeO, 18.59.

On further standing the ether–hexane mother liquors from above deposited 105 mg. of a second compound which after recrystallization from methanol–water melted 226–228°, $[\alpha]_D$ −36° (chloroform). Analyses and infrared indicated that this substance was methyl 3-iso-18-desoxyreserpate (XLIV); $\lambda_{max}^{CHCl_3}$ 3.44, 3.60, 3.66 $\mu$.

*Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59; 3MeO, 23.3. Found: C, 69.13; H, 7.79; MeO, 23.9.

The hydrochloride of XLIV was prepared by dissolving the base in methanolic hydrogen chloride, evaporating the solution to dryness and recrystallizing the residue from methanol–ether, m.p. 247–250°.

*Anal.* Calcd. for $C_{23}H_{31}O_4N_2Cl \cdot {}^1/_2H_2O$: C, 62.22; H, 7.27; Cl, 7.99; 3MeO, 21.0. Found: C, 62.18; H, 7.10; Cl, 8.27; MeO, 21.25.

Further concentration of the ether–hexane mother liquors from above gave a third crop of crystals weighing 49 mg. Recrystallization from methanol–water gave colorless plates, m.p. 220–221°, $[\alpha]_D$ −40° (chloroform). Analyses showed that this substance was methyl 3-iso-17-desmethoxy-18-desoxy-$\Delta^{17(16)}$-reserpate (XLV), $\lambda_{max}^{Nujol}$ 5.80 $\mu$.

*Anal.* Calcd. for $C_{22}H_{26}O_2N$: C, 72.10; H, 7.15; 2MeO, 16.9. Found: C, 72.15; H, 7.10; MeO, 15.64.

**Reduction of Methyl 18-Bromo-18-desoxyreserpate with Platinum and Hydrogen.**[4]—Methyl 18-bromo-18-desoxyreserpate (271 mg.) was dissolved in 5 ml. of dioxane and diluted with 12 ml. of methanol. Methanolic potassium hydroxide (0.62 ml. of 1 *N*) and 100 mg. of platinum oxide were added and the mixture shaken under hydrogen for 1.5 hours. The catalyst was filtered off through Celite and carbon dioxide gas was introduced to neutralize the excess

base. After evaporating the solution to dryness, the organic material was taken up in chloroform and filtered from inorganic salts. The filtrate was again taken to dryness *in vacuo* leaving 208 mg. of residue. Crystallization from ether gave fine needles of methyl 18-desoxyreserpate (XLIV), 175 mg., m.p. 227–229°, $[\alpha]_D$ −39° (chloroform).

*Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59. Found: C, 69.06; H, 7.66.

**Attempted Reaction of Sodium Acetate on Methyl Reserpate Bromide.**[5]—One gram of methyl reserpate bromide was refluxed with 4 g. of sodium acetate in 30 ml. of ethanol–water (9:1) for four days. The solution was concentrated to a small volume *in vacuo*, diluted with water, and the solid product filtered. Crystallization from methanol yielded 0.6 g. of methyl reserpate bromide, m.p. 210–215°. Its identity was established by the usual criteria.

**Action of Alkali on Methyl Reserpate Bromide.**[5] (a).—Methyl reserpate bromide (300 mg.) was refluxed in a mixture of 10 ml. of methanol and 3 ml. of 1 *N* aqueous sodium hydroxide for 3 hours. The methanol was distilled *in vacuo* to a volume of a few ml. This was diluted with 10 ml. of water and neutralized with acetic acid. The amino acid which precipitated was suspended in ethanol and methylated with ethereal diazomethane. The reaction mixture was worked up in the usual way and the residue recrystallized from methanol. Starting material (0.2 g.) of m.p. 210–215° was obtained. Its identity was established by the usual criteria.

(b).—The above reaction was repeated except that the refluxing was continued for 18 hours. It was worked up in the same manner as described above. The crude methylated residue was recrystallized from methanol to yield 0.10 g. of methyl reserpate bromide. The mother liquor from this step (methyl reserpate is very soluble in methanol) was concentrated to dryness and treated with 2 ml. of pyridine and 2 ml. of acetic anhydride at room temperature overnight. This was distilled to a small volume, treated with ice-water, ammonia and extracted with chloroform. Recrystallization of the residue remaining after evaporation of the chloroform to dryness gave 40 mg. of methyl reserpate acetate, m.p. 288–290°. Its identity was established by the usual criteria.

**Quaternization of Methyl Reserpate Iodide.**[5]—Methyl reserpate iodide (100 mg.) was refluxed in 1 ml. of dimethylformamide for 15 min. The reaction mixture was diluted with 5 ml. of water and the solid separating was recrystallized from ethanol to yield 25 mg. of the iodide of XLI. The identity of the sample was established by the usual criteria.

