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

Rauwolfia Alkaloids. XXXVII. Methyl *neo*-Reserpate, An Isomer of Methyl Reserpate[1]

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Received February 16, 1961

Extended treatment of methyl reserpate with refluxing methanolic sodium methoxide resulted in its conversion to an isomer, methyl *neo*-reserpate. The structure and stereochemistry of methyl *neo*-reserpate have been determined, and a mechanism for its formation is proposed. The derived structure (II) is consistent with all the chemical facts and with the conformational requirements of the molecule.

The conversion of reserpine to methyl reserpate (I) is well known.[2] The trimethoxybenzoate ester at C-18 was cleaved selectively by subjecting reserpine to methanolysis conditions. As methyl reserpate can be converted back to reserpine by esterification with trimethoxybenzoyl chloride, it is clearly identical with reserpine at all six optically active centers. The stereochemistry of reserpine, and therefore also of methyl reserpate, has been rigorously established by degradation,[3] chemical conversions,[3] and synthesis.[4]

While studying the methanolysis of reserpine to methyl reserpate, we found that the residues from crystallization of methyl reserpate always had optical rotations which had been shifted in the positive direction. When methyl reserpate itself was subjected to extended methanolysis (in refluxing methanol containing sodium methoxide), its optical rotation was also shifted toward the positive (see Table I).

The material recovered after refluxing for sixty-four hours was chromatographed on alumina, rechromatographed on Florisil, and crystallized several times from isopropyl alcohol to give a pure compound. The isomeric nature of this material, which we have called methyl *neo*-reserpate, was demonstrated by isolation of several solvates as well as the anhydrous compound, and by formation of the hydrochloride, methiodide, picrate, *p*-toluenesulfonate, and *p*-bromobenzenesulfonate derivatives. The ultraviolet absorption spectrum and pK_a value of methyl *neo*-reserpate were essentially the same as those of methyl reserpate (I), suggesting that no fundamental change had occurred in the indole ring system or in the vicinity of N_b (tertiary nitrogen of ring C). Studies on the structure and stereochemistry, described below, have established structure II for methyl *neo*-reserpate. Structure II differs from structure I only in the stereochemistry at carbon atoms 16 and 17.

TABLE I

OPTICAL ROTATION OF PRODUCT FROM TREATMENT OF METHYL RESERPATE WITH SODIUM METHOXIDE IN METHANOL

Reflux Time	$[\alpha]_D$ ($CHCl_3$)
0	−108°
4 Hr.	−72°
21 Hr.	+12°
64 Hr.	+32°
14 Days	+46°

A considerable amount of structural information was obtained by the comparison of the products from treatment of methyl reserpate tosylate and methyl *neo*-reserpate tosylate (V) with refluxing collidine. In the case of methyl reserpate tosylate,[3] the major product isolated (28%) resulted from internal quaternization of N_b with C-18. As direct displacement of the 18β-tosylate is sterically impossible, it has been assumed that the 17α-methoxyl group participates first in the elimination of the 18β-tosylate, and then in the attack of N_b. Two other products were isolated. A small amount of 17,18-unsaturated material (<1%) was isolated[5] which resulted from the elimination of *p*-toluenesulfonic acid toward C-17. It was assumed[3] that this compound isomerized under the reaction conditions to the second major product (13.5%), methyl anhydroreserpate (VII).

With methyl *neo*-reserpate tosylate (V), no quaternary salt was formed. This suggests that the 18-tosylate of methyl *neo*-reserpate tosylate is still β-oriented, because an α-tosylate would be displaced readily. It further suggests that since the 17-methoxyl group was not able to assist the quaternization, it is probably β-oriented also. The minor product (1.8%) was methyl anhydroreserpate (VII). Although it was formed in low yield,

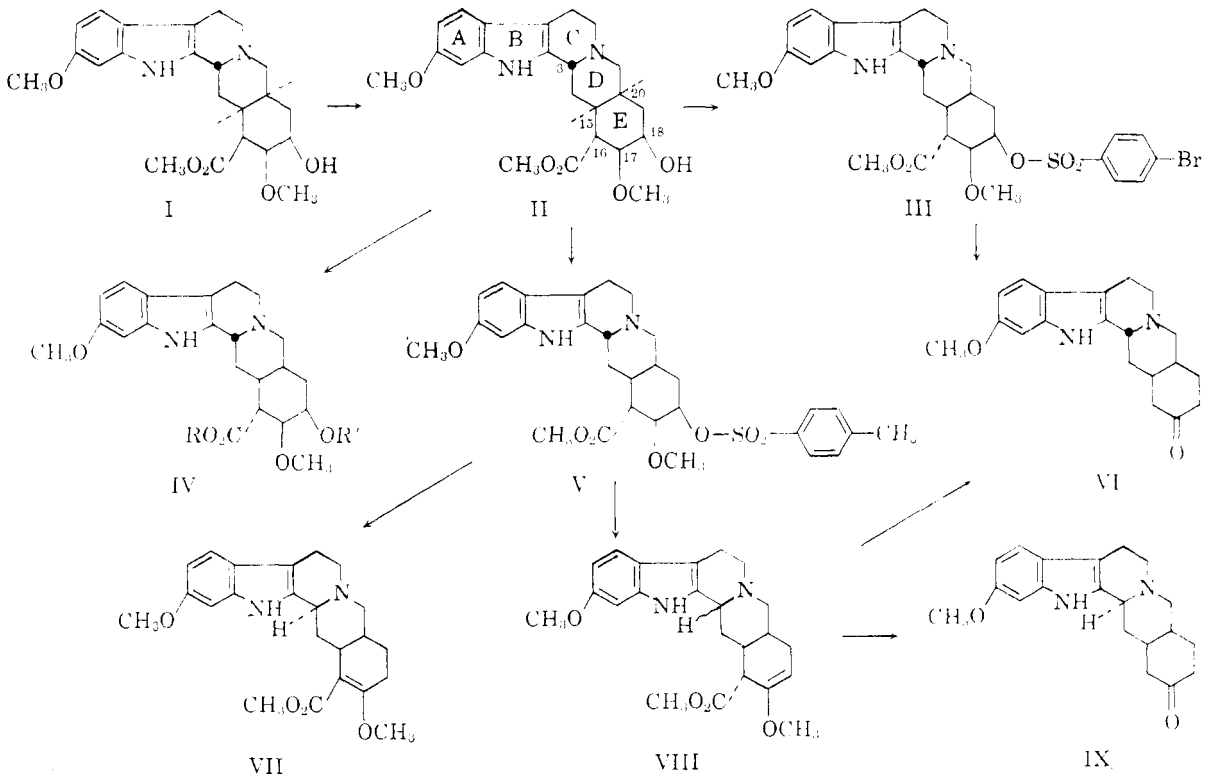
(1) Presented at the 138th Meeting, American Chemical Society, New York, N. Y., September 1960.

