tion was applied to an alumina column (1.5 × 10 cm.), and after 400 ml. of benzene was passed through, 66 mg. (38%) of the oxazolidone was eluted with 450 ml. of chloroform–benzene (3:7). Crystallization from benzene and then ethyl acetate gave oxazolidone IX of m.p. 201.5–202°, $[\alpha]^{25}D$ +148° (*c* 0.24, ethanol).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1. Found: C, 69.0; H, 6.1.

B. **Attempted Cyclization of 10-*trans*-Hydroxy-N-carbethoxydihydrodesoxynorcodeine** (VIIIa).—A procedure identical with that applied to the *cis* isomer above was followed with 350 mg. of 10-*trans*-hydroxy-N-carbethoxy dihydrodesoxynorcodeine, and the reaction product was separated into neutral and basic fractions. The neutral material was recovered *trans*-N-carbethoxy compound ($[\alpha]^{24}D$ −122°, 255 mg., 73% recovery) and the basic fraction was 10-*trans*-hydroxydihydrodesoxynorcodeine (53 mg., 19%).

Comparison of Reactivity 10-*trans*- and 10-*cis*-Hydroxydihydrodesoxycodeine (IIa, IIb). **A. Hydrogenolysis.**—During an overnight period at room temperature, one mole of hydrogen was absorbed by a solution of 159 mg. of 10-*trans*-hydroxydihydrodesoxycodeine in 8.5 ml. of acetic acid and 0.3 ml. of 60% aqueous perchloric acid containing 150 mg. of 5% palladized carbon. From the reaction mixture there was isolated in the usual way 130 mg. (86% yield) of dihydrodesoxycodeine, m.p. 103–106°; *d*-acid tartrate, m.p. 154–156° (reported[4] m.p. 106–107° and 155–156°, respectively).

Identical conditions with the *cis*-alcohol resulted in no hydrogen absorption and recovery of starting material.

B. **Oppenauer Oxidation.**—Using the procedure previously described[25] 600 mg. (2 mmoles) of 10-*trans*-hydroxydihydrodesoxycodeine was subjected to oxidation by benzophenone for 3.5 hours in the presence of potassium *t*-butoxide and the product was separated by chromatography on alumina. Benzene eluted 460 mg. (77% yield) of 10-ketodihydrodesoxycodeine (identified by its ultraviolet absorption spectrum) and benzene–chloroform (1:1) removed 110 mg. (18%) of the *trans*-alcohol, m.p. 145–147°.

From 10-*cis*-hydroxydihydrodesoxycodeine under the same conditions, the only isolable product was 10-ketodihydrodesoxycodeine in 96% yield.

C. **Chromic Acid Oxidation.**—The same procedure used for the introduction of the 10-hydroxyl group into dihydrodesoxycodeine (I) was applied to 10-*trans*-hydroxydihydrodesoxycodeine (IIa). From 200 mg. of *trans*-alcohol, 149 mg. of alkaloidal material was isolated from the oxidation reaction and this was rectified in the usual manner by chromatography on alumina. A 21% yield (42 mg.) of ketone and a 53% recovery (105 mg.) of *trans*-alcohol were obtained.

With the *cis*-alcohol, the same oxidation procedure resulted in a 71% yield of ketone and a 5% recovery of crude *cis*-alcohol.

D. **Manganese Dioxide Oxidation.**—A solution of 100 mg. of the 10-hydroxy compound in 10 ml. of chloroform was shaken at room temperature with 1 g. of manganese dioxide[5] and the progress of the oxidation was followed by withdrawal of aliquots and examination of the absorption at 322 mμ. Complete conversion to ketone required 19 hours with the *trans*-alcohol and only 3 hours with the *cis*. In each case, a quantitative yield of 10-ketodihydrodesoxycodeine was isolated.

Dihydrodesoxynorcodeine (X).—After a 2.5-hour reflux, a solution of 550 mg. (5.2 mmoles) of cyanogen bromide and 1.14 g. (4 mmoles) of dihydrodesoxycodeine in 15 ml. of chloroform was evaporated, the residue was dissolved in benzene, and the benzene solution was concentrated to dryness after being washed with 1 *N* hydrochloric acid and filtered. The residue thus obtained was hydrolyzed by heating under reflux for 20 hours with 60 ml. of 2 *N* hydrochloric acid and 10 ml. of ethanol. The ethanol then was evaporated, the aqueous solution was washed with benzene before being made alkaline with 6 *N* sodium hydroxide, and the alkaline solution was extracted thoroughly with chloroform. Evaporation of the chloroform left a residue which, with aqueous *d*-tartaric acid, was converted to the *d*-acid tartrate, m.p. 200–210° with decomposition after crystallization from aqueous ethanol and drying at 140° (10 μ); $[\alpha]^{20}D$ −26.0° (*c* 0.53, ethanol).

Anal. Calcd. for $C_{21}H_{27}O_8N$: C, 59.9; H, 6.5. Found: C, 59.6; H, 6.4.

Treatment of the *d*-acid tartrate with aqueous sodium hydroxide and extraction with chloroform gave, on evaporation, dihydrodesoxynorcodeine of m.p. 113–114° after sublimation at 90° (30 μ); $[\alpha]^{20}D$ −75.6° (*c* 1.09, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.2; H, 7.8. Found: C, 75.2; H, 7.9.

BERKELEY, CALIFORNIA

(25) H. Rapoport, R. Naumann, E. R. Bissell and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

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

Rauwolfia Alkaloids. XIX.[1] The Constitution of Deserpidine and Reserpine

BY H. B. MACPHILLAMY, C. F. HUEBNER, E. SCHLITTLER, A. F. ST. ANDRÉ AND P. R. ULSHAFER

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The previously reported Rauwolfia alkaloid deserpidine has been degraded by two routes to known compounds. This was accomplished by converting methyl deserpidate tosylate (IV) to methyl 18-iodo-18-desoxydeserpidate (VII). Treatment of this substance with zinc and acetic acid removed the halogen and yielded methyl 18-desoxydeserpidate (VIII). Cleavage of the 17-methoxyl group and reesterification of the 16-carboxyl function gave α-yohimbine (rauwolscine) (X). In another series of reactions IV on treatment with lithium aluminum hydride was found to yield deserpidinol (V). Cleavage of the methoxyl group produced a substance identical with α-yohimbyl alcohol (VI). Evidence is presented which shows that reserpine and its derivatives and, with less ease, also deserpidine and its derivatives, undergo an epimerization at the C-3 center. The stereochemical implications of these findings as related to the structure of deserpidine and reserpine are discussed.

In a previous communication from this Laboratory[2] the isolation of a new Rauwolfia alkaloid, deserpidine, has been reported. On the basis of the analytical data, the isolation of 3,4,5-trimethoxybenzoic acid on hydrolysis, the interpretation of infrared and ultraviolet absorption spectra and the similarity of its pharmacological and chemical properties with those of reserpine,[3,4] it was proposed that this new alkaloid is 11-desmethoxyreserpine. In a recent communication[1] the conversion of deserpidine to α-yohimbine (rauwolscine)[5] was described. The stereochemical implications of this interrela-

(1) Paper XVIII, H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. André, THIS JOURNAL, **77**, 1071 (1955).

(2) E. Schlittler, P. R. Ulshafer, M. L. Pandow, R. Hunt and L. Dorfman, *Experientia*, **11**, 64 (1955).

(3) A. Furlenmeier, R. A. Lucas, H. B. MacPhillamy, J. M. Mueller and E. Schlittler, *ibid.*, **9**, 331 (1953).

(4) L. Dorfman, A. Furlenmeier, 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 (1954).

(5) A. Chatterjee, A. K. Bose and S. Pakrashi, *Chemistry and Industry*, 491 (1954).

tionship together with certain epimerization reactions of deserpidine and reserpine have led us to propose complete formulas for deserpidine and reserpine. The present paper describes the isolation of deserpidine and the preparation of some of its derivatives together with the experimental work which led to the structural proposals expressed in the previous papers.

