Rauwolfia Alkaloids. XLV. Preparation and Transformations of the Ketone Derived from Methyl Reserpate

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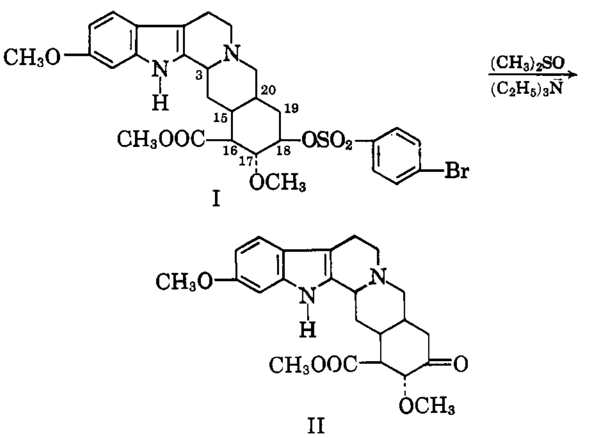
Oxidation of the carbinol function of methyl reserpate has been effected by treatment of methyl reserpate *p*-bromobenzenesulfonate with dimethyl sulfoxide in the presence of triethylamine. The product, "methyl ketoreserpate," lends itself to a wide variety of transformations. These include, aside from expected reactions of the ketone function, elimination of the C-17 methoxyl group from the ketone and several of its derivatives, and conversion of one of these demethoxylated products to a D-E *trans* ring system. It was also possible to cleave ring E of methyl ketoreserpate oxime by subjecting it to Beckmann rearrangement conditions.

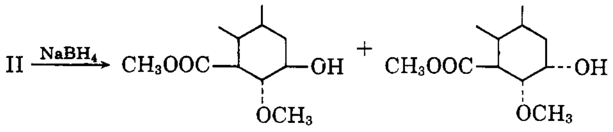
Interest in the separation and enhancement of the sedative and hypotensive properties of reserpine has stimulated a program in this laboratory which has involved numerous modifications of the structure of the molecule. In early efforts, considerable emphasis was placed on variation of the ester function at position 18, while later a number of ethers derived from methyl reserpate and from methyl 18-epireserpate were prepared.[1] It was recognized at an early date that the ketone derived from an oxidation of the carbinol function of methyl reserpate would be of considerable utility for far-reaching transformations of ring E of the alkaloid, but attempts at the preparation of the carbonyl compound by conventional oxidation methods were uniformly unsuccessful. The desired substance, to which we have chosen for convenience to assign the trivial name "methyl ketoreserpate," was finally obtained by reaction of methyl reserpate *p*-bromobenzenesulfonate (I) with dimethyl sulfoxide in the presence of triethylamine.[2]



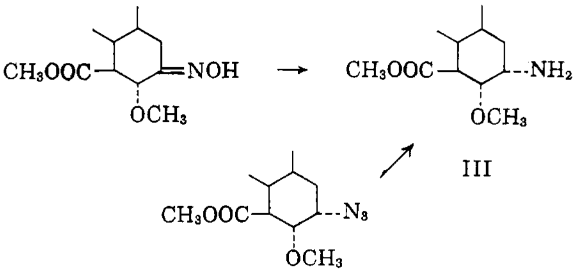
I

II

Subsequently, it was found that this oxidation can also be carried out with other benzenesulfonate esters of methyl reserpate as well as with those derived from methyl 18-epireserpate.[1] That no stereochemical changes were effected in the molecule other than at C-18 in the oxidation process was demonstrated by reduction of the ketone (II) with sodium borohydride. A mixture was obtained which consisted of approximately equal amounts of methyl reserpate and methyl 18-epireserpate, as shown by paper chromatography. The epimers were separated by fractional crystallization and identified by comparison with authentic samples.



An early series of experiments on the ketone involved the preparation of carbonyl derivatives, including the cyclic ethylene ketal, semicarbazone and oxime. Hydrogenation of the oxime with platinum oxide in glacial acetic acid yielded a mixture of products, from which only one amino compound could be isolated in pure form. This was found to be methyl 18-desoxy-18α-aminoreserpate (III), since it did not undergo lactam formation on treatment either with aluminum isopropoxide in refluxing xylene[3] or with acetic anhydride. Further evidence for the α-configuration of the amino group was obtained on preparation of the same amine by hydrogenation of methyl 18-epireserpate azide which, in turn, was prepared by reaction of methyl reserpate *p*-bromobenzenesulfonate with sodium azide. By analogy to the reaction of the brosylate with alcohols, water and other displacement reagents,[1] it may be inferred that displacement by azide ion proceeds with inversion.



III

Attempts were also made to insert functional groups at C-18 by reaction of the ketone with Wittig reagents. Treatment with carbomethoxymethyltriphenylphosphonium bromide in the presence of sodium methoxide did not lead to the desired olefinic ester; rather, secondary reactions not involving the Wittig reagent took place in the strongly basic medium (*vide infra*). Treatment of the ketone with the preformed ylid, on the other hand, yielded only unchanged starting material. Similar results were also observed with more reactive Wittig reagents such as those from benzyltriphenylphosphonium bromide and from methoxymethyltriphenylphosphonium bromide. Reaction of the ketone

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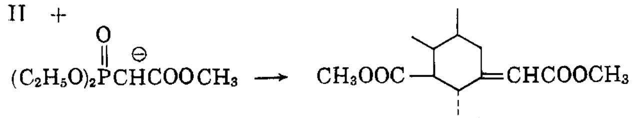
[1] M. M. Robison, R. A. Lucas, H. B. MacPhillamy, R. L. Dziemian, I. Hsu, and R. J. Kiesel, *J. Am. Chem. Soc.*, **83**, 2694 (1961).