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

(3) P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Huebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. MacPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schlittler, A. F. St. André, E. E. van Tamelen, F. L. Weisenborn, E. Wenkert, and O. Wintersteiner, *J. Am. Chem. Soc.*, **81**, 2481 (1959), and references cited therein.

(4) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(5) H. B. MacPhillam *et al.*, unpublished work.



its isolation proved three things: that methyl *neo*-reserpate and methyl reserpate have the same 5-ring skeleton; that methyl *neo*-reserpate has retained the *cis*-junction between rings D and E; and that the positions of attachment of the functional groups on ring E are unchanged from those of methyl reserpate.

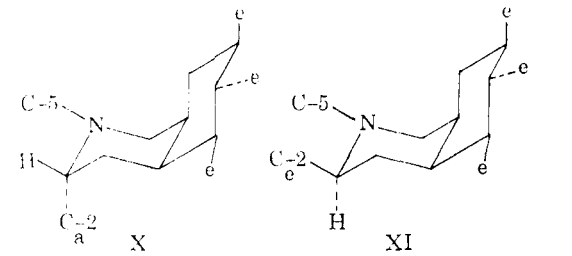
The major product (75%) from the collidine reflux was an isomer of methyl anhydroreserpate (VII) in which the double bond was *not* conjugated with the carbomethoxyl but was conjugated only with the methoxyl group: ν_{max}^{Nujol} 1748 cm.$^{-1}$ (s), 1688 cm.$^{-1}$ (m). This product was different from the known[5] (17,18-unsaturated) isomer of methyl anhydroreserpate isolated from methyl reserpate tosylate. The difference between the two 17,18-unsaturated compounds can only be at C-3 and/or C-16. They cannot differ *only* at C-3 because refluxing collidine containing *p*-toluenesulfonic acid permits C-3 to take the more stable configuration. As the two 17,18-unsaturated isomers differed at C-16, the isomer from methyl reserpate tosylate must have the 16β-configuration and the isomer from methyl *neo*-reserpate tosylate must have the 16α-configuration (VIII). The formation of VIII in high yield supports the 17β, 18β assignments, since ready elimination of *p*-toluenesulfonic acid is best explained as a *trans* diaxial elimination. From the amounts of VII and VIII isolated, it is evident that the double bond at 17,18 was *not* isomerized to the 16,17-position under the reaction conditions, as had been supposed[3] for the methyl reserpate series. In fact, the double bond of VIII was not isomerized to the 16,17-position with either acid or base.[6]

Consistent with the 16α assignment was the inability of the carbon on C-16 to interact with N_b after lithium aluminum hydride reduction of methyl *neo*-reserpate tosylate (V) and treatment of the resulting 16-hydroxymethylene compound with tosyl chloride in pyridine, an interaction that went readily[3] in the methyl reserpate series. Furthermore, the *trans*-relation of groups on C-16 and C-18 was supported by the inability of *neo*-reserpic acid (IV, R = R′ = H) to form a lactone under conditions used successfully with reserpic acid and 3-*iso*-reserpic acid: acetic anhydride–pyridine,[2] acetic anhydride–acetic acid,[3] and *N,N′*-dicyclohexylcarbodiimide–pyridine.[4] An attempt to form a lactone from methyl *neo*-reserpate using aluminum isopropoxide in refluxing xylene, conditions which had given a 91% yield of lactone with methyl reserpate,[4] gave back starting methyl *neo*-reserpate.

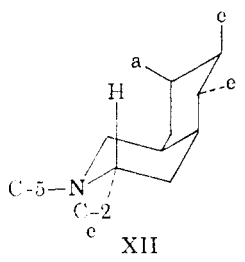
Compound VIII was hydrolyzed to the same two ketones (VI and IX), epimeric at C-3, which had previously been isolated[7] from methyl anhydroreserpate (VII).

(6) The greater stability of the double bond at 17,18 as compared with 16,17 is of interest. One would expect the double bond to be more stable at 16,17 not only because of conjugation with the 16-ester group, but also because *cis*-1-octalin is considered to be more stable than *cis*-2-octalin [*cf.* D. A. H. Taylor, *Chem. & Ind.*, 250 (1954)].

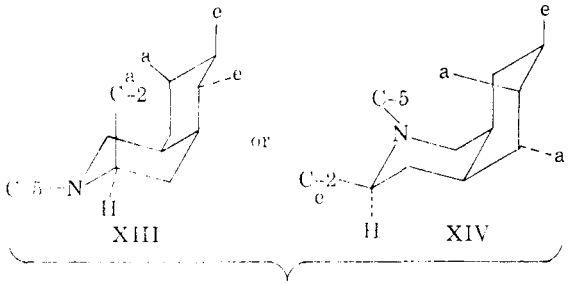
(7) C. F. Huebner, A. F. St. André, E. Schlittler, and A. Uffer, *J. Am. Chem. Soc.*, **77**, 5725 (1955).