Before using derivatives of methyl deserpidate[2] for further degradation studies, it was necessary to show that the basic ring system and functional groups of the alkaloid had not undergone any rearrangement by treatment with the alkali. Therefore, methyl deserpidate (I) was esterified with 3,4,5-trimethoxybenzoyl chloride and the resulting product was found to be identical in every respect with the natural deserpidine. A number of other esters of deserpidic acid were prepared and are given in Table II.

When deserpidine was treated with lithium aluminum hydride, deserpidinediol (II) was formed. This substance was subjected to selenium dehydrogenation and methylyobyrine (III) (1-(2,6-dimethylbenzyl)-9H-pyrid[3,4b]indole) was isolated. This provided evidence for the presence of the yohimbane-type ring system and indicated that in deserpidinediol the hydroxymethyl group, and hence the carbomethoxy group in deserpidine, was in the C-16 position analogous to reserpine[6] and other yohimbine type alkaloids.

When methyl deserpidate tosylate (IV) was subjected to detosylation with collidine as was done with reserpine,[3,4,7] in order to form the anhydro compound, the only substance isolated was a very insoluble material. This appears to be a tosyl salt and is being investigated further. However, when the tosylate IV was treated with lithium aluminum hydride, the tosyl group was reductively eliminated,[8] and the carbomethoxy group reduced to give deserpidinol (V). This substance on treatment with hydrobromic acid yielded the dihydroxy compound VI which was shown to be identical with α-yohimbyl alcohol[9] prepared from α-yohimbine (rauwolscine). Furthermore, when the tosylate IV was treated with sodium iodide or lithium bromide, the corresponding halides VII could be prepared. They were dehalogenated readily by treatment with zinc in acetic acid and yielded methyl 18-desoxydeserpidate (VIII). The 17-methoxyl group of VIII was cleaved by hydrobromic acid and after re-esterification of the unisolated amino acid IX, a substance was isolated which proved to be identical with a sample of α-yohimbine (X) isolated from *R. canescens* leaves.[10]

The degradation of deserpidine to α-yohimbine permits certain conclusions about the stereochemistry of the ring system present in this alkaloid. In the absence of any epimerization during the described sequence of degradation reactions, one could assign to deserpidine the allo-yohimbane configuration since Chatterjee, *et al.*,[5] have shown that this is the configuration of α-yohimbine. However, epimerization does, in fact, occur at the asymmetric center C-3 during the treatment of both deserpidinol (V) and methyl 18-desoxydeserpidate (VIII) with hydrobromic acid concomitantly with the desired demethylation. This indicates that deserpidine possesses the 3-epiallo configuration at C-3, 15 and 20. The lability of the hydrogen atom at C-3 in the yohimbé alkaloids already has been pointed out by Cookson.[11]

This epimerization is shown by the following examples: Successive treatment of 3-epi-α-yohimbine (XI), the recently described alkaloid from *Rauwolfia serpentina*,[12] with hydrobromic acid and then with diazomethane yielded α-yohimbine (X) in which the asymmetric center at C-3 has been epimerized to give a compound of the more stable allo configuration. It has been reported already[12] that the same conversion has been accomplished by the oxidation of XI with lead tetraacetate followed by reduction with sodium borohydride. Similar reactions are reported in this paper with deserpidinediol (II). When this compound was oxidized in an analogous fashion with lead tetraacetate and the tetradehydro derivative XII, in which the asymmetry at C-3 has been destroyed, subsequently reduced, a new diol resulted which is designated 3-iso-deserpidinediol (XIII).[13] Transformation of II into XIII could be brought about also by heating at 200° with strong alkali in diethylene glycol.

For further documentation of this epimerization reaction we may turn to the reserpine series where it was first discovered. When methyl reserpate was acetylated by refluxing in acetic anhydride for six hours, a new isomeric O-acetate XIV (methyl 3-iso-reserpate acetate) was obtained which was different from the previously described acetate prepared by the action of acetic anhydride and pyridine at room temperature.[3,4] This difference was shown most strikingly by the new acetate's complete lack of reserpine-like pharmacological activity in contrast to the relatively high activity of the normal methyl reserpate acetate. Further studies defined the conditions under which this isomerization occurs. Extended refluxing in acetic anhydride or in acetic acid or refluxing in collidine in the presence of catalytic amounts of *p*-toluenesulfonic acid for two hours, or heating at 200° in diethylene glycol in the presence of potassium hydroxide, all bring about the isomerization. Epimerization occurs with greater ease in the reserpine than in the deserpidine series. Treatment of deserpidine or its derivatives under the relatively weak acid conditions of refluxing acetic acid or collidine–*p*-toluenesulfonic acid left them

(6) C. F. Huebner, H. B. MacPhillamy, A. F. St. André and E. Schlittler, THIS JOURNAL, **77**, 472 (1955).

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

(8) P. Karrer, R. Schwyzer, A. Flam and R. Saemann, *Helv. Chim. Acta*, **35**, 865 (1952).

(9) A. Chatterjee and S. Pakrashi, *Science and Culture (India)*, **19**, 109 (1953).

(10) A. Mookerjee, *J. Indian Chem. Soc.*, **18**, 33 (1941).

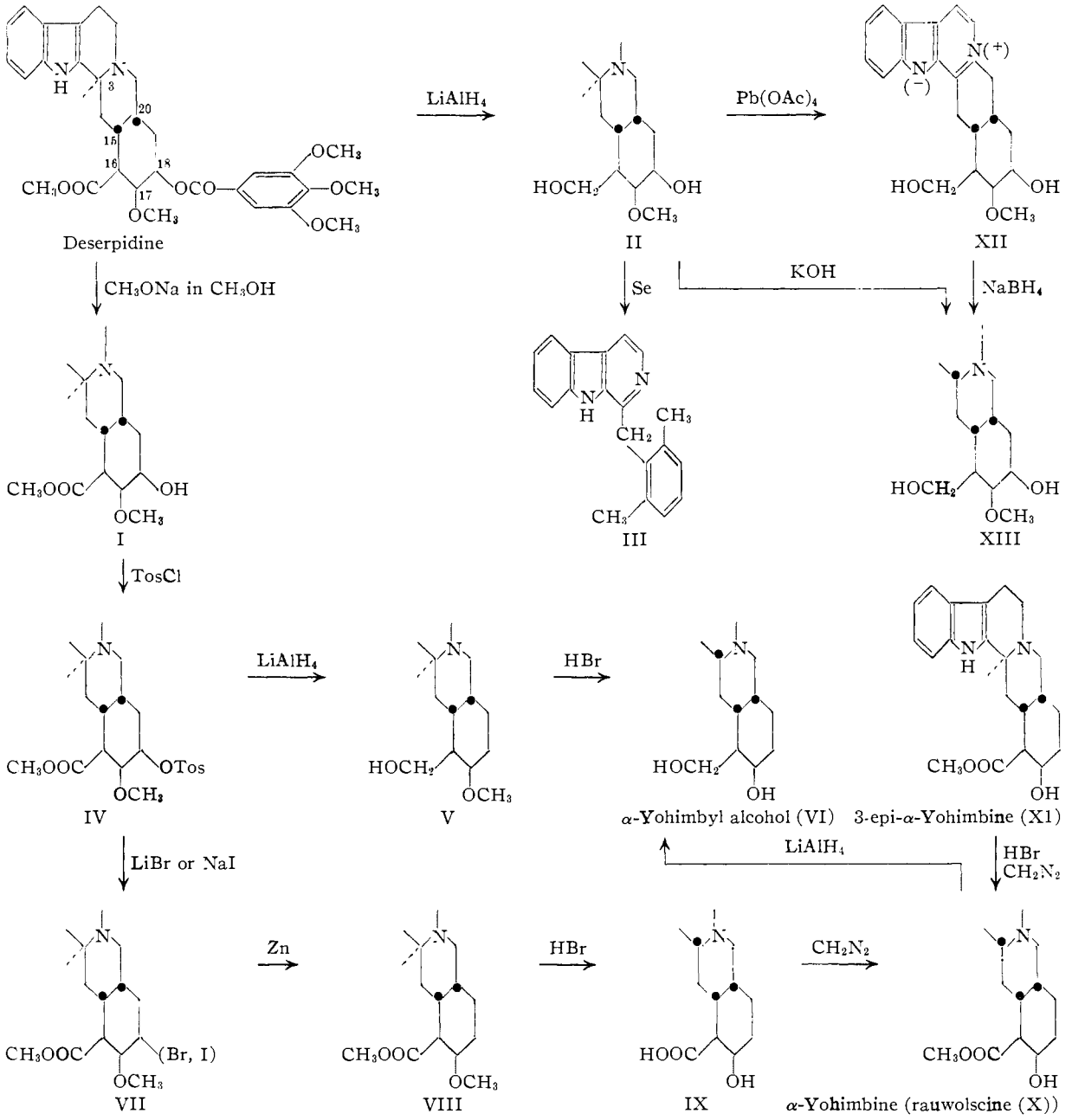
(11) R. C. Cookson, *Chemistry and Industry*, 337 (1953).