[2] *Cf.* N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959).

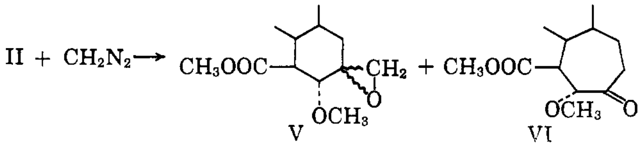
[3] *Cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstad, *Tetrahedron*, **2**, 1 (1958) for use of this reagent in lactonization of methyl reserpate.

with the phosphonate carbanion $(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\overset{\ominus}{C}HCOOCH_3$,[4] however, did lead to the formation of the desired olefin (IV), though in low yield.



IV

The ketone also reacted with diazomethane to yield a difficultly separable mixture of products. On the basis of infrared, chemical and nuclear magnetic resonance indications these are formulated as the epoxide (V) and seven-membered ring ketone (VI).



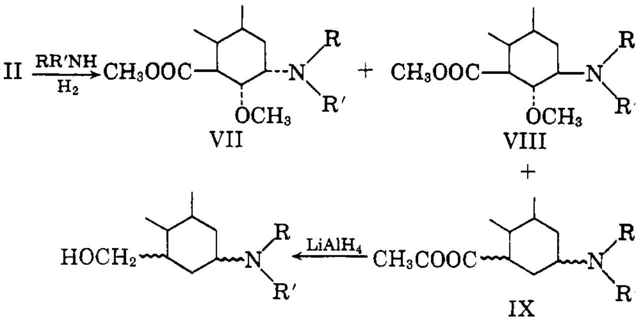
V VI

Nuclear magnetic resonance spectra[5] show that the configurations at C-3, C-16 and C-17 were not changed in the reaction. Doublets at 4.12 δ ($J = 12$ c.p.s.) for methyl ketoreserpate, at 4.07 δ ($J = 10$ c.p.s.) for "methyl homoketoreserpate" (VI), and at 3.81 δ ($J = 11$ c.p.s.) for the epoxide (V) are due to the splitting of the C-17 protons by the C-16 hydrogens. In the case of VI the doublet indicates the vicinal positions of the three functional groups in ring E and thus serves to differentiate VI from the other possible ketone which might have been formed by insertion of the methylene group between C-17 and C-18. Further, the coupling constants for the compounds are indicative of the *trans*-diaxial relationships of the C-16 and C-17 protons.

That the C-3 hydrogens in the three examples are still equatorial and that the substances therefore all possess the "3-normal" configuration is indicated by the broad band at approximately 4.5 p.p.m. for methyl ketoreserpate and at 4.4 p.p.m. for the epoxide.[6] In the case of the ketone (VI) the corresponding band is in the region 3.8–4.1 p.p.m.[7] It is obscured by the peaks associated with the C-17 hydrogen and the protons of the carbomethoxy and aromatic methoxy groups; however, the proton count indicates the presence of eight hydrogens (two methoxy groups, C-17 and C-3).

For further characterization of methyl homoketoreserpate, an oxime and semicarbazone were prepared, but difficulty in the separation of V and VI precluded any extensive investigation of their chemistry.

Reductive aminations of methyl ketoreserpate were also investigated. The use of *n*-propylamine in the presence of a palladium–charcoal catalyst led not only to the expected mixture of α- (VII-a) and β-amino (VIII-a) derivatives, but also to a methyl 17-desmethoxy-18-desoxy-18-*n*-propylaminoreserpate (IX-a). In the last case no attempt was made to define the stereochemistry at C-16 and C-18. The configurations of the two expected products were demonstrated by comparison with the known α-amine obtained from the reaction of methyl reserpate brosylate with *n*-propylamine. By analogy to the other brosylate displacements this substance was again assumed to have the α-amino configuration. Further it was also possible to prepare the β-amino compound by a displacement reaction starting with methyl 18-epireserpate *m*-nitrobenzenesulfonate. A similar double inversion has been carried out with alcohols to prepare methyl reserpate methyl ether.[1] That methoxyl elimination in the case of the third product had taken place at C-17, rather than at the carbomethoxy group, was shown by lithium aluminum hydride reduction. This process resulted in the loss of another methoxyl group, a situation which would not have obtained had the original elimination been due to lactam formation or some other process involving the ester function. Similar eliminations of the C-17 methoxyl under basic conditions were also encountered with other ketone derivatives (*vide infra*).

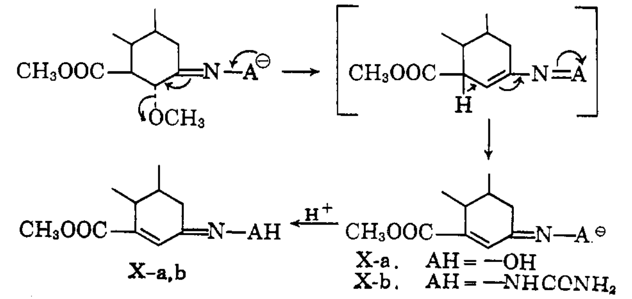


VII VIII IX

a. R = $CH_3CH_2CH_2$—, R′ = H
b. RR′ = —$CH_2CH_2CH_2CH_2CH_2$—
c. RR′ = —$CH_2CH_2CH_2CH_2$—

Reductive aminations were also effected with secondary amines. Piperidine yielded as the sole isolable product the 17-desmethoxy compound (IX-b), while pyrrolidine produced the desmethoxy compound (IX-c) and the 18α-amino derivative (VII-c). In the case of VII-c the product was also inverted at C-3. The structure of this substance was again demonstrated by comparison with a product obtained from a displacement reaction.