Methyl reserpate Methyl 3-*iso*-reserpate



Methyl *neo*-reserpate



Methyl 3-*iso*-*neo*-reserpate

Formation of ketones VI and IX confirms the conclusions on the skeleton and the location of functional groups of methyl *neo*-reserpate—*i.e.*, that they are identical with those of methyl reserpate.

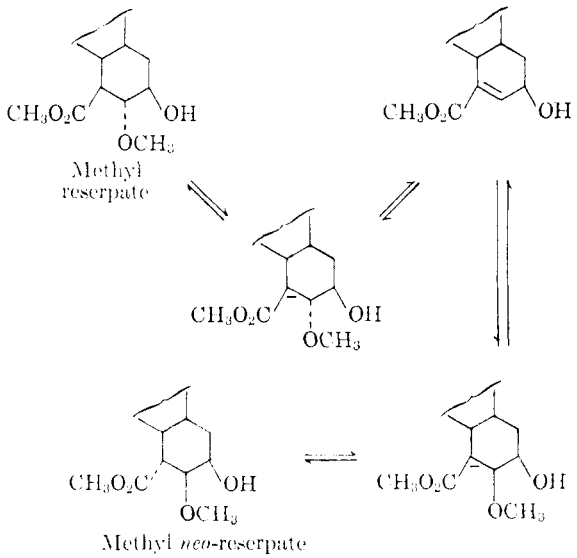
Sodium methoxide in refluxing methanol would not be expected to affect the hydrogen on C-3. When methyl *neo*-reserpate brosylate (III) was refluxed in aqueous dioxane containing triethylamine, debrosylation and hydrolysis took place. Treatment with aqueous acid then gave 3-epiallo-reserpone (VI). Isolation of VI, uncontaminated by its C-3 isomer IX, proved the β-orientation of the C-3 hydrogen.

When methyl *neo*-reserpate (II) was refluxed in collidine in the presence of *p*-toluenesulfonic acid, conditions which isomerized methyl reserpate to methyl 3-*iso*-reserpate,[8] II was recovered unchanged in 70–75% yield. Methyl *neo*-reserpate, therefore, unlike methyl reserpate, is more stable with a C-3β than with a C-3α hydrogen. Consideration of the stable chair conformations of the possible compounds explains these orders of stability.

Methyl reserpate in its all-chair conformation (partial formula X) can have either all substituents in ring E equatorial, or C-2 (which is part of ring B) equatorial, but not both. Methyl 3-*iso*-reserpate (partial formula XI), on the other hand, *can* have C-2 and the substituents on ring E all in the stable equatorial conformation at the same time. Methyl reserpate can therefore be epimerized in high yield at C-3 to methyl 3-*iso*-reserpate.

Methyl *neo*-reserpate has C-2 and two of the three substituents on ring E equatorial (partial formula XII). An axial 18-hydroxyl group is consistent with the ready elimination (presumably *trans* diaxial) of the tosylate and the brosylate groups from compounds V and III, and with the greater difficulty of esterification of methyl *neo*-reserpate. The tendency of methyl *neo*-reserpate to form stable solvates with hydroxylic solvents may involve bonding of the solvent with both the axial hydroxyl and N_b simultaneously. The epimer of methyl *neo*-reserpate having the 3α-hydrogen would necessarily have two of the four groups axial (partial formulas XIII and XIV). Methyl *neo*-reserpate, therefore, does not epimerize appreciably to its 3-isomer.

The driving force for the formation of methyl *neo*-reserpate (II) from methyl reserpate (I) is essentially the same as that for the formation of methyl 3-*iso*-reserpate. Methyl reserpate in its chair conformation must assume either an axial C-2 or an axial orientation of the three groups on ring E. Formation of the 3-*iso* compound relieves strain by changing 3-epiallo (3βH) to 3-allo (3αH). In refluxing methanol containing sodium methoxide, where conditions do not permit C-3 isomerization, the instability of methyl reserpate is relieved by changing the orientation of two of the three groups on ring E. We interpret this conversion as proceeding through a reverse Michael addition, to form the apoyohimbine-type compound shown below, followed by Michael addition of methanol to give methyl *neo*-reserpate. This sequence is an extension



Methyl *neo*-reserpate

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

of the work of Godtfredsen and Vangedal[9] who carried out a Michael addition on apoyohimbine and isolated, similarly, the 16α-carbomethoxy, 17β-methoxy derivative.

The 3′,4′,5′-trimethoxybenzoyl and 4′-(ethoxycarbonyloxy)-3′,5′-dimethoxybenzoyl esters of methyl *neo*-reserpate (IV, R = CH_3, R′ = CO—Ar) were prepared as analogs of reserpine and syrosingopine, respectively, which are active hypotensive agents. The esters of methyl *neo*-reserpate had no hypotensive activity, showing once again the highly specific spatial requirements for functional groups of biologically active compounds.

EXPERIMENTAL[10]

Methyl neo-reserpate (II) *from methyl reserpate* (I). A mixture of 17.5 g. of sodium methoxide and 100.0 g. of methyl reserpate in 1465 ml. of anhydrous methanol was stirred and refluxed for 64 hr. under a drying tube. The cooled solution was diluted with 1465 ml. of water, containing 53 g. of sodium chloride, and extracted with three 735-ml. portions of methylene chloride. The extracts were combined, washed with water and aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The filtered methylene chloride solution was worked up in two different ways: (a) Original isolation: the methylene chloride solution was stripped to dryness, leaving 74.4 g. of brown powder, m.p. 132–175°, $[\alpha]_D$ +31.6°.