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

(13) The prefix 3-iso- is used rather than 3-epi- since the change in steric orientation involves a hydrogen. It has been proposed that epi be reserved to refer to a hydroxyl group (L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. vii.)

CHART I

TRANSFORMATIONS OF DESERPIDINE



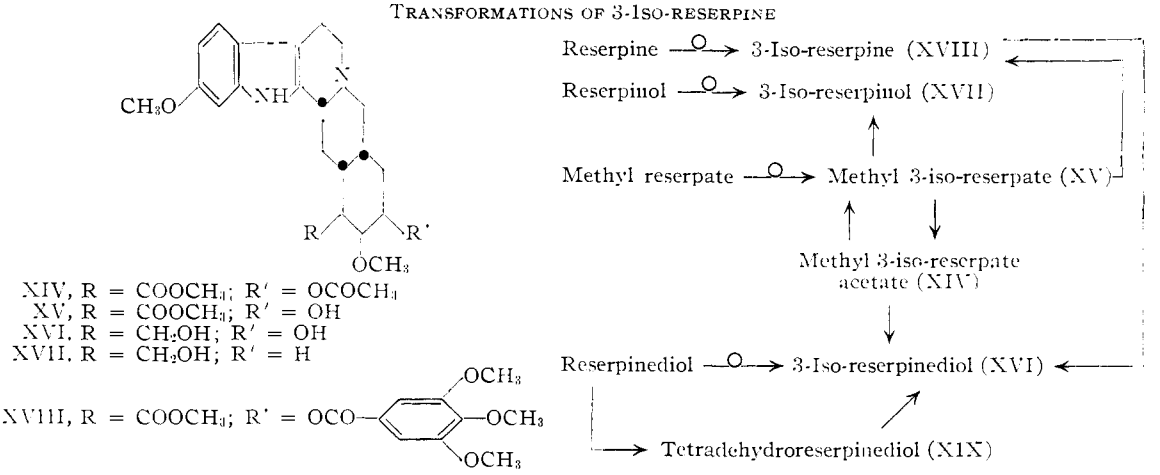
unchanged. It has been noted that hydrobromic acid or strong alkali is necessary to bring about the epimerization.

Using the above-mentioned procedures, methyl reserpate, reserpinediol, reserpinol and reserpine itself, have been epimerized to the corresponding 3-iso-compounds, XV, XVI, XVII and XVIII. It is interesting to record that 3-iso-reserpine is also devoid of reserpine-like activity. Interconversions among the 3-iso compounds were carried out in the manner described for the normal series[3] (see Chart II). Thus methyl 3-iso-reserpate (XV) was reduced with lithium aluminum hydride to 3-iso-reserpinediol (XVI). XV was tosylated and reduced to 3-iso-reserpinol (XVII) by treatment with lithium aluminum hydride. Finally XV was acylated with 3,4,5-trimethoxybenzoyl chloride to give 3-iso-reserpine (XVIII). XVI, XVII and XVIII prepared in this way were identical to samples prepared by direct isomerization of the parent substances. The iso compounds were distinctly different from the normal compounds in melting point, rotation and infrared spectra. XVI and XVII were further characterized as acetates.

That this epimerization involves the C-3 and only the C-3 position is shown by the fact that lead tetraacetate oxidation of reserpinediol to tetradehydroreserpinediol (XIX), followed by sodium borohydride reduction, led to 3-iso-reserpinediol (XVI) identical with the compound obtained by

CHART II

TRANSFORMATIONS OF 3-ISO-RESERPINE



the acid- or base-catalyzed isomerization of reserpinediol. Epimerization of reserpinediol at C-15, C-16 or C-20 by acid or base would be unprecedented. The remote possibility that the hydroxyl at C-18 in reserpinediol has been oxidized to a carbonyl by lead tetraacetate and reduced by sodium borohydride with possible inversion is ruled out, since the infrared absorption spectrum of XIX shows no carbonyl.

The preceding evidence makes it abundantly clear that reserpine and deserpidine belong to the less stable of a pair of stereoisomers epimeric at C-3. Thus deserpidine is a derivative of 3-epiallo-yohimbane.[11] Reserpine would be expected to have the same configuration as deserpidine on the basis of the similarity of chemical reactions and pharmacological activity. However, a firmer experimental foundation for the *cis* fusion of rings D and E in reserpine was desired. This was obtained by showing that a negatively rotating reserpane derived from reserpine had an identical infrared spectrum to that of synthetic *dl*-11-methoxy-allo-yohimbane. This will be the subject of a further communication.

In all cases reported above, the epimerization at C-3 proceeded to completion as far as could be measured. Since the energy barrier between the epiallo and the allo configuration is probably small, the direction of the equilibrium may not always be completely in favor of the allo configuration but may depend upon the type of substitution present. For example, when α-yohimbine was subjected to Oppenauer oxidation, both allo-yohimbone[15] and 3-epiallo-yohimbone[12] were obtained in a ratio of approximately 9:1. Furthermore, when methyl anhydroreserpate[3] was hydrolyzed with acid, two reserpones epimeric at C-3 were isolated in a ratio of about 3:2, one positively and the other negatively rotating. The details of these experiments will be reported at a later date.

Having disposed of the configuration at C-3, C-15 and C-20, we may now turn to a discussion of the relationships at C-16, C-17 and C-18. Lactone formation in reserpic acid[3] shows that the carboxyl at C-16 and the hydroxyl at C-18 are in cis arrangement. Epimerization at C-16 during lactone formation has been ruled out since the lactone gave reserpinediol on reduction with lithium aluminum hydride and methyl reserpate on treatment with sodium methoxide.[3] The question of whether inversion in methyl deserpidate at C-16, caused by the labilizing influence of the carbomethoxy group on the α-hydrogen, has occurred during its described transformation to α-yohimbine (X) can be answered in the negative, since deserpidinol (V), in which the carbomethoxy has been converted to hydroxymethyl, gives α-yohimbyl alcohol (VI). There is no reason to suppose that inversion at C-17 happens during the cleavage of the methyl ether since the C-17 -O linkage should be unaffected.[16] The configuration of deserpidine and reserpine at five asymmetric centers (C-3, C-15, C-16, C-17 and C-20) is therefore that of 3-epi-α-yohimbine (**X**). Although two proposals have been made concerning the stereochemistry of α-yohimbine[4,17] there is no conclusive evidence as to the relationship between the asymmetric centers C-16 and C-17 or between the centers C-15 and C-16.

Acknowledgment.—It is a pleasure to acknowledge the very able assistance of Mrs. D. Davies, Miss R. Hunt, Miss M. Pandow and Mrs. W. Rosen. The efforts of these co-workers have contributed greatly to the successful completion of this work. We also wish to express our appreciation to Mr. L. Dorfman and his associates for the microanalyses and for the ultraviolet and infrared spectra.

Experimental[18]

Isolation of Deserpidine.[2-19]—About 5 kg. of ground root of *R. canescens* were extracted batchwise with boiling meth-

(14) This hitherto unknown isomer of the ring system present in the yohimbé alkaloids was synthesized by G. Stork and R. K. Hill, THIS JOURNAL, **76**, 949 (1954). Their nomenclature has been followed.

(15) A. Le Hir, M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 1027 (1953).