An anticipated elimination of the C-17 methoxy group was observed when methyl ketoreserpate oxime and methyl ketoreserpate semicarbazone were treated with methanolic sodium methoxide. From these reactions high yields of elimination products were obtained. The reaction course may be formulated as below; the formation of the anion of the oxime (X-a)



X-a,b

X-a. AH = —OH
X-b. AH = —NHCONH₂

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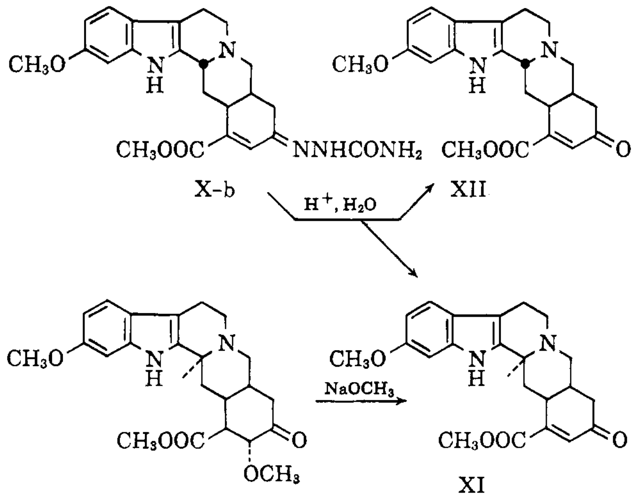
[4] W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

[5] Spectra were obtained with the Varian A-60 spectrometer at 60 Mc./sec. using deuterated chloroform as solvent and tetramethylsilane as internal reference. Chemical shifts are quoted in field-independent δ units (p.p.m.) where δ is defined by the relation $\delta = 10^6 (H_{ref} - H)/H_{ref}$.

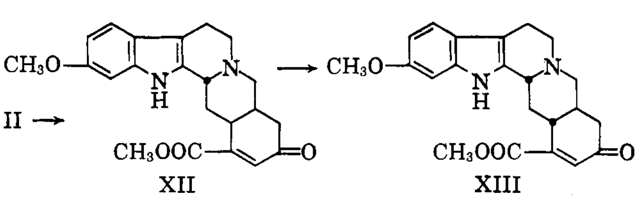
[6] *Cf.* W. E. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961).

[7] Dr. E. Wenkert has kindly informed us of unpublished results from his laboratory which indicate that the signal from a truly axial C-3 proton is to be found at about 3.2 p.p.m.

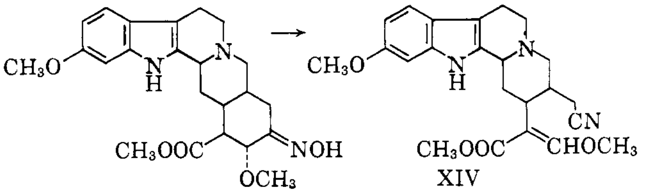
or semicarbazone (X-b) in these cases may be expected to stabilize the molecule against further, secondary reactions (*vide infra*). In neither product was C-3 epimerized, as shown by the infrared spectra.[8] The olefinic semicarbazone (X-b) was subjected to hydrolytic cleavage with aqueous acetic acid in the presence of pyruvic acid. Under carefully controlled conditions the corresponding keto ester (XII) was formed, while under slightly harsher conditions the isomeric C-3 inversion product (XI) predominated. When the same reaction sequence was carried out starting from methyl 3-iso-18-ketoreserpate, the C-3 epimer of X-b on hydrolytic cleavage again yielded both C-3 inverted and uninverted products. It may be noted that in this situation with all ring-E substituents planar the "3-iso" (*allo*yohimbane) configuration is not more stable than the "3-normal" (*epiallo*yohimbane) structure.[9] Confirmation of the 3-iso structure of XI was obtained by its direct formation on treatment of methyl 3-iso-18-ketoreserpate with methanolic sodium methoxide.



When methyl ketoreserpate itself was treated with methanolic sodium methoxide, still another isomer (XIII) of the olefinic ketone was isolated, in yields up to 50%. Although this substance was clearly different from the "3-iso" material (XI) obtained from the acid hydrolysis, it still possessed the infrared absorptions in the 2800-cm.$^{-1}$ region characteristic for the 3-axial hydrogen of a 3-iso structure.[10] An explanation for the third product was found when it was noted that in the unsaturated keto esters, unlike X-a and X-b, the C-15 hydrogen is vinylogously activated by the ketone carbonyl. Thus if the initial elimination product from treatment of the ketone with methoxide were the 3-normal (*epiallo*) unsaturated ketone (XII), enolization and subsequent epimerization at C-15 could produce the more stable XIII, an enantiomer of the *normal* yohimbane structure. The first piece of evidence for the structure of XIII was obtained on acid equilibration. Treatment with acid under the conditions which led to partial C-3 epimerization in the semicarbazone hydrolyses allowed recovery of 85% of unchanged starting material. Such a result is expected on the basis of structure XIII, for epimerization of C-3 in this isomer would involve conversion of the *normal* yohimbane structure to the much less stable *pseudo* configuration. More significantly, treatment of the 3-normal ketone (XII, obtained from the acid hydrolyses) with methanolic sodium methoxide resulted in facile isomerization to form XIII. It may be noted that while C-15 is also activated in the 3-iso series, the 3-iso olefinic keto ester (XI) would not be expected to epimerize at C-15 on base treatment, since this would involve a transformation of the relatively stable *allo* ring system to the much less stable *pseudo* configuration.



In another series of reactions it was found possible to cleave ring E of methyl ketoreserpate oxime by treatment with phosphorus pentachloride, in a type of second-order Beckmann rearrangement. The resulting nitrile (XIV) presents obvious possibilities for conversion to alkaloids of the corynantheidine type.