Anal. Calcd. for $C_{23}H_{30}N_2O_5 \cdot H_2O$ (432.53): C, 63.87; H, 7.46; N, 6.48. Found: C, 63.04; H, 6.95; N, 6.33.

Fifty grams of this brown powder was chromatographed on 2.5 kg. of neutral alumina (activity grade II) in a column 2.5 × 42 inches. Elution with benzene containing 5% methanol gave 23.4 g. of solid, $[\alpha]_D$ +53°. The material was decolorized by passing it through a column of 410 g. of Florisil in a methylene chloride-acetone (1:1) solution. Removal of solvent left a yellow crystalline powder, which was crystallized twice from isopropyl alcohol to give 11.5 g. (15% yield from I) of the monosolvate of II, m.p. 148–152°, $[\alpha]_D$ +51.9°. The solvent was not removed by vacuum drying at 110° and 0.5 mm. for 20 hr.

Anal. Calcd. for $C_{23}H_{30}N_2O_5 \cdot C_3H_8O$(474.61): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.75; H, 8.10; N, 6.04.

(b) Subsequent workups: The methylene chloride solution was concentrated to 350 ml., seeded, and chilled overnight at 5°. The white powder was collected and dried, giving 27.0 g. of crude II, m.p. 140–147°. Crystallization from isopropyl alcohol gave 22.2 g. (20.7% from I) of white crystalline II isopropanolate, m.p. 146–150°, resolidifying and remelting 227–228° dec., $[\alpha]_D$ +52.7°.

Anal. Found: C, 65.80; H, 7.76; N, 6.15.

From the methylene chloride mother liquors, by workup as described in (a) above, an additional 7.6% of II isopropanolate was isolated, bringing the total recovery from I to 28.3%.

Crystallization of II isopropanolate from ethanol gave II ethanolate (which also would not desolvate under the drying conditions described in (a) above), m.p. 156–160°, $[\alpha]_D$ +56.2°.

Anal. Calcd. for $C_{23}H_{30}N_2O_5 \cdot C_2H_5OH$ (460.58): C, 65.20; H, 7.88; N, 6.08. Found: C, 65.27; H, 7.33; N, 6.36.

Crystallization of II isopropanolate from methanol gave II methanolate, m.p. 224–225° dec., $[\alpha]_D$ +55.8°, λ_{max}^{alc} 226–228 mμ (ε 38,080), 267–272 mμ (ε 4,860), 297 mμ (ε 6,290).

Anal. Calcd. for $C_{23}H_{30}N_2O_5 \cdot CH_3OH$ (446.55): C, 64.55; H, 7.68; N, 6.27. Found: C, 64.86; H, 7.80; N, 6.16.

Vigorous drying conditions (110°, 0.5 mm., 20 hr.) on II methanolate gave anhydrous II, m.p. 156–160°, $[\alpha]_D$ +57.8° λ_{max}^{alc} 226–227 mμ (ε 36,680), 268–271 mμ (ε 4,740), 297–298 mμ (ε 6, 110), pK_a 7.24 (40% methanol), 7.42 (80% Methyl Cellosolve); equivalent weight by electrometric titration, 415.67.

Anal. Calcd. for $C_{23}H_{30}N_2O_5$ (414.51): C, 66.65; H, 7.30; N, 6.76; CH_3O, 22.46. Found: C, 66.39; H, 7.55; N, 6.44; CH_3O, 22.30.

Methyl neo-reserpate hydrochloride. A suspension of 0.50 g. of II isopropanolate in 10 ml. of methanol was treated with gaseous hydrogen chloride at 5–10° for 25 min. Dilution of the methanol with 100 ml. of ether precipitated white crystals, which were collected, washed with ether and dried, giving 0.43 g. (90.5%) of product, m.p. 281–283° dec., $[\alpha]_D$ +7.1° (chloroform-methanol 4:1).

Anal. Calcd. for $C_{23}H_{31}N_2O_5Cl$ (450.97): C, 61.26; H, 6.93; N, 6.21; Cl, 7.86. Found: C, 61.10, H, 7.10; N, 5.92; Cl, 7.81.

The monohydrate had m.p. 274–276° dec., $[\alpha]_D$ +3.3° (chloroform-methanol 4:1). *Anal.* Calcd. for $C_{23}H_{31}N_2O_5Cl \cdot H_2O$ (468.99): C, 58.90; H, 7.09; N, 5.97. Found: C, 58.82; H, 7.09, N, 5.97.

Methyl neo-reserpate methiodide. A solution of 0.50 g. of II isopropanolate in 10 ml. of acetone was treated with 0.5 ml. of methyl iodide and allowed to stand overnight at room temperature in the dark. The white precipitate was collected, washed, and dried, giving 0.55 g. (95.3%) of product, m.p. 280–283° dec. One crystallization from 95% ethanol gave 0.44 g. of product, m.p. 283.5–285° dec., $[\alpha]_D$ −55.9° (pyridine).

Anal. Calcd. for $C_{24}H_{33}N_2O_5I \cdot 1/2\ H_2O$ (556.45): C, 50.98; H, 6.06; N, 4.95; I, 22.45. Found: C, 50.78; H, 6.15; N, 4.61; I, 22.09.

Methyl neo-reserpate picrate. A solution of 0.50 g. of II isopropanolate in 15 ml. of 95% ethanol was diluted with 10 ml. of a saturated picric acid in 95% ethanol solution. After being refluxed for 5 min., the solution was concentrated to half volume and chilled at 5° overnight, giving 0.67 g. of yellow-orange crystals, m.p. 160–165° dec. Two crystallizations from 95% ethanol followed by one recrystallization from methanol gave 0.31 g. of yellow crystals, m.p. 235–237° dec., $[\alpha]_D$ +26.7° (chloroform-methanol 4:1).