(16) R. L. Burwell, *Chem. Revs.*, **54**, 615 (1954).

(17) A. Le Hir, M. M. Janot and R. Goutarel, *Bull. Soc. Chim. France*, 1027 (1953).

(18) All melting points are uncorrected. Analytical samples were dried at 100° and 0.001 mm. for 12 hours. Despite these vigorous drying conditions certain substances retained water of crystallization. This is especially evident in the alcohol derivatives.

(19) We wish to express our thanks to Dr. W. Fischer, Vice-president in charge of the Production Department, to Dr. A. C. Shabica, Director of the Developmental Research Division and to their colleagues for the preparation of a considerable quantity of this material which greatly facilitated our work.

anol. The combined extracts were concentrated *in vacuo* to a volume of 4 l. At this stage insoluble material was filtered off and the solution was further concentrated to a volume of 900 ml. when a red-brown viscous sirup resulted. Water (4 l.) and about 15 ml. of concentrated aqueous ammonia were added in order to obtain a *p*H of 7.2. After standing overnight the supernatant was decanted from a red-brown tarry residue which, when dried under vacuum at room temperature for 3 days, gave 170 g. of a partially dried and very hygroscopic dark brown solid. Of this 40 g. was triturated with 200 ml. of boiling ethanol and filtered. The filtrate was evaporated and the resulting brown solid was subjected to a distribution between equal volumes of chloroform and methanol–water (1:1). The distribution was carried out in 6 separatory funnels, each containing 200 ml. of upper and 200 ml. of lower phase. The lower phases of the fifth and sixth funnels, after drying over sodium sulfate, were combined and on evaporation of the solvent yielded 9 g. of a brown solid. This was triturated with two portions each of 50 ml. of benzene. The soluble portions were combined and chromatographed on 180 g. of aluminum oxide (Woelm, Activity I, almost neutral) eluting with benzene and benzene containing small amounts of methanol. White crystalline material, m.p. 260–266°, was obtained from a methanol crystallization of the fractions eluted with benzene–0.5% methanol. This material was recrystallized from methanol to give slightly impure reserpine as a first crop and deserpidine as a second crop (small white prisms).

Deserpidine occurs in at least two different crystalline forms. From methanol it can be obtained as thick prisms (m.p. 225–227°) or as fine needles (m.p. 229–231°). By appropriate seeding of a methanol solution, it is possible to convert one form to the other. In chloroform solution both forms have the same infrared spectrum, whereas in Nujol mull the spectra are slightly different. A third modification, obtained from methanol, is a hemihydrate effervescing at 146–150° and finally melting at 225–228°. With acetone and ethyl acetate, solvated forms also were obtained which showed slightly different infrared spectra in Nujol mull.

Anal. Calcd. for $C_{32}H_{38}N_2O_8$: C, 66.42; H, 6.62; N, 4.84; OCH_3(5), 26.81. Found: C, 66.42; H, 6.76; N, 4.89; OCH_3, 26.90.

Preparation of Deserpidine Salts.—Methylene chloride was added to a suspension of 200 mg. of deserpidine in 3 ml. of methanol until solution was complete. A slight excess of 10% aqueous oxalic acid then was added and the solution was evaporated to a small volume. The white crystals of the oxalate thus obtained were filtered, washed with methanol and dried. The nitrate and the sulfate were prepared in the same way. The hydrochloride was obtained by treating a suspension of deserpidine in methanol with methanolic hydrogen chloride. After complete evaporation of the solvent and thorough drying, the residue was recrystallized from ethanol.

TABLE I

Deserpidine salts	M.p., °C. dec.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
HNO_3	254–260	59.89	59.52	6.13	6.32	6.55	6.45
$H_2C_2O_4$	239–243	61.07	60.80	6.05	5.91	4.19	4.32
$H_2SO_4 \cdot 1^1/_2H_2O$	266–269	54.61	54.73	6.16	6.25	3.98	3.98
$HCl \cdot 1^1/_2H_2O$	253–256	59.85	59.71	6.59	6.68	4.36	4.52

Deserpidic Acid.—To 1 g. of deserpidine in 25 ml. of methanol was added a solution of 2 g. of potassium hydroxide in 5 ml. of water. The mixture was refluxed for 2 hours under nitrogen during which period all the deserpidine dissolved. To the cooled solution 3 ml. of glacial acetic acid was added, giving a *p*H of about 6. The solution then was evaporated *in vacuo* to a white solid froth which was triturated with 5 portions each of 25 ml. of acetone at room temperature. The filtrates were evaporated, the white solid froths thus obtained were combined and recrystallized from methanol to give white octahedral prisms, m.p. 267–269° dec. The product then was dissolved in a large volume of methanol and methylene chloride and this solution was concentrated until a small volume of methanol remained. Two such recrystallizations gave a product, m.p. 270–273° dec., $[\alpha]^{25}D$ −158° (pyridine), which was dried for analysis under high vacuum at 110° for 36 hours. This substance rapidly turns yellow on exposure to light and air.

Anal. Calcd. for $C_{21}H_{26}N_2O_4 \cdot {}^1/_2H_2O$: C, 66.48; H, 7.17; N, 7.39. Found: C, 66.26; H, 7.28; N, 7.43.

Deserpidic Acid Lactone.—To 0.13 g. of deserpidic acid, in 40 ml. of pyridine, 1 ml. of acetic anhydride was added. After standing for 3 days at 5° the organic solvents were evaporated *in vacuo* and the acetic anhydride completely removed by repeated evaporation with dry toluene. By recrystallization from acetone, white needles, m.p. 310–315°, were obtained. These were dissolved in methanol–methylene chloride and the solution evaporated to a small volume. The lactone thus obtained melted at 315–318°, $[\alpha]^{25}D$ +12° (chloroform).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.32; H, 6.62; N, 7.84.

A Nujol mull infrared spectrum showed the characteristic lactone absorption at 1765 cm.$^{-1}$. Hydrolysis of the lactone with aqueous methanolic potassium hydroxide gave deserpidic acid, isolated as described above for its preparation from deserpidine and identified by its m.p. and infrared spectrum.

Ethyl Deserpidate.—Deserpidic acid, as a suspension in methanol, was ethylated with an ethereal solution of diazoethane. The residue after removal of solvents was a brownish froth which was then dissolved in dilute acetic acid. On addition of a saturated solution of sodium nitrate and standing for a few days, a crystalline nitrate separated, m.p. 272–275° dec.

Anal. Calcd. for $C_{23}H_{31}N_3O_7$: C, 59.98; H, 6.79; N, 9.12. Found: C, 60.08; H, 6.57; N, 9.15.

Methanolysis of Deserpidine; Methyl Deserpidate (I).—A suspension of 0.5 g. of deserpidine in a solution of 0.05 g. of sodium in 25 ml. of methanol was refluxed for one hour, cooled, and then concentrated *in vacuo* to a volume of 10 ml. This solution was diluted with 30 ml. of water, and concentrated hydrochloric acid was added until it was strongly acidic. This aqueous solution then was extracted repeatedly with ether. The combined ether extracts were washed with water, dried over sodium sulfate and evaporated. The residue, 0.19 g., was recrystallized first from dilute methanol and then from hexane, and the crystals thus obtained were identified as methyl 3,4,5-trimethoxybenzoate.

The above acidic aqueous solution was made basic with concentrated aqueous ammonia and repeatedly extracted with methylene chloride. The combined extracts were dried and concentrated *in vacuo* to give 0.33 g. of an amorphous residue, 0.03 g. of which was dissolved in 1 ml. of dilute acetic acid and a few drops of saturated sodium nitrate solution added. After standing at room temperature 0.03 g. of a crystalline nitrate of I was obtained, which could be recrystallized from methanol; m.p. 271–276° dec.

Anal. Calcd. for $C_{22}H_{29}N_3O_7$: C, 59.05; H, 6.53; N, 9.39. Found: C, 58.73; H, 6.74; N, 9.63.