Pharmacological evaluation of methyl ketoreserpate and its oxime as their hydrochloride salts revealed that neither exhibited significant hypotensive activity; both compounds caused sedation in the dog when administered intravenously. Detailed pharmacological studies of these and other methyl ketoreserpate derivatives will be reported elsewhere by Drs. W. Barrett and A. J. Plummer of these laboratories.

Experimental[11]

Methyl Ketoreserpate (II).—A mixture of 12.7 g. of methyl reserpate *p*-bromobenzenesulfonate, 2.4 g. of triethylamine and 100 ml. of dimethyl sulfoxide was sealed in a pressure bottle after thorough purging with nitrogen and heated in a steam bath with magnetic stirring for 28 hr. The solvent was removed from the slightly turbid orange solution *in vacuo* and the residue was taken up in methylene chloride. The extract was washed with 5% aqueous sodium carbonate solution and with saturated brine, then dried and evaporated. The resulting 7.5 g. of crude ketone, m.p. 230–231°, was dissolved in about 30 ml. of methylene chloride and filtered through a column of 30 g. of Florisil, elution being continued with more methylene chloride. The combined product from about 1000 ml. of eluate was triturated with ether to yield 5.9 g. of II, m.p. 234–235°. Recrystallization from 95% ethanol by addition of methylene chloride and evaporation of the latter from the hot solution afforded, after processing of the mother liquor, 4.94 g. (60%) of pure ketone, m.p. 238–239°. The analytical sample, prepared by further recrystallizations from the same solvent, had m.p. 241–242°, $[\alpha]^{26}\text{D}$ $-17°$. The infrared spectrum (Nujol) showed only one broad carbonyl band at 1725 cm.$^{-1}$.

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[8] E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

[9] E. Schlittler in R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, Mass., 1957, p. 86.

[10] W. E. Rosen, *Tetrahedron Letters*, **14**, 481 (1961).

[11] Melting points are uncorrected. All optical rotations were determined in chloroform solution $c = 1\%$ and all ultraviolet spectra in ethanol solution. Melting points are "decomposition" unless otherwise noted.

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.85, 67.08; H, 6.96, 6.99; N, 6.63, 6.83.

The ketone synthesis was also carried out under other experimental conditions in attempts to increase the yield or convenience of the preparation. In one variation approximately half as much dimethyl sulfoxide was used, the reaction period was limited to 3 hr., and the total reaction mixture was poured into water, rather than evaporating excess sulfoxide. Extraction into methylene chloride and a similar workup from this point afforded, typically, yields of approximately 50%.

The ketone was also prepared from methyl 18-epireserpate brosylate.[1] In this case the crude product obtained on evaporation after washing the methylene chloride solution with sodium carbonate and brine was extracted with several portions of cold 3% hydrochloric acid. Precipitation of the ketone from the acid solutions with ammonia was followed by extraction into methylene chloride. Evaporation of the dried extracts and trituration of the residue with ether afforded a 27% yield of ketone, m.p. 229–230°. Recrystallization afforded material m.p. 238–240°, identical with the methyl reserpate brosylate product by mixture melting point, infrared and paper chromatographic criteria.

Methyl Ketoreserpate Hydrochloride.—The salt was prepared by dissolution of 0.82 g. of the ketone in 25 ml. of warm acetone and addition of 0.2 ml. of concentrated hydrochloric acid in 2.2 ml. of acetone. The resultant gel crystallized on scratching; m.p. 229–233°.

Anal. Calcd. for $C_{23}H_{28}N_2O_5 \cdot HCl \cdot H_2O$: C, 59.16; H, 6.69; N, 6.00. Found: C, 59.64; H, 6.90; N, 5.97.

Methyl Ketoreserpate Maleate.—To a solution of 0.41 g. of II in 15 ml. of warm acetone was added a solution of 0.12 g. of maleic acid in a few milliliters of acetone. The salt, obtained on scratching and chilling, had m.p. 189–191°.

Anal. Calcd. for $C_{23}H_{28}N_2O_5 \cdot C_4H_4O_4 \cdot {}^1/_2\ H_2O$: C, 60.35; H, 6.19; N, 5.21. Found: C, 60.80; H, 6.38; N, 4.95.

Reaction of II with Sodium Borohydride.—To a suspension of 0.82 g. of the ketone in 35 ml. of methanol 0.8 g. of sodium borohydride was added and the mixture was allowed to stand for 0.5 hr. The solvent was evaporated *in vacuo*, ice–water was added and the white solid was collected by filtration, washed with water and dried; 0.8 g., m.p. 175–180° with ebullition. Paper chromatographic comparison with the pure substances indicated that this mixture consisted of approximately 40% methyl reserpate and 50–60% methyl 18-epireserpate, with only trace impurities. Fractional crystallization from 15 ml. of acetonitrile afforded methyl 18-epireserpate. After a second recrystallization 0.43 g. of the hydrated material[1] was obtained, which softened at about 170° and had m.p. 221–223°, undepressed on admixture with an authentic sample. The infrared spectrum was identical with that of methyl 18-epireserpate monohydrate. Evaporation of the mother liquors from the first crystallization to a low volume and scratching afforded 0.27 g. of crude methyl reserpate. Two recrystallizations from the same solvent yielded fine filaments, m.p. 242–244°, undepressed on admixture with an authentic sample. The infrared spectrum was identical with that of the known material.