Anal. Calcd. for $C_{29}H_{33}N_5O_{12}$ (643.62): C, 54.12; H, 5.17; N, 10.88. Found: C, 54.61; H, 5.38; N, 10.01.

A spectrophotometric determination of the molecular weight[11] gave 639.76.

Methyl neo-reserpate 18-O-(3′,4′,5′-trimethoxybenzoate). A mixture of 2.0 g. of II isopropanolate in 100 ml. of dry pyridine was treated with 6.0 g. of 3,4,5-trimethoxybenzoyl chloride and then refluxed for 3 hr. in a moisture-free atmosphere. The cooled suspension was filtered and the white solid was washed with methylene chloride and dried, giving 2.73 g. of methyl *neo*-reserpate trimethoxybenzoate hydrochloride, m.p. 256–257.5°. The crude hydrochloride was suspended in 41 ml. of methanol, ammonium hydroxide was added (to *p*H 8), the solution was decolorized with activated charcoal, and the filtered solution was diluted with 200 ml. of water. The white precipitate was collected, washed with water, and dried, giving 1.88 g. (71.3%) of crude product. One crystallization from benzene-isopropyl alcohol, followed by precipitation from a methanol solution with water, gave 1.05 g. of product, m.p. 163–170°, $[\alpha]_D$ +28.9°.

Anal. Calcd. for $C_{33}H_{40}N_2O_9 \cdot 1/2H_2O$ (617.71): C, 64.17; H, 6.69; N, 4.53. Found: C, 64.25; H, 6.72; N, 4.67.

(9) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **11**, 1013 (1957).

(10) Optical rotations were taken in chloroform solution at 25–28° unless otherwise specified. Melting points were determined in an electrically heated aluminum block and are uncorrected. Most of the alkaloids either darkened or decomposed at their melting point. Analytical samples were routinely dried in vacuum at 75° for 3–5 hr.

(11) K. G. Cunningham, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

The monohydrate[12] had m.p. 163–169°, $[\alpha]_D$ +21.2°.

Anal. Calcd. for $C_{33}H_{40}N_2O_9 \cdot H_2O$(626.72): C, 63.24; H, 6.76; N, 4.47. Found: C, 63.24; H, 6.67; N, 4.04.

Methyl neo-reserpate 18-O-(4′-ethoxycarbonyloxy-3′,5′-dimethoxybenzoate). A solution of 6.95 g. of 4-ethoxylcarbonyloxy-3,5-dimethoxybenzoyl chloride (m.p. 74–75°, prepared by reaction of the corresponding acid, m.p. 181–183°, with thionyl chloride) in 35 ml. of dry pyridine was added to a solution of 2.0 g. of methyl *neo*-reserpate isopropanolate in 25 ml. of dry pyridine, and the mixture was allowed to stand overnight at room temperature in the dark. The yellow precipitate was collected, washed with methylene chloride, slurried with hot methanol, and dried, giving 1.59 g. of methyl *neo*-reserpate 4′-ethoxycarbonyloxy-3′,5′-dimethoxybenzoate hydrochloride, m.p. 263–265°. The hydrochloride was dissolved in 16 ml. of acetone by addition of triethylamine, the solution was diluted with 16 ml. of methanol, and the free base was precipitated by addition of 200 ml. of water. The white powder was collected, washed with water and dried, giving 1.41 g. of product, m.p. 155–163°, $[\alpha]_D$ +18.6°.

Anal. Calcd. for $C_{35}H_{42}N_2O_{11}$ (666.74): C, 63.05; H, 6.35; N, 4.20. Found: C, 62.84; H, 6.54; N, 4.41.

neo-Reserpic acid hydrochloride (IV·HCl, R = R′ = H). A solution of 5.00 g. of II isopropanolate in 300 ml. of methanol containing 20.0 g. of potassium hydroxide was refluxed under nitrogen for 3.5 hr. The methanol was removed at 40° at reduced pressure, and the residue was taken up in 100 ml. of water and washed four times with 50-ml. portions of chloroform. The aqueous solution was stripped to dryness (40°, reduced pressure) and the residue was taken up in 90 ml. of methanol and acidified with 7*N* hydrochloric acid. The precipitated potassium chloride was removed by filtration and rinsed with 40 ml. of chloroform-methanol (4:1). The combined filtrates were taken to dryness at reduced pressure, the residue was taken up in 200 ml. of chloroform-methanol (4:3), insoluble potassium chloride was removed by filtration and the filtrate was taken to dryness once again. The crude product residue was dissolved in methanol, decolorized with activated charcoal, and diluted dropwise with 500 ml. of anhydrous ether. The precipitated solid was reprecipitated from methanol-ether in the same way, giving 3.47 g. (65.8%) of a light yellow granular solid, m.p. 237–242° dec., $[\alpha]_D$ +54.5° (methanol).

Anal. Calcd. for $C_{22}H_{28}N_2O_5 \cdot HCl \cdot H_2O$ (454.96): C, 58.08; H, 6.87, N, 6.16. Found: C, 57.97; H, 6.61; N, 5.89.