Reconstitution of Deserpidine.—To a solution of 0.5 g. of methyl deserpidate (I) in 4 ml. of pyridine was added dropwise, with cooling and stirring, 0.5 g. of 3,4,5-trimethoxybenzoyl chloride in 2 ml. of benzene. The mixture was kept at 5° for 5 days and then was poured into 50 ml. of ice-water. A solution of 2 ml. of concentrated ammonia in 10 ml. of water was added with stirring and after 5 minutes the mixture was extracted with 3 portions of methylene chloride. The combined methylene chloride extracts were washed with 2 portions each of 10 ml. of half-saturated sodium chloride solution, dried and taken to dryness *in vacuo*. The residue, a light tan solid froth, was recrystallized from 5 ml. of acetone to give white needles. Two further crystallizations from methanol gave prisms, m.p. 227–230°, $[\alpha]^{23}D$ −134° (chloroform).

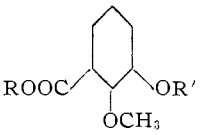
Anal. Calcd. for $C_{32}H_{38}N_2O_8$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.78; H, 6.78; N, 4.85.

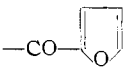
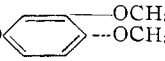
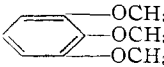
The infrared spectrum, taken in Nujol, was identical with the one of the natural product. The hypotensive and sedative activity was the same as that for the isolated deserpidine.

Methyl Deserpidate Tosylate (IV).—To a solution of 0.46 g. of methyl deserpidate in 5 ml. of pyridine was added dropwise and with cooling 0.46 g. of *p*-toluenesulfonyl chloride in 1 ml. of dry benzene. The reaction then was allowed to stand at 5° for 5 days. The further working up was the same as in the case of the reconstitution of deserpidine and 0.63 g. of the crude semi-crystalline tosylate was obtained. This was recrystallized first from benzene and subsequently

Table II

Deserpidate Tosylate Esters



R	R'	Formula	M.p., °C.	$[\alpha]^{25}D$ (CHCl3)	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found
CH_3	—COCH=CH— 	$C_{34}H_{40}N_2O_8$	133–143 216–217 double m.p.	−101°	67.52 67.57	6.66 6.82	4.63 4.55
CH_3	—CO—CH_3	$C_{24}H_{30}N_2O_5$	275–278	−132	67.58 67.35	7.09 7.33	6.57 6.45
CH_3	—CO— 	$C_{27}H_{30}N_2O_6$	244–247	−141	67.76 67.00	6.32 6.96	5.85 5.71
CH_3	—CO— 	$C_{31}H_{36}N_2O_7$	213–216	−140	67.86 67.74	6.61 6.94	5.11 5.07
C_2H_5	—CO— 	$C_{33}H_{41}N_3O_{11}$	258–260 d.	−114	60.44 60.68	6.30 6.25	6.41 6.49

from methanol when finally slightly pinkish-tan prisms were obtained, m.p. 226–228°, $[\alpha]^{26}D$ −85° (chloroform).

Anal. Calcd. for $C_{29}H_{34}N_2O_6S$: C, 64.67; H, 6.36; N, 5.21. Found: C, 64.51; H, 6.42; N, 4.97.

An additional number of esters were prepared and their physical and analytical data are given in Table II.

Deserpidinediol (II).—Deserpidine was reduced with lithium aluminum hydride and the reaction product worked up as described for reserpine[3,4]; 3 g. of crude II was obtained from 10 g. of deserpidine. After recrystallization from acetone the pure material sintered at 194° (loss of solvent) and melted at 231° dec. Even after being twice sublimed the material apparently still contained solvent.

Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 70.76; H, 7.92; N, 7.85. Found: C, 69.97; H, 7.79; N, 7.76.

The diacetate of the above diol was prepared by reaction with acetic anhydride in pyridine as previously described.[3,4] It was recrystallized from methanol and sublimed, m.p. 263–266°, $[\alpha]^{25}D$ −15° (chloroform).

Anal. Calcd. for $C_{25}H_{32}O_5N_2$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.26; H, 7.22; N, 6.74.

1-(2,6-Dimethylbenzyl)-9H-pyrid[3,4-b]indole (III) from II.—A mixture of 2.5 g. of deserpidinediol (II) and 3 g. of red selenium was heated to 270–280° for 20 minutes. The melt then was cooled, pulverized and, after the addition of 1 g. of Hyflo, was extracted continuously with acetone for 20 hours. The acetone was evaporated *in vacuo*, the residue dissolved in 30 ml. of a benzene–acetone mixture (1:1) and filtered over 30 g. of aluminum oxide (Activity II–III). The first benzene–acetone eluates gave 0.486 g. of a brown oil and 0.195 g. of a crystalline fraction, m.p. 205–211°. According to its infrared spectrum, this was a mixture of yobyrine and methylyobyrine and could not be separated into its components. The brown oil was rechromatographed over aluminum oxide (Activity II–III) in benzene solution and thus 0.132 g. of a crystalline fraction, m.p. 215–220°, was obtained. This material was recrystallized from cyclohexane and sublimed at 140–180° (0.001 mm.). The sublimate, m.p. 219–221.5°, did not depress the melting point of the methylyobyrine prepared from yohimbyl alcohol. The two infrared spectra were identical.

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.01; H, 6.54; N, 9.80.

Deserpidinol (V).—A solution of 2 g. of the tosylate IV in 25 ml. of freshly distilled tetrahydrofuran was added dropwise to a slurry of 1.5 g. of lithium aluminum hydride in 60 ml. of the same solvent. After complete addition, the reaction was refluxed for 5 hours. About 50 ml. of water then was added carefully and the tetrahydrofuran evaporated *in vacuo*. The aqueous suspension then was filtered and the filter-cake triturated 5 times with hot acetone. The combined hot acetone extracts were filtered and the acetone removed *in vacuo*. The residue was dissolved in chloroform and this was washed repeatedly with water. The dried chloroform solution was evaporated and the residue crystallized from methanol; m.p. 232–236° dec., $[\alpha]^{25}D$ −2° (chloroform).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.78; H, 8.38; N, 8.29.

α-Yohimbyl Alcohol (Rauwolscinyl Alcohol) (VI).—A suspension of 500 mg. of deserpidinol (V) in 5 ml. of hydrobromic acid (b.p. 123–125°) was refluxed under nitrogen for 90 minutes. It was then cooled and poured into 50 ml. of water. The precipitate thus obtained was filtered, washed with water and dissolved in methanol. Addition of ammonium hydroxide precipitated a solid which was extracted with chloroform. Also the acid filtrate (see above) was basified and extracted with chloroform. The combined chloroform extracts were washed, dried, evaporated *in vacuo* and the residue recrystallized from methanol. This material was solvated and for analysis it was therefore sublimed, m.p. 229–231°.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03. Found: C, 73.55; H, 7.55.

The infrared spectrum of VI was identical with the one of α-yohimbyl alcohol, prepared from α-yohimbine (rauwolscine) (X) according to Chatterjee and Pakrashi.[9]

Methyl 18-Bromo-18-desoxydeserpidate (VII).—A mixture of 500 mg. of the tosylate IV, 500 mg. of lithium bromide and 10 ml. of acetonitrile was refluxed for 16 hours. The cooled solution was filtered to remove the precipitated lithium *p*-toluenesulfonate and the filtrate was evaporated to dryness. The residue was dissolved in chloroform and water. The aqueous phase was separated and extracted 3 times with chloroform. The combined chloroform extracts were washed with water, dried and the solvent removed. The resulting crystalline material was recrystallized by dissolving it in a small amount of ethylene dichloride, adding methanol and then removing the ethylene dichloride by distillation. The hot solution was filtered and, on cooling, 230 mg. of product separated, m.p. 181–182° dec., $[\alpha]^{25}D$ −24° (chloroform).

Anal. Calcd. for $C_{22}H_{27}BrN_2O_3$: C, 59.06; H, 6.08; N, 6.26. Found: C, 58.98; H, 6.31; N, 6.43.

In a similar manner a mixture of 2.0 g. of tosylate IV, 2.0 g. of sodium iodide and 40 ml. of acetonitrile yielded 1.2 g. of crystalline iodide. In spite of repeated recrystallizations this material could not be obtained analytically pure and, therefore, was used directly for further reactions.