Methyl Ketoreserpate Semicarbazone.—A mixture of 5.15 g. of ketone, 5 g. of semicarbazide hydrochloride, 125 ml. of pyridine and 250 ml. of absolute ethanol was refluxed under nitrogen for 2 hr., then evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of cold water by stirring and the product precipitated by addition of ammonium hydroxide. Filtration, washing with water and drying, followed by recrystallization from acetonitrile afforded 4.47 g. of product melting over the range 187–199° with bubbling. Further recrystallizations from methanol produced the analytical sample which after drying had m.p. 196–201°, $[\alpha]^{22}D$ +58.5°.

Anal. Calcd. for $C_{24}H_{31}N_5O_5$: C, 61.39; H, 6.66; N, 14.92. Found: C, 61.48; H, 6.84; N, 14.87.

Methyl Ketoreserpate Oxime.—A mixture of 8.24 g. of ketone, 8 g. of hydroxylamine hydrochloride, 200 ml. of pyridine and 200 ml. of absolute ethanol was refluxed for 3 hr., then kept overnight at room temperature. The solvent was removed *in vacuo*, the residue was dissolved in about 100 ml. of water and the product was precipitated by addition of ammonia. The oily solid was improved in form by addition of a small amount of methanol to the suspension and stirring. After filtration and washing with water the wet precipitate was recrystallized from methanol–methylene chloride (Darco) to yield 6.6 g. of white plates, m.p. 236–237°. The analytical sample, prepared by further recrystallizations, had the same melting point.

Anal. Calcd. for $C_{23}H_{29}N_3O_5$: C, 64.62; H, 6.84; N, 9.83. Found: C, 64.67; H, 6.92; N, 10.08.

Methyl Ketoreserpate Ethylene Ketal.—A solution of 4.1 g. of methyl ketoreserpate, 6.2 g. of ethylene glycol and 2.0 g. of *p*-toluenesulfonic acid in 350 ml. of dry ethylene dichloride was refluxed for 7 hr. under a nitrogen atmosphere in a Soxhlet apparatus so arranged that the condensate passed through a bed of Drierite. The mixture, after standing overnight, was washed with 5% sodium carbonate solution, with water and with saturated brine, then dried over sodium sulfate and evaporated. The residue was triturated with cold ether to induce crystallization and the ether-insoluble portion was recrystallized from 1:2 benzene–cyclohexane (Darco). From the recrystallization and processing of the mother liquors a total of 2.25 g. of ketal, m.p. 206–207°, was obtained. The analytical sample had the same melting point; $[\alpha]^{24}D$ −56°.

Anal. Calcd. for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 66.07; H, 7.24; N, 6.27.

Hydrogenation of Methyl Ketoreserpate Oxime.—The oxime (0.85 g.) was hydrogenated at atmospheric pressure in 60 ml. of glacial acetic acid, with pre-reduced catalyst from 0.5 g. of platinum oxide. Hydrogenation was interrupted when approximately 105 ml. of hydrogen had been absorbed. Filtration and evaporation *in vacuo* were followed by dissolution of the residue in methylene chloride, washing with 5% sodium carbonate and with brine, then drying and evaporation. Although the resultant white solid could be recrystallized directly, it was a mixture of products as shown by paper chromatography, and satisfactory analytical values were not obtained. The crude material was chromatographed on 40 g. of activity II–III neutral alumina in methylene chloride solution. After elution of impurities with methylene chloride the main body of product was removed from the column using 1% methanol in methylene chloride. The resulting 0.3 g. of material, after recrystallization from 1:2 benzene–cyclohexane (Darco) melted partially at about 160°, then completely at 216° with decomposition. The **methyl 18-desoxy-18α-aminoreserpate** (III) had $[\alpha]^{24}D$ −65°. Its homogeneity was shown by paper chromatography on formamide-impregnated paper (pH 5.6) with 10% pyridine in chloroform as the mobile phase.

Anal. Calcd. for $C_{23}H_{31}N_3O_4$: C, 66.80; H, 7.56; N, 10.16. Found: C, 66.71; H, 7.68; N, 9.64.

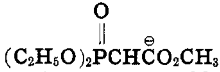
Treatment of the amine with aluminum isopropoxide in refluxing xylene for 2 hr. resulted in extensive decomposition. No major spot was detected on paper chromatography of the crude product. In another experiment 0.41 g. of amine and 2 ml. of acetic anhydride were heated for 15 min. on the steam bath, cooled and poured into 15 ml. of ice–water. The mixture was made alkaline with ammonia and the solid was extracted into methylene chloride. The extract was washed with brine and evaporated and the residue was washed with benzene. The 0.17 g. of **methyl 18-desoxy-18α-acetamidoreserpate**, m.p. 272–275°, was recrystallized from acetonitrile for analysis, m.p. 279–280°, $[\alpha]^{24}D$ +20°.

Anal. Calcd. for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30; N, 9.23. Found: C, 66.05; H, 7.33; N, 9.35.

Methyl 18-Epireserpate Azide.—A mixture of 9.51 g. of methyl reserpate brosylate, 9.75 g. of sodium azide, 150 ml. of water and 300 ml. of dioxane (purified by passage through a column of alumina) was heated on the steam bath in a nitrogen atmosphere for 27 hr., after which most of the dioxane was removed *in vacuo*. The residue was mixed with methylene chloride and the solution was washed with water and with brine, then dried and evaporated. The 5.7 g. of azide was contaminated with methyl epireserpate. It was purified by recrystallizations from acetonitrile–methylene chloride by evaporation of most of the latter solvent. The analytical sample melted at 238–239.5° and had $[\alpha]^{23}D$ −47°.

Anal. Calcd. for $C_{23}H_{29}N_5O_4$: C, 62.85; H, 6.65; N, 15.94. Found: C, 63.01; H, 6.60; N, 15.85.