Methyl neo-reserpate p-toluenesulfonate (V). A solution of 20.0 g. (0.0422 mole) of methyl *neo*-reserpate isopropyl alcohol solvate in 200 ml. of dry pyridine was stirred and cooled in an ice bath, and 32.3 g. (0.170 mole) of *p*-toluenesulfonyl chloride was added portionwise over 20 min., keeping the temperature below 15°. The red solution was allowed to stand at room temperature for 3 days, poured onto 600 ml. of ice water, and extracted five times with 100-ml. portions of methylene chloride. The combined, dark extracts were washed once with 5% aqueous sodium hydroxide and twice with water, dried over anhydrous sodium sulfate, filtered, and stripped to dryness at reduced pressure. The dark red residue was thoroughly slurried with 50 ml. of benzene, and then washed three more times with benzene, and dried, giving 15.79 g. (65.8%) of off-white solid, m.p. 223–225° dec. This material was homogeneous by paper chromatography, and was suitable for subsequent reactions.

An analytical sample was prepared by crystallization from methylene chloride-benzene followed by recrystallization from acetone-benzene. The white prisms, which had the same melting point, developed a pale yellow color on exposure to light; $[\alpha]_D$ + 10.1°.

Anal. Calcd. for $C_{30}H_{36}N_2O_7S$ (568.66); C, 63.36; H, 6.38; N, 4.93; S, 5.64. Found: C, 63.61; H, 6.57; N, 4.88; S, 5.83.

Preparation of VIII *and methyl anhydroreserpate* (VII) *from methyl neo-reserpate p*-toluenesulfonate (V). A suspension of 9.8 g. of methyl *neo*-reserpate tosylate (V) in 80 ml. of 2,4,6-collidine was stirred and refluxed (the vapor temperature was allowed to climb to 169–170° by boiling before refluxing was begun) for 3 hr. (complete solution after 2 hr.). No solids separated after cooling to room temperature or after chilling overnight at 5°. The collidine was removed at reduced pressure as a water-collidine azeotrope, and the residue was taken up in chloroform. The solution showed characteristic ionic tosylate absorption (λ_{max} 1015 cm.$^{-1}$, 1038 cm.$^{-1}$, 1128 cm.$^{-1}$, and 1164 cm.$^{-1}$) in the infrared, but after being washed with dilute ammonia (and dried) it showed no such absorption. Solvent was removed at reduced pressure and the 7.17 g. of brown oily residue was dissolved in 25 ml. of benzene and chromatographed on 300 g. of acid-washed alumina (activity grade III). Benzene eluted a mixture of VII and VIII, and benzene-acetone (1:1) eluted 5.1 g. (74.7%) of crude VIII as an orange-colored amorphous solid, m.p. 125–133°. Two crystallizations of the benzene-acetone eluate from acetone gave white crystals of pure VIII, m.p. 239–240° dec., $[\alpha]_D$ +43.3°.

Anal. Calcd for $C_{23}H_{28}N_2O_4$ (396.47): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.77; H, 7.24; N, 7.30.

The infrared spectrum in Nujol showed strong absorption at 1748 cm.$^{-1}$, showing an unchanged carbomethoxy group, and medium absorption at 1688 cm.$^{-1}$, typical of enol ethers.

The benzene eluate was rechromatographed, and material eluted with benzene-acetone (1:1) was crystallized from acetone, giving 0.12 g. (1.8%) of a yellow solid, m.p. 252–258° dec. Recrystallization from ethyl acetate gave pale yellow crystals of methyl anhydroreserpate (VII) m.p. 271–272° dec., $[\alpha]_D$ −122.6°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4$ (396.47): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.67; H, 7.12; N, 6.96.

The infrared spectrum in Nujol was identical with that of authentic methyl anhydroreserpate. (Reported for VII: m.p 270–271° dec.,[2] $[\alpha]_D^{25}$ −129°.[7])

Attempted isomerization of VIII. (a) Base treatment: A solution of 0.30 g. of VIII in 3.0 ml. of 1*N* methanolic sodium methoxide was allowed to stand at room temperature overnight. The starting material was recovered and identified by melting point (233–239° dec.), infrared spectrum, and paper chromatography.

(b) Acid treatment: A solution of 0.20 g. of VIII in 2.0 ml. of CP chloroform, containing a small amount of gaseous hydrogen chloride, was allowed to stand at room temperature (in the dark, under nitrogen) for 3 weeks. The infrared spectrum was unchanged from that of the starting solution.

3-Epialloreserpone (VI) *and 3-alloreserpone* (IX) *from* VIII. Following the procedure described by Heubner *et al.*[7] for the conversion of methyl anhydroreserpate (VII) to VI and IX, 2.00 g. of VIII was dissolved in 25 ml. of 95% ethanol and 121 ml. of 12% aqueous hydrochloric acid and refluxed for 3 hr. The dark solution was made basic with 50% aqueous sodium hydroxide and extracted portionwise with a total of 200 ml. of methylene chloride. The combined yellow-brown extracts were washed twice with water, dried over anhydrous sodium sulfate, filtered and stripped to dryness at reduced pressure. The 1.18 g. of tan residue was chromatographed in benzene solution on 35 g. of neutral alumina (Woelm activity grade II-III). The third benzene fraction (50 ml.) and first benzene-10% acetone fraction removed 0.41 g. (25.0%) of IX, which was slurried with methanol to give white crystals having m.p. 237–240° dec., $[\alpha]_D$ −143.8°, $\lambda_{max}^{95\% C_2H_5OH}$ 227 mμ (ε 36,430), 269–71 mμ (ε 4,800), 298 mμ (ε 6,000).

Anal. Calcd. for $C_{20}H_{24}N_2O_2$ (324.43): C, 74.04; H, 7.46; N, 8.67. Found: C, 73.74; H, 7.45; N, 8.72.

(12) Methyl *neo*-reserpate trimethoxybenzoate, like raujemidine,[13] but in contrast to reserpine, melted low, formed a monohydrate and had a single carbonyl band in the infrared at 1721 cm.$^{-1}$

(13) P. R. Ulshafer, M. L. Pandow, and R. H. Nugent, *J. Org. Chem.*, **21**, 923 (1956).