Methyl 18-Desoxydeserpidate (VIII).—Ten grams of zinc dust was added portionwise to a refluxing solution of 1.2 g. of iodo compound VII in 50 ml. of glacial acetic acid and the refluxing was continued for 18 hours. The cooled solution was then filtered and the zinc washed with dilute acetic acid and water. The combined aqueous solutions were concentrated to a small volume *in vacuo* and extracted with chloroform. The chloroform solution was washed with water, dilute ammonia and again with water and then the dried solution was evaporated. When the residue was triturated

with methanol a crystalline material was obtained which was recrystallized from the same solvent; m.p. 272–275°, $[\alpha]^{25}D$ −28° (chloroform).

Anal. Calcd. for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.94; H, 7.49; N, 7.67.

The same compound was obtained, when the corresponding bromide was dehalogenated with Raney nickel in the presence of hydrogen under alkaline conditions.

α-Yohimbic Acid (Rauwolscinic Acid) (IX) and α-Yohimbine (Rauwolscine) (X).—A suspension of 500 mg. of desoxy compound VIII in 4.5 ml. of freshly distilled concentrated hydrobromic acid (b.p. 123–125°) was heated to 105° for 90 minutes. During this period complete solution occurred. The reaction was cooled, poured on ice and the flocculent precipitate thus obtained was filtered and dissolved in a minimum amount of methanol. On careful addition of ammonium hydroxide the free amino acid was precipitated. The acid filtrate (see above) was neutralized similarly, the two alkaline solutions were combined and repeatedly extracted with butanol. Finally the butanol was evaporated *in vacuo*. The residue (IX) could not be obtained in crystalline form and was, therefore, dissolved in methanol and treated with an excess of ethereal diazomethane solution. After 3 hours all the material had dissolved and the organic solvents and the diazomethane were removed by distillation. The residue, dissolved in benzene, was chromatographed over aluminum oxide (Woelm, Activity II–III). Benzene–acetone (9:1) eluted a crystalline material which, after crystallization from methanol, melted at 240–242°, $[\alpha]^{25}D$ −22° (ethanol).

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.08; H, 6.96; N, 7.77.

The infrared spectrum of this compound was identical with the one of rauwolscine (α-yohimbine) isolated from leaves of *R. canescens*.

α-Yohimbine (Rauwolscine) (X) from 3-Epi-α-yohimbine (XI) by Hydrobromic Acid.—One gram of 3-epi-α-yohimbine (XI) was heated with 5 ml. of 48% aqueous hydrobromic acid for three hours at 100°. Most of the hydrobromic acid then was distilled off *in vacuo*. The addition of acetone and ethyl acetate caused the precipitation of a dark brown, powdery, crude hydrobromide. One hundred milligrams of this material was dissolved in methanol and treated with a large excess of ethereal diazomethane. After 10 minutes, the mixture was evaporated to dryness and dissolved in a few ml. of ethanol. Addition of ethanolic hydrogen chloride caused the crystallization of crude α-yohimbine hydrochloride. This was converted to the base with ammonia and after two recrystallizations from methanol, 30 mg. of α-yohimbine (X) was obtained, m.p. 238–239°. The m.p. of a mixture with an authentic sample was 238–239° and their infrared spectra were identical.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39. Found: C, 71.18; H, 7.38.

3-Iso-deserpidinediol (XIII).—(a) Deserpidinediol (II) (500 mg.) was added to a solution of 600 mg. of potassium hydroxide in 5 ml. of diethylene glycol heated to 200°. After 6 hours at this temperature the reaction mixture was diluted with 10 ml. of water and shaken with 100 ml. of chloroform. The crystalline iso-diol appeared at the interface. Evaporation of the chloroform gave a small additional amount of the iso-diol. These were combined and recrystallized from ethanol–water to yield 170 mg. of 3-iso-deserpidinediol (XIII), m.p. 150–151° (hot-stage). The infrared spectrum in Nujol mull was distinctly different from that of deserpidinediol (II).

Anal. Calcd. for $C_{21}H_{28}N_2O_3 \cdot 1^1/_2H_2O$: C, 65.74; H, 8.14. Found: C, 65.95; H, 7.50.

The compound was further characterized by the preparation of a diacetate since the diol crystallized as a hydrate and exhibited the double m.p. typical of the solvated alkaloid alcohols. Acetylation by treatment with acetic anhydride–pyridine gave **3-iso-deserpidinediol diacetate**, m.p. 235–236°, after recrystallization from ethanol. The infrared spectrum in Nujol mull was distinctly different from the normal diol diacetate.

Anal. Calcd. for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32. Found: C, 68.37; H, 6.95.

(b) To a solution of 100 mg. of deserpidinediol in 5 ml. of acetic acid held at 60° was slowly added 11 ml. of a 0.0509 *M* lead tetraacetate solution in acetic acid. The oxidant was added so that only a small excess was ever present as tested by starch–iodide paper. After completion of the reaction (about 30 minutes) the acetic acid was evaporated to a few ml. *in vacuo*, 100 ml. of chloroform and 10 ml. of water was added and the mixture shaken and cooled during careful basification with 50% aqueous sodium hydroxide. The chloroform solution was washed with a small amount of water, dried and made just acid by the dropwise addition of 8 *N* ethanolic hydrogen chloride. Evaporation of the chloroform gave crude **tetradehydrodeserpinediol (XII)** as a yellow resin. Efforts to crystallize it or its derivatives were unsuccessful. The resin was dissolved in 10 ml. of methanol and 100 mg. of sodium borohydride was added portionwise over 5 minutes. The solution was refluxed for 30 minutes and concentrated to half-volume. Ten milliliters of water was added and concentration continued until about 5 ml. remained. A mixture of brown oil and crystalline material had separated. Two recrystallizations from ethanol–water gave 7 mg. of 3-iso-deserpidinediol (XIII), m.p. 148–150°. The m.p. of a mixture with a sample prepared by the direct base-catalyzed epimerization was 148–150° and the infrared spectra of the two samples were indistinguishable.

Methyl 3-Iso-reserpate Acetate (XIV).—(a) One gram of methyl reserpate was refluxed with 10 ml. of acetic anhydride for six hours. About half of the acetic anhydride was removed *in vacuo* and 50 g. of ice-water added to the residue. After hydrolysis of the excess acetic anhydride, the small amount of black tarry material separating was removed. Ammonium hydroxide was added with cooling to the filtrate. The crude precipitated acetate was filtered and purified by washing with ethanol in which it is rather insoluble. This yielded 0.7 g. of XIV, m.p. 260–265°. Recrystallization from acetone–water gave fine needles, m.p. 270–271°, $[\alpha]^{25}D$ −130° (chloroform).

Anal. Calcd. for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.56; H, 6.90; N, 5.91.

XIV is readily distinguishable from the normal methyl reserpate acetate in that its infrared spectrum in Nujol mull shows only one carbonyl maximum at 1728 $cm.^{-1}$, whereas the latter shows two; at 1736 and at 1712 $cm.^{-1}$.

(b) Methyl reserpate acetate (50 mg.), m.p. 297–298°,[20] was refluxed for 16 hours in 5 ml. of acetic acid. Distillation of most of the acetic anhydride, dilution with water and addition of ammonium hydroxide gave XIV as the crude base which on recrystallization from acetone–water melted at 270–271°.

(c) Acetylation of methyl 3-iso-reserpate with acetic anhydride and pyridine at room temperature gave XIV, m.p. 270–271°.

Methyl 3-Iso-reserpate (XV).—(a) Methyl reserpate (3 g.) was refluxed in 20 ml. of collidine containing 200 mg. of *p*-toluenesulfonic acid for 4 hours. The reaction mixture was cooled, gently shaken with dilute ammonium hydroxide to remove the acid catalyst, and the collidine distilled *in vacuo* to a small volume. Fifty milliliters of water was added and the solvents completely removed by distillation. The dark brown sirup resulting was dissolved in 30 ml. of ethanol and made acid (*p*H 3) by the careful addition of 5 *N* aqueous nitric acid. Scratching and cooling caused the separation of the **nitrate** of **XV**. After standing overnight 1 g. was collected which crystallized nicely from water; m.p. 265–270°.