The azide (0.44 g.) was hydrogenated in 50 ml. of 95% ethanol using 0.25 g. of 20% palladium–charcoal at atmospheric pressure. Hydrogenation was carried out for 4.5 hr., during which period the apparatus was flushed several times with fresh hydrogen. The product, after recrystallization from 1:3 benzene–cyclohexane, exhibited the usual melting point behavior, softening at about 160° and melting at about 210–212°. Paper chromatographic and infrared comparison showed it to be identical with the major product from the oxime hydrogenation.



$(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\overset{\ominus}{C}HCO_2CH_3\overset{\oplus}{Na}$

Reaction of II with $(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\overset{\ominus}{C}HCO_2CH_3\overset{\oplus}{Na}$.—Methyl P,P-diethylphosphonoacetate[12] (6.3 g.) was added slowly with stirring to a slurry of 1.5 g. of sodium hydride–mineral oil dispension (54% NaH) in 160 ml. of dry 1,2-dimethoxyethane under nitrogen. Stirring was continued at room temperature for about 2 hr. until all of the hydride had dissolved, after which a solution of 4.12 g. of methyl ketoreserpate in 100 ml. of dimethoxyethane was added. The mixture, which turned red on addition of the ketone, was heated at 60° for 4 hr., then allowed to stand overnight. The solution was filtered through Filter-Cel to remove a small quantity of insoluble material and the filtrate was poured into 750 ml. of cold water. After stirring for 0.5 hr. the solid was separated by filtration and dissolved as completely as possible in 150 ml. of ether. The ether solution was washed with water and with brine, then dried and evaporated to about 40 ml., at which point 200 ml. of low-boiling petroleum ether was added. The resulting solid was separated by filtration and extracted with several portions of boiling cyclohexane. The residue from evaporation of the solvent was triturated thoroughly with low-boiling petroleum ether. The combined solids from several such operations were dissolved in 20 ml. of hot isopropyl alcohol and treated with Darco. The red filtrate was then poured into about 500 ml. of water. Evaporation of the alcohol from the cloudy solution caused the precipitation of a tan solid which was separated by filtration, dried and dissolved in a few milliliters of warm benzene. Addition of about 100 ml. of hot cyclohexane, treatment with Darco and slow cooling prouced 1.3 g. of the olefinic ester, m.p. 115–125°. The poorly-crystalline material was further purified by dissolution in ether, treatment with Darco, partial evaporation and addition of petroleum ether. The final sample obtained by this procedure weighed 0.87 g. and softened from about 110° up with final melting at 132–135°. In spite of the wide melting range, paper chromatography indicated the product to be essentially pure. The infrared spectrum (Nujol) showed a broad carbonyl band at 1710–1730 cm.$^{-1}$ and a C=C absorption at 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.96; H, 7.20; N, 5.67.

Reaction of Methyl Ketoreserpate with Diazomethane.—A solution of 10.3 g. of methyl ketoreserpate in 25–30 ml. of methylene chloride was cooled to 0° and 154 ml. of 0.245 *M* diazomethane in methylene chloride[13] was added with stirring. One gram of lithium bromide in a total of 75 ml. of anhydrous methanol was next added in two portions over a period of 45 min. Nitrogen evolution was observed after each addition. The reaction mixture was kept in a refrigerator at about 5° for 3 days during which time it darkened considerably. The solvent was removed *in vacuo*, the residue was washed with ether and the insoluble portion was dissolved in methylene chloride. The solution was washed with water and with saturated brine, dried, filtered through a bed of Darco, then passed through a column of Florisil. Elution with more methylene chloride afforded a total of 4.4 g. of mixed product. After several recrystallizations from isopropyl alcohol–methylene chloride (Darco) with evaporation of most of the latter it was possible to effect a separation of the ketone and epoxide by fractional crystallization from this solvent-pair. The ketone was originally obtained as the less soluble fraction on crystallization from excess solvent, while the epoxide was recovered from the mother liquors. The course of the separations was followed by paper chromatography. From the above reaction 0.6 g. of the ketone of greater than 90% purity could be isolated, while 0.5 g. of epoxide of 80–90% purity was obtained. The analytical sample of **methyl homoketoreserpate** (VI) was obtained on further recrystallizations from the same solvent-pair as white crystals, m.p. 240–241°, $[\alpha]^{27}\mathrm{D}$ −95°. The infrared spectrum exhibited a wide carbonyl absorption in the region 1715–1730 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57. Found: C, 67.60; H, 7.31; N, 6.89.

The **epoxide** (V) was obtained on further recrystallizations from isopropyl alcohol–methylene chloride as white filaments, m.p. 245–257° alone and m.p. 220–225° on admixture with methyl homoketoreserpate. This product, $[\alpha]^{26}\mathrm{D}$ −49°, showed one narrow carbonyl band in the infrared at 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57. Found: C, 67.24; H, 7.14; N, 6.73.

Methyl homoketoreserpate oxime was prepared by the method described for methyl ketoreserpate oxime and recrystallized from ethanol–water. The solvated derivative, which melted at about 180–190° with ebullition, was hygroscopic. On drying at 105° it was obtained as the sesquihydrate.

Anal. Calcd. for $C_{24}H_{31}N_3O_5\cdot{}^3/_2\ H_2O$: C, 61.52; H, 7.31; N, 8.97. Found: C, 61.80; H, 7.52; N, 8.89.

On redrying at 140° the hemihydrate was obtained.

Anal. Calcd. for $C_{24}H_{31}N_3O_5\cdot{}^1/_2\ H_2O$: C, 63.98; H, 7.16. Found: C, 63.84; H, 7.35.

Methyl homoketoreserpate semicarbazone was also prepared by the method used for the corresponding methyl ketoreserpate derivative and was recrystallized from 1:2 ethanol–water; fine needles, m.p. 204–208° with ebullition.