The infrared spectrum (Nujol) and paper chromatogram were identical with those of authentic IX,[7] and different from those of authentic VI.[7] Recrystallization from methanol gave white needles of IX which melted 242–244.5° dec., $[\alpha]_D$ −152.0°, infrared spectrum unchanged.

Anal. Found: C, 73.75; H, 7.61; N, 8.71. 3-Alloreserpone (IX)[14] was reported[7] to have m.p. 236–239° dec., $[\alpha]_D$ −135°.

Three subsequent benzene-10% acetone fractions gave 0.60 g. (36.6%) of VI, which was slurried with methanol to give white crystals, m.p. 237–240° dec., $[\alpha]_D$ +89.9°.

Anal. Found: C, 74.23; H, 7.50; N, 8.88.

The infrared spectrum (Nujol) was identical with that of authentic VI[7] but different from that of authentic IX. Recrystallization from methanol gave white prisms of VI, which melted 242–244° dec., $[\alpha]_D$ +89.9°, infrared spectrum unchanged.

Anal. Found: C, 74.12; H, 7.28; N, 8.82.

3-Epialloreserpone (VI) was reported[7] to have m.p. 240–243°, $[\alpha]_D^{24}$ +72°.

The isomeric ketones VI and IX gave a mixture melting point depression of 30°, as previously observed.[7]

Attempted formation of neo-reserpic acid lactone. (a) From methyl *neo*-reserpate (II): following the reaction conditions described for lactonization of methyl reserpate,[4] 0.50 g. of methyl *neo*-reserpate isopropanolate was added to a solution of 3.27 g. of aluminum isopropoxide in 48 ml. of xylene. After being refluxed for 2 hr., the solution was allowed to cool, and 0.37 g. (74.0%) of starting material was deposited, m.p. 216–219° dec., $[\alpha]_D$ + 53.0°; it had a paper chromatogram and an infrared spectrum identical with those of starting II.

Anal. Found: C, 65.41; H, 7.76.

Paper chromatography of the mother liquors showed the presence of starting material, but not lactone.

(b) From *neo*-reserpic acid: reaction of *neo*-reserpic acid hydrochloride with either acetic anhydride–pyridine (under conditions which lactonized reserpic acid[2]), or acetic anhydride–acetic acid (under conditions which lactonized 3-*iso*-reserpic acid[3]) or *N,N'*-dicyclohexylcarbodiimide-pyridine (under conditions which lactonized 3-*iso*-reserpic acid[4]) gave materials which contained no lactone according to infrared spectroscopy and paper chromatography.

Attempted isomerization of methyl neo-reserpate (II). A solution of 3.00 g. of methyl *neo*-reserpate isopropanol solvate and 0.20 g. of *p*-toluenesulfonic acid monohydrate in 25 ml. of collidine was refluxed for 4 hr. (the vapor temperature was allowed to climb to 168–170° by boiling before refluxing was begun). Collidine was removed at reduced pressure as a collidine-water azeotrope by successive addition of portions of water, and the yellow-brown residue was taken up in methylene chloride, washed twice with dilute aqueous ammonia and once with water, and dried over anhydrous magnesium sulfate. After filtration, the methylene chloride was replaced by 30 ml. of isopropyl alcohol, and the solution was cooled at 5° overnight. The white crystals of methyl *neo*-reserpate isopropanolate were collected, washed, and dried, giving 2.20 g. (73.3%) of white needles which was identical with starting II isopropanolate (melting point, infrared spectrum, paper chromatogram and optical rotation).

The isopropyl alcohol mother liquors were stripped to dryness, leaving 0.67 g. (22.3%) of red-brown residue which was different from II in its paper chromatographic behavior and had $[\alpha]_D$ −27.5°.

Methyl neo-reserpate p-bromobenzenesulfonate (III). A solution of 10.00 g. of II isopropanolate in 67.5 ml. of dry pyridine was cooled in an ice bath, and 15.50 g. of *p*-bromobenzenesulfonyl chloride was added portionwise over 5 min. with swirling and cooling. The yellow-amber solution was blanketed with nitrogen and allowed to stand at room temperature in the dark for 5 days. The red-brown crystalline cake was partitioned between 200 ml. of methylene chloride and 100 ml. of water, the aqueous layer was extracted once more with 50 ml. of methylene chloride, and the combined methylene chloride solution was washed with 50-ml. portions of water (twice), saturated aqueous sodium bicarbonate (twice) and water (once), and dried over anhydrous sodium sulfate. The filtered solution was stripped to dryness at reduced pressure, and the brown residue was slurry-washed five times with 50-ml. portions of benzene and twice with 50-ml. portions of acetone, to give 10.83 g. (81.2%) of pale yellow-tan solid III, m.p. 203–209°. An analytical sample was prepared by passing a solution of III in a large volume of methylene chloride–acetone (2:1) through a bed of activated charcoal, removing solvent at reduced pressure, and slurry-washing the product with acetone. Pure white III had m.p. 212–214° (yellow melt, bubbles), $[\alpha]_D$ +22.0°.

Anal. Calcd. for $C_{29}H_{33}N_2O_7BrS$ (633.58): C, 54.98; H, 5.25; N, 4.42. Found: C, 54.85; H, 5.32; N, 4.36.