Anal. Calcd. for $C_{23}H_{31}N_3O_8$: C, 57.85; H, 6.54; N, 8.80. Found: C, 57.78; H, 6.30; N, 8.61.

The nitrate of XV was converted to the base by addition of ammonium hydroxide to its hot aqueous solution. Recrystallization from methanol–water gave plates melting at 220–221°, $[\alpha]^{25}D$ −62° (ethanol).

Anal. Calcd. for $C_{23}H_{30}N_2O_5$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.40; H, 7.28; N, 6.55.

When methyl reserpate was refluxed in collidine alone it was recovered unchanged, none of the allo compound being detected. These two substances may be separated readily since methyl reserpate does not crystallize as a nitrate, therefore, remaining in solution.

(b) Five grams of methyl 3-iso-reserpate acetate (XIV) was refluxed in a solution of 0.5 g. of sodium in 200 ml. of anhydrous methanol for one hour. The methanol was concentrated *in vacuo* to a small volume, diluted with water

(20) The melting point of this substance was previously erroneously reported[3] to be 268–271°.

and the mixture extracted with chloroform. The sirupy residue remaining after removal of the solvent was dissolved in a few ml. of methanol and, after seeding, 3.0 g. of XV was obtained, m.p. 210–212°.

3-Iso-reserpinediol (XVI).—(a) One gram of reserpinediol was refluxed in 15 ml. of collidine containing 150 mg. of *p*-toluenesulfonic acid for 3 hours. The acid was removed by washing with dilute ammonium hydroxide and most of the collidine was distilled off. Water was added and distillation *in vacuo* continued to dryness. The gummy residue was dissolved in a few ml. of ethanol and the crystalline hydrochloride obtained by acidification with 8 *N* ethanolic hydrogen chloride. Conversion of this salt to the base gave 0.75 g. of XVI which then crystallized. After recrystallization from ethanol–water it melted at 218–220°, $[\alpha]^{25}D$ −59° (ethanol). The m.p. of a mixture with reserpinediol hydrate (m.p. 211–213°) was 180–190°. XVI, in contrast to the normal isomer, is very soluble in acetone or ethanol.

Anal. Calcd. for $C_{22}H_{30}N_2O_4 \cdot {}^1/_2H_2O$: C, 66.77; H, 7.91. Found: C, 66.35; H, 8.06.

Acetylation of XVI with acetic anhydride–pyridine at room temperature in the usual manner gave the **diacetate** as a characteristic derivative. Recrystallization from ethanol–water gave plates, m.p. 210–212°, $[\alpha]^{24}D$ −88° (chloroform).

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.41; N, 5.91.

(b) Reserpinediol (0.5 g.) was heated in a solution of 0.3 g. of potassium hydroxide in 10 ml. of diethylene glycol at 200° for 6 hours. After dilution with 25 ml. of water, the solution was extracted thoroughly with chloroform. The chloroform was washed with water, dried over sodium sulfate and concentrated to dryness. The residue remaining was converted to the crystalline hydrochloride and to the base XVI as described above, yield 0.2 g., m.p. 219–220°.

(c) A mixture of 1 g. of reserpinediol and 1 g. of sodium acetate in 10 ml. of acetic anhydride was refluxed for 6 hours. Half the acetic anhydride was distilled off and the remainder hydrolyzed with ice-water. Addition of ammonium hydroxide yielded a dark brown gum which partly recrystallized on dissolving in hot ethanol. The highly insoluble **N-acetyl 3-iso-reserpinediol diacetate** was recrystallized from acetone–water to give 0.15 g. of fine needles, m.p. 223–226°.

Anal. Calcd. for $C_{28}H_{36}N_2O_7$: C, 65.61; H, 7.08. Found: C, 65.26; H, 7.19.

The infrared absorption spectrum in Nujol mull showed an amide carbonyl at 1694 cm.$^{-1}$ as well as an ester carbonyl at 1731 cm.$^{-1}$.

Fifty milligrams of triacetate was refluxed for 2 hours in 10 ml. of methanol containing 100 mg. of potassium hydroxide. Most of the methanol was evaporated, the solution diluted with water and the crystalline XVI collected. After recrystallization from ethanol–water followed by a recrystallization from acetone–water it melted at 218–220°.

3-Iso reserpinediol (XVI) from Methyl 3-Iso-reserpate Acetate (XIV).—A solution of 1.5 g. of XIV in 100 ml. of absolute tetrahydrofuran was added with stirring to a solution of 1.5 g. of lithium aluminum hydride in 50 ml. of absolute ether held at room temperature. After refluxing for 2 hours, the excess reagent was destroyed by the careful addition of ethyl acetate. With vigorous stirring 5 ml. of water was added. The inorganic salts were filtered, washed copiously with acetone and the filtrate concentrated to dryness *in vacuo*. From the crude gummy base, a crystalline hydrochloride (1.5 g.) was prepared, which was in turn converted to the crystalline base as described above, m.p. 220–222°.

Tetradehydroreserpinediol (XIX) Hydrochloride.—To a solution of 0.5 g. of reserpinediol in 10 ml. of acetic acid held at 35–40° was added dropwise 54 ml. of 0.0509 *M* lead tetraacetate in the manner previously described. After 30 minutes, most of the acetic acid was removed by distillation *in vacuo*. Chloroform and a small amount of water was added and the mixture carefully basified with 50% aqueous sodium hydroxide. The chloroform extract was washed with a small amount of water, dried over sodium sulfate and acidified by the careful addition of 8 *N* ethanolic hydrogen chloride. Evaporation to dryness gave a gummy residue which crystallized on rubbing with alcohol. It was dissolved in hot water and a few drops of concentrated hydrochloric acid added. On cooling 0.25 g. of XIX hydrochloride separated in fine, light yellow needles, m.p. 280–282° dec. In solution XIX exhibited an intense yellow-green fluorescence. The ultraviolet absorption spectrum was virtually identical to that of py-methylharmine hydrochloride, a typical anhydronium compound. It exhibited maxima at 251–252 mμ (log ε 4.52) and 325 mμ (log ε 4.33) and minima at 226–227 mμ (log ε 4.13) and 283 mμ (log ε 3.30). The infrared spectrum in a Nujol mull showed no indication of a band in the carbonyl region.

Anal. Calcd. for $C_{22}H_{27}ClN_2O_4 \cdot {}^1/_3H_2O$: C, 62.16; H, 6.54; N, 6.59. Found: C, 62.07; H, 6.63; N, 6.59.

The hydrochloride was converted to the base XIX by the addition of sodium hydroxide to its hot aqueous solution. After recrystallization from ethanol, light yellow needles were obtained, m.p. 280–282° dec.

3-Iso-reserpinediol (XVI) from XIX.—To 50 mg. of XIX dissolved in 10 ml. of methanol was added 100 mg. of sodium borohydride. After refluxing for 30 minutes most of the solvent was distilled off. Water was added and distillation continued until crystallization of the diol XVI was complete. It was filtered off and recrystallized from ethanol-water, m.p. 219–220°. The m.p. of a mixture with a sample prepared by direct isomerization of reserpinediol was undepressed. The infrared spectra of the two samples were indistinguishable.

3-Iso-reserpinol (XVII).—One gram of reserpinol was refluxed for 18 hours in 30 ml. of collidine containing 0.15 g. of *p*-toluenesulfonic acid. The mixture was washed with dilute ammonium hydroxide and the collidine distilled off *in vacuo*. The residue was dissolved in 10 ml. of ethanol and acidified with 8 *N* ethanolic hydrogen chloride causing the crystallization of 0.7 g. of XVII hydrochloride. This was converted to the amorphous base by the addition of ammonium hydroxide to its aqueous solution. XVII crystallized from acetone–water in plates, m.p. 191–192°.

Anal. Calcd. for $C_{22}H_{30}N_2O_3 \cdot {}^1/_3H_2O$: C, 70.16; H, 8.21. Found: C, 70.38; H, 8.03.