Anal. Calcd. for $C_{25}H_{33}N_5O_5\cdot H_2O$: C, 59.86; H, 7.03; N, 13.96. Found: C, 60.20; H, 7.24; N, 14.00.

Reductive Amination of the Ketone with *n*-Propylamine.—Hydrogenation of a mixture of 4.0 g. of methyl ketoreserpate, 40 ml. of *n*-propylamine, 100 ml. of absolute ethanol and 2.0 g. of 10% palladium–charcoal at room temperature and atmospheric pressure for 3 days resulted in the apparent uptake of 430 ml. of hydrogen. Filtration and evaporation *in vacuo* was followed by chromatography of a methylene chloride solution of the product on 55 g. of Woelm activity II–III neutral alumina. The first major product eluted by methylene chloride was recrystallized from ethyl acetate-methylene chloride to yield 1.5 g. of **methyl 18-desoxy-18α-*n*-propylaminoreserpate** (VII-a), m.p. 226–228°, $[\alpha]^{24}\mathrm{D}$ −13°.

Anal. Calcd. for $C_{26}H_{37}N_3O_4$: C, 68.54; H, 8.19; N, 9.22; OCH_3, 20.42. Found: C, 68.42; H, 8.27; N, 9.35; OCH_3, 21.20.

This compound was also prepared from a mixture of 3.17 g. of methyl reserpate brosylate, 5.91 g. of *n*-propylamine and 100 ml. of dioxane (purified by passage through alumina). The mixture was sealed in a pressure bottle after thorough purging with nitrogen and heated and stirred in a steam bath for a period of 8 days. After evaporation to dryness *in vacuo* the residue was dissolved as completely as possible in methylene chloride, insoluble material was separated by filtration and the solution was washed with aqueous sodium carbonate, with water and with brine. Drying and evaporation were followed by trituration of the residue with low-boiling petroleum ether. After filtration the 2.05 g. of tan product, m.p. 210–212°, was recrystallized from acetonitrile (Darco). The analytical sample, m.p. 219.5–220°, had $[\alpha]^{24}\mathrm{D}$ −13°. The identity of the two substances was demonstrated by mixture melting point and paper chromatographic and infrared comparisons.

Anal. Found: C, 68.69; H, 8.37; N, 9.41.

The second reductive amination product, eluted from the column with 5% methanol in methylene chloride, yielded 0.16 g. of needles, m.p. 190–193°, $[\alpha]^{24}\mathrm{D}$ −93°, after recrystallizations from ethyl acetate-petroleum ether and from ethyl acetate–ether. This was the isomeric **methyl 18-desoxy-18β-*n*-propylaminoreserpate** (VIII-a).

Anal. Calcd. for $C_{26}H_{37}N_3O_4$: C, 68.54; H, 8.19; N, 9.22. Found: C, 68.53; H, 8.10; N, 9.21.

The substance was also prepared by reaction of 3.0 g. of **methyl 18-epireserpate *m*-nitrobenzenesulfonate**,[14] 24 g. of *n*-propylamine and 75 ml. of purified dioxane. The mixture was heated in a sealed vessel on the steam bath for 3 days then evaporated *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with sodium carbonate solution and with brine. Filtration through Filter-Cel followed by evaporation and trituration of the residue with ethyl acetate–ether yielded 1 g. of crude product, m.p. 188–191°. This was further purified by chromatography on activity II–III alumina and recrystallization; m.p. 191–193°, $[\alpha]^{27}\mathrm{D}$ −92°. It was identical with the reductive amination product as shown by all the usual criteria.

Anal. Found: C, 68.67; H, 7.90; N, 9.29.

The third reductive amination product, the 17-desmethoxy compound (IX-a) was obtained from the mother liquors of the β-amino derivative. One gram of combined residues from several reductive aminations was subjected to rechromatography on 40

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(12) G. M. Kosolapoff, "Organophosphorus Compounds," 1st ed., J. Wiley and Sons, Inc., New York, N.Y., 1950, Chap. 7.

(13) R. E. Lutz *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(14) Unpublished results from this laboratory.

g. of grade II–III neutral alumina. On elution with 5% methanol in methylene chloride there was obtained 0.8 g. of material which after repeated recrystallizations from ethyl acetate yielded 0.46 g. of product, m.p. 170–172°, $[\alpha]^{26}\text{D}$ $-40°$.

Anal. Calcd. for $C_{25}H_{35}N_3O_3$: C, 70.56; H, 8.29; N, 9.88; OCH_3, 14.60. Found: C, 70.15; H, 8.45; N, 10.10; OCH_3, 14.49.

A mixture of 0.2 g. of the desmethoxy compound and approximately 0.35 g. of lithium aluminum hydride in 50 ml. of ether was allowed to stand overnight, then refluxed for 1 hr. The excess hydride was decomposed by addition of water and the slurry was filtered. The solid was washed with methylene chloride and the combined organic phase was evaporated to yield a residue which was recrystallized from a mixture of ethyl acetate and low-boiling petroleum ether. The resulting alcohol (0.1 g.) had m.p. 183–185°, $[\alpha]^{24}\text{D}$ $+8°$.

Anal. Calcd. for $C_{24}H_{35}N_3O_2$: C, 72.51; H, 8.87; N, 10.57; OCH_3, 7.82. Found: C, 72.65; H, 8.90; N, 10.97; OCH_3, 8.21.

Reductive Amination with Piperidine.—Reaction was carried out as in the propylamine case but with one-half quantities. After 4 days the apparent hydrogen uptake was 280 ml. Chromatography by the usual method afforded, in the first methylene chloride eluates, the 17-desmethoxy compound (IX-b), which after recrystallizations from ethyl acetate had m.p. 203–206°, $[\alpha]^{24}\text{D}$ $-32°$. The yield was 0.35 g.