**3,4,5,6-Tetradehydroreserpine Perchlorate (XLVIa).**[6] A mixture of 1.80 g. of reserpine (XXXIVc), 5.40 g. of maleic acid and 400 mg. of palladium black in 200 ml. of 50% aqueous methanol was refluxed for 72 hours. After filtration of the catalyst the solution was concentrated to 100 ml. on the steam-bath, treated with 5.0 ml. of perchloric acid and cooled for 18 hours. The resulting precipitate was washed thoroughly with boiling ether, and the residue suspended in 100 ml. of cold methanol and filtered from 450 mg. of unreacted reserpine. Evaporation of the methanol solution left 980 mg. (47%) of crude solid, m.p. 156–180°. Crystallization from methanol–isopropyl alcohol gave yellow plates, m.p. 194–196°; ultraviolet spectrum (EtOH): $\lambda_{max}$ 265 mμ (log ε 4.37), 295 mμ (log ε 4.05) and 382 mμ (log ε 3.83); $[\alpha]_D$ −124° ($CHCl_3$).

*Anal.* Calcd. for $C_{33}H_{37}O_{13}N_2Cl \cdot CH_3OH$: C, 55.40; H, 5.61; N, 3.80. Found: C, 55.11; H, 6.02; N, 3.80.

**9,10,11,12-Tetrahydro-3,4,5,6-tetradehydrodeserpidine Perchlorate (XLVII).** (a)[6].—A mixture of 80 mg. of 3,4,5,6-tetradehydrodeserpidine perchlorate (XLVIb)[2c] and 50 mg. of $PtO_2$ in 75 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 27 hours, at which time the hydrogen uptake had become negligible. Filtration of the catalyst and removal of the solvent left a colorless glass, which was taken up in 2 ml. of methanol and treated with 5 ml. of water and a drop of perchloric acid. On cooling for 12 hours, 50 mg. (62%) of a solid, m.p. 184–190°, separated. Crystallization from aqueous methanol gave colorless crystals, m.p. 188–190°; ultraviolet spectrum (EtOH): $\lambda_{max}$ 250 mμ (log ε 4.17), 270 mμ (log ε 4.10) and 335 mμ (log ε 3.62); $[\alpha]_D$ −39° ($CHCl_3$).

*Anal.* Calcd. for $C_{32}H_{33}O_{12}N_2Cl$: C, 56.59; H, 5.79; N, 4.13. Found: C, 55.90; H, 5.25; N, 4.25.

(b).[6]—A mixture of 400 mg. of 3,4,5,6-tetradehydroreserpine perchlorate (XLVIa) and 150 mg. of $PtO_2$ in 125 ml. of glacial acetic acid was hydrogenated for 30 hours at room temperature and 45 lb. pressure. The reaction mixture was worked up as above yielding 230 mg. (61%) of product, m.p. 175–185°. Several crystallizations from aqueous methanol gave XLVII, m.p. 188–190°, m.m.p. 188–189° with sample above; identical infrared spectrum (KBr) with that of above sample; ultraviolet spectrum (EtOH): $\lambda_{max}$ 250 mμ (log ε 4.16), 270 mμ (log ε 4.10) and 335 mμ (log ε 3.61); $[\alpha]_D$ −40° ($CHCl_3$).

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# Synthesis of L-α-Lecithins Containing Shorter Chain Fatty Acids. Water-soluble Glycerolphosphatides. I

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The didecanoyl-, dioctanoyl- and dihexanoyl-L-α-lecithins have been synthesized from the appropriate D-α,β-diglycerides by the procedure of Baer and Kates for the synthesis of the enantiomeric forms of α-lecithins. The required, but unknown, D-α,β-diglycerides of capric, caprylic and caproic acid were prepared by the method of Sowden and Fischer. The water-soluble L-α-(dihexanoyl)-lecithin should prove to be an excellent substrate for chemical and biochemical studies in homogeneous aqueous systems.

In 1950, Baer and Kates reported a general method for the synthesis of enantiomeric α-lecithins,[1] and described in detail the preparation of distearoyl-, dipalmitoyl- and dimyristoyl-L-α-lecithin. The lecithins were obtained by phosphorylation of the appropriate D-α,β-diglyceride with phenylphosphoryl dichloride and pyridine, esterification of the resulting phenylphosphatidyl chloride with choline chloride, isolation of the phenyllecithin as reineckate, conversion of the reineckate to sulfate, and removal of the protective phenyl group by catalytic hydrogenolysis. Two years later, Baer and Maurukas[2] succeeded in simplifying this procedure, by replacing the rather time-consuming separation of the phosphorylation products *via* their reinecke salts with a procedure based on the different solubilities of the phosphorylation products in ethanol, benzene and

(1) E. Baer and M. Kates, THIS JOURNAL, **72**, 942 (1950).

(2) E. Baer and J. Maurukas, *ibid.*, **74**, 158 (1952).