The acetate, prepared as a characteristic derivative by reaction with acetic anhydride–pyridine at room temperature, melted at 178–179° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82. Found: C, 69.60; H, 7.87.

Methyl 3-Iso-reserpate Tosylate.—To a cooled solution of 1.6 g. of methyl 3-iso-reserpate (XV) in 15 ml. of pyridine was added 3.5 g. of *p*-toluenesulfonyl chloride. After standing overnight, ice was added to the mixture and the voluminous precipitate of fine needles was filtered and washed with water. It was suspended in 50 ml. of chloroform and shaken during the careful addition of 1 *N* sodium hydroxide. The solid gradually dissolved in chloroform. The chloroform was washed with water, dried over sodium sulfate and concentrated to dryness *in vacuo* leaving the crystalline tosylate as a residue. Recrystallization from acetone–water yielded methyl 3-iso-reserpate tosylate as fine, hair-like needles, yield 1.4 g., m.p. 229–230°, $[\alpha]^{21}D$ −58° (chloroform).

Anal. Calcd. for $C_{30}H_{36}N_2O_7S \cdot {}^1/_2H_2O$: C, 62.31; H, 6.46; N, 4.85; S, 5.54. Found: C, 62.07; H, 6.55; N, 4.91; S, 5.63.

3-Iso-reserpinol (XVII) from Methyl 3-Iso-reserpate Tosylate.—A solution of 0.5 g. of methyl 3-iso-reserpate tosylate in 50 ml. of anhydrous tetrahydrofuran was added dropwise to a solution of 0.5 g. of lithium aluminum hydride in anhydrous ether. After refluxing for 2 hours, the excess reagent was destroyed with ethyl acetate. After the addition of 10 ml. of water, most of the solvent mixture was distilled off *in vacuo*. An additional 10 ml. of water was added and the suspension thoroughly extracted with chloroform. Removal of the chloroform gave a gummy residue which was converted into 300 mg. of crude XVII *via* the crystalline hydrochloride. This was acetylated with acetic anhydride–pyridine to yield the **acetate.** On recrystallization it melted at 177–178° and the m.p. of the mixture with a sample prepared by direct isomerization of reserpinol was undepressed. The infrared spectra of the two samples in a Nujol mull were identical.

3-Iso-reserpine (XVIII).—(a) Five grams of reserpine was refluxed in 50 ml. of acetic anhydride for 18 hours. About 40 ml. was distilled *in vacuo* and the remainder decomposed by the addition of ice. Ammonia was added and the crude base extracted with chloroform. The dark sirupy

residue remaining after removal of the chloroform was dissolved in about 5 ml. of ethanol and carefully acidified with 5 *N* aqueous nitric acid. 3-Iso-reserpine (XVIII) soon separated as the crystalline nitrate. This was filtered, washed with ethanol and converted to the base by shaking with chloroform in the presence of excess 1 *N* aqueous sodium hydroxide. The chloroform solution was washed with water, dried over sodium sulfate and the solvent evaporated. The light yellow sirupy residue crystallized on scratching in the presence of a few ml. of ethanol. The solid was filtered and recrystallized from ethanol–water to yield 1 g. of XVIII, m.p. 150–155° with frothing, $[\alpha]^{24}D$ −164° (chloroform). It is readily distinguishable from reserpine by its low melting point and high solubility in acetone. Similarly, refluxing 1 g. of reserpine in acetic acid for 3 days gave 0.6 g. of XVIII.

Anal. Calcd. for $C_{33}H_{40}N_2O_9 \cdot {}^1/_3H_2O$: C, 64.73; H, 6.69; N, 4.56. Found: C, 64.65; H, 6.35; N, 4.81.

(b) A solution of 0.5 g. of methyl 3-iso-reserpate (XV) and 1.5 g. of 3,4,5-trimethoxybenzoyl chloride in 15 ml. of pyridine was allowed to stand 5 days in the ice-box. Three-quarters of the pyridine was distilled off *in vacuo*, water was added and the mixture was made alkaline with dilute sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was washed with dilute hydrochloric acid, dilute sodium hydroxide and water. The solvent was removed *in vacuo* and the residue dissolved in a small volume of ethanol. It was made acid with 8 *N* ethanolic hydrogen chloride, a large volume of ether was added to precipitate the alkaloid salts which were suspended in chloroform and converted to the base by shaking with dilute ammonia. The residue remaining after removal of the chloroform was taken up in a small volume of ethanol and acidified with 5 *N* nitric acid. The crystalline XVIII nitrate was collected, converted to the base and recrystallized from ethanol–water as described above, yielding 90 mg., m.p. 152–156°. The m.p. of the mixture with a sample prepared by the direct isomerization of reserpine was unchanged.

3-Iso-reserpinediol (XVI) Diacetate from 3-Iso-reserpine (XVIII).—A solution of 200 mg. of XVIII in 20 ml. of tetrahydrofuran was added dropwise to 500 mg. of lithium aluminum hydride in 20 ml. of ether. After refluxing for 1 hour, the excess reagent was destroyed with ethyl acetate and the mixture made acid by the addition of hydrochloric acid. The solvents were distilled almost to dryness and 25 ml. of 0.5 *N* hydrochloric acid added. The solution was extracted with benzene and the residue remaining after removal of the solvent was esterified with 3,5-dinitrobenzoyl chloride in pyridine to yield 3,4,5-trimethoxybenzyl 3,5-dinitrobenzoate, m.p. 144–145°, after recrystallization from acetone–ethanol.

Anal. Calcd. for $C_{17}H_{16}N_2O_9$: N, 7.14. Found: N, 7.55.

The acid extract left after benzene extraction was made basic with a sodium carbonate solution and extracted with chloroform. The crude XVI remaining after removal of the chloroform was acetylated with acetic anhydride–pyridine. The XVI diacetate obtained melted 213–214° and the m.p. of a mixture with a sample prepared by the direct isomerization of reserpinediol showed no depression.

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.04; N, 6.06.

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Cyclitols. III. Some Tosyl Esters of Inositols. Synthesis of a New Inositol[1,2]

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Two anhydro-inositols (III and IX) have been prepared from partially tosylated inositol derivatives. Acid hydrolysis gave, in one case, a new methyl ether of (−)-inositol, in the other case the new 1,2,3/4,5,6-inositol for which the name *neo*-inositol is proposed.

Tosyl esters have been of manifold use in carbohydrate chemistry.[5] In particular, their reaction with alkalies to give epoxides, and the subsequent opening of the epoxide ring with Walden inversion, has been useful in the interconversion of sugars. Similar reactions have not been applied so far in cyclitol chemistry as the required partially tosylated derivatives were not known. The easy preparation of isopropylidene cyclitols[6] placed in our hand intermediates from which various mono- and ditosyl inositols could be synthesized and their reactions investigated. This paper reports on two cases of epoxide formation; other reactions, *e.g.*, one with sodium iodide, will be described in a subsequent communication.

The readily available diisopropylidenepinitol[6,7] (I) served as the first starting material. Tosylation gave the monotosyl compound from which, by removal of the isopropylidene groups, 3-*O*-methyl-4-*O*-tosyl-(+)-inositol (II) was produced. When this compound, or preferably its tetraacetate, was treated with sodium methoxide at room temperature, it lost the tosyl group and gave the 1-*O*-methyl ether of 2,3-anhydro-*allo*-inositol which was isolated as its triacetate III. This epoxide III was hydrolyzed by hot dilute sulfuric acid giving approximately equal amounts of the two possible products, pinitol (IV) and 1-methyl-(−)-inositol (V), isolated as their pentaacetates. The properties of these two methyl ethers are so similar that separation could only be achieved by handpicking of their well-developed crystals. All these reactions proceeded in good yield.

Demethylation of V confirmed that it was a derivative of (−)-inositol. The whole series of reactions therefore constitutes an inversion of (+)- into (−)-inositol. Since the structure of pinitol has been proved rigidly[8] the structure of V is also established. (+)- and (−)-inositols have a twofold simple axis of symmetry: each therefore can give rise to only three different monomethyl ethers. The fact that V is neither identical nor enantiomorphous with quebrachitol serves as additional proof

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