3-Epialloreserpone (VI) *from methyl neo-reserpate p-bromobenzenesulfonate* (III). A solution of 5.00 g. of III and 1.00 g. of triethylamine in a mixture of 118 ml. of dioxane and 40 ml. of distilled water was refluxed for 2 weeks. Samples were taken from the yellow solution at intervals, and paper chromatographic examination showed the gradual accumulation over several days of a highly polar intermediate, presumably the enol ether of 16-carboxy-3-epialloreserpone. The reaction mixture was acidified with concentrated hydrochloric acid, refluxed for 2 hr., made basic with aqueous sodium hydroxide, and extracted with three 150-ml. portions of methylene chloride. The combined extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. Crystallization from methylene chloride–methanol (boiling off the methylene chloride) gave 0.90 g. (35.3%) of yellow prisms of VI, m.p. 239–241° dec., $[\alpha]_D$ +80.5°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$ (324.43): C, 74.04; H, 7.46; N, 8.67. Found: C, 73.89; H, 7.55; N, 8.26.

An alternative work-up which exposed the polar intermediate to only mild contact with aqueous acid gave the same result: the reaction mixture was stripped to dryness at reduced pressure and the yellow solid residue was extracted repeatedly with warm aqueous acid. The aqueous acid extracts were basified with aqueous ammonia and the flocculent yellow precipitate was collected and dried, giving 1.61 g. (62.8%) of yellow solid VI (paper chromatography), melting incompletely 130–140°. Crystallization from acetonitrile gave 0.70 g. (27.3%) of small, light yellow prisms, m.p. 237–240° dec., $[\alpha]_D$ +87.2°; a mixture melting point with authentic VI showed no depression. The infrared spectrum and paper chromatographic behavior were identical with authentic VI.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$ (324.43): C, 74.04; H, 7.46; N, 8.67. Found: C, 73.57; H, 7.53; N, 9.88.

Recrystallization from methylene chloride–methanol gave 0.55 g. of pale yellow prisms, m.p. 238–242° dec., $[\alpha]_D$ +87.3°.

Anal. Found: C, 74.13; H, 7.58; N, 9.19.

Acknowledgment. The authors are pleased to acknowledge the valuable assistance of the following people in the work described in this paper: discussions with Mr. L. Dorfman, Dr. H. B. MacPhillamy, Dr. M. M. Robison, and Dr. E. Wenkert; microanalytical data from Mr. L. Dorfman and his associates of the CIBA Microanalytical Section;

(14) Compound IX was originally called "reserpone."[15] It was later found[7] to have the allo-configuration, identical at C-3 with the 3-*iso*-reserpine series,[8] and has therefore been called "isoreserpone"[3] also. The isomeric compound VI first isolated by Huebner, St. André, Schlittler, and Uffer[7] and having the same configuration at C-3 as reserpine has recently been called "reserpone."[3]

(15) C. F. Huebner, H. B. MacPhillamy, A. F. St. André, and E. Schlittler, *J. Am. Chem. Soc.*, **77**, 472 (1955).

electrometric titrations by Dr. M. J. Allen, formerly of the CIBA Chemical Research Division; paper chromatograms by Mr. B. Korzun and co-workers; biological tests on the esters of methyl *neo*-reserpate by Dr. A. J. Plummer and Dr. W. Barrett of the CIBA Macrobiologic Division; technical assistance by Mr. M. P. Linfield.

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The Absolute Configuration of the Glycol Grouping in the Diterpene Cafestol

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Received February 21, 1961

Epoxynorcafestanone (III) was converted stereospecifically, *via* the olefin VI, to tetrahydrocafestol (II). This reaction sequence allows the (R)-configuration to be assigned to C-16 of the diterpene cafestol.

Cafestol, the pentacyclic diterpene constituent of coffee oil, recently[1] has been assigned structure and absolute configuration I, in which the configuration of all asymmetric centers save C-16 has been assigned. The configuration at the A/B ring fusion (antipodal to the steroids) was unambiguously determined by means of optical rotatory dispersion studies.[1,2] The establishment of configuration at the B/C/D ring junctures rested primarily on the coincidence of the rotatory dispersion curves[3] of the norketone III[4,5] derived from cafestol (I) and the norketone IV[6,7] derived from phyllocladene (V), whose absolute configuration has been assigned as indicated in V.[8-10] Subsequent degradative experiments coupled with rotatory dispersion measurements afforded additional evidence for the configuration at the B/C/D ring junctures as depicted in I.[11]

The present work demonstrates that the remaining asymmetric center at C-16 has the (R)-configuration[12] as indicated in VII.[13]

The norketone (III, epoxynorcafestanone) obtained by lead tetraacetate cleavage of tetrahydrocafestol (II)[14] was converted to the olefin (VI) by treatment with Wittig's reagent. The structure of VI, which was apparent from its method of formation as well as by its subsequent transformations, was confirmed by microanalysis and by its infrared spectrum. Hydroxylation of VI with osmium tetroxide led to a single glycol (VII, purified *via* its acetate, VIIa) whose relative configuration followed from consideration of the steric course of the hydroxylation step. Molecular models of the olefin VI (*cf.* VIII) indicate that attack at C-16 from the β-face of the molecule is severely hindered by the axial hydrogen atom attached to C-11. The large steric demands of osmium tetroxide in the formation of the intermediate cyclic osmate ester therefore require attack from the side of the methylene bridge; thus, the resulting glycol must have the (relative) configuration shown in VII (C-16 hydroxyl *cis* to the methylene bridge). This argument is supported by the high degree of stereospecificity actually observed. Infrared examination of the crude synthetic glycol and its acetate, as well as materials recovered from the mother liquors, failed to reveal the presence of an epimeric compound. As the synthetic glycol (VII) and its acetate (VIIa) proved to be identical, respectively, with tetrahydrocafestol (II) and tetrahydrocafestyl acetate (IIa), the natural product has the configuration depicted in VII. That this also represents the *absolute* configuration follows from the previously assigned absolute configuration of the methylene bridge.

This result accords nicely with the scheme pro-

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(14) No configuration is implied for the points of attachment of the tetrahydrofuran moiety to ring A.