Anal. Calcd. for $C_{27}H_{37}N_3O_3$: C, 71.81; H, 8.26; N, 9.31. Found: C, 71.62; H, 8.30; N, 9.02.

Reductive Amination with Pyrrolidine.—Reaction as in the piperidine case resulted in the apparent uptake of 335 ml. of hydrogen in 3 days. Chromatography by the usual procedure afforded, in the first methylene chloride eluates, 0.7 g. of solid, which yielded 0.2 g. of needles after recrystallizations from ethyl acetate; m.p. 275–277°, $[\alpha]^{24}\text{D}$ $-28°$. This was the 18α-amino derivative (VII-c) with, however, the 3-iso configuration, as shown by infrared absorptions at 2700 and 2770 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}N_3O_4$: C, 69.35; H, 7.98; N, 8.99; OCH_3, 19.91. Found: C, 69.63; H, 7.99; N, 9.08; OCH_3, 20.56.

The product was also prepared from a mixture of 4.5 g. of methyl reserpate *m*-nitrobenzenesulfonate, 5.4 g. of pyrrolidine and 280 ml. of purified dioxane. The reaction mixture was heated and stirred in a pressure bottle at steam-bath temperature for 6 days. After separation of a small quantity of insoluble material the solution was evaporated to dryness and the residue was worked up by the usual procedure. The analytical sample, recrystallized from methanol–methylene chloride, had m.p. 268–269°, $[\alpha]^{27}\text{D}$ $-32°$. The product was identical with the substance obtained from the reductive amination as shown by infrared and paper chromatographic comparisons. None of the "3-normal" epimer was isolated from this solvolysis.

Anal. Found: C, 69.09; H, 8.10; N, 8.78.

The 17-desmethoxy compound (IX-c) was obtained on further elution of the reductive amination product with 5% methanol in methylene chloride. A total of 1.0 g. of material from three such experiments was recrystallized from ethyl acetate, rechromatographed on alumina as above, and recrystallized again to yield 0.76 g. of fine filaments, m.p. 245–247°, $[\alpha]^{24}\text{D}$ $-36°$.

Anal. Calcd. for $C_{26}H_{35}N_3O_3$: C, 71.36; H, 8.06; N, 9.60; OCH_3, 14.20. Found: C, 71.25; H, 8.17; N, 10.03; OCH_3, 15.00.

Reaction of Methyl Ketoreserpate Oxime with Sodium Methoxide.—To a solution of 0.46 g. of sodium in 50 ml. of anhydrous methanol 4.27 g. of oxime was added and the mixture was refluxed in a nitrogen atmosphere for 2 hr., then allowed to stand overnight at room temperature. After evaporation of the solvent *in vacuo* the residue was dissolved in cold water and the product was precipitated by addition of solid ammonium chloride. Methanol was added and the slurry stirred to bring the solid into a filterable form, after which it was separated and washed with water. Recrystallization from ethanol–methylene chloride (Darco) afforded 2.82 g. of yellow product (X-a), m.p. 268–269°. The colorless analytical sample, m.p. 270–271°, was obtained by further recrystallizations from the same solvent pair. The unsaturated oxime exhibited ultraviolet absorption maxima at 229 mμ (ϵ = 39,670) and 266 mμ (ϵ = 22,760), a shoulder at 301 mμ (ϵ = 9760) and a minimum at 245 mμ (ϵ = 16,360). The single, strong carbonyl band in the infrared was found at 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63; OCH_3, 15.70. Found: C, 66.62; H, 6.57; N, 10.85; OCH_3, 15.86.

Methyl Ketoreserpate Semicarbazone–Sodium Methoxide Reaction.—To a solution of 0.37 g. of sodium in 80 ml. of anhydrous methanol 3.75 g. of the semicarbazone was added. The solution was warmed gently and swirled under nitrogen until all of the solid dissolved. It was then allowed to stand under nitrogen for 24 hr., during which period the product (X-b) crystallized. Chilling, filtration, and washing with methanol afforded 3.3 g. of product, m.p. 253.5–257°. After recrystallization from ethanol–methylene chloride 2.9 g. (83%) of pure material, m.p. 260–262°, was obtained. The single carbonyl absorption band was found at 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}N_5O_4$: C, 63.14; H, 6.22; N, 16.01; OCH_3, 14.20. Found: C, 63.36; H, 6.26; N, 15.98; OCH_3, 14.46.

Hydrolysis of X-b to Yield XI.—A mixture of 0.88 g. of semicarbazone, 30 ml. of glacial acetic acid, 10 ml. of water and 7.2 ml. of 1.66 *N* aqueous pyruvic acid was heated at 70° under nitrogen for 40 hr., then allowed to stand at room temperature for an additional day. The orange solution was filtered through Darco, diluted to 300 ml. with water and made basic with ammonia. The amorphous precipitate was separated by filtration, washed with water and dissolved as completely as possible in ether. After separation of a small amount of insoluble material the ether solution was washed with water and with brine, then dried and evaporated to a low volume. Dilution to about 200 ml. with cyclohexane was followed by evaporation of the remaining ether. After chilling and removal of about 0.1 g. of amorphous solid the cyclohexane solution was evaporated to dryness *in vacuo*. Recrystallization of this residue from methanol afforded 0.1 g. of the unsaturated ketone (XI), m.p. 224–225°, $[\alpha]^{24}\text{D}$ $-244°$. The infrared spectrum ($CHCl_3$) of the free base showed two carbonyl absorption bands at 1675 and 1715 cm.$^{-1}$ and bands characteristic of the 3-iso structure at 2680 and 2740 cm.$^{-1}$. Since the free base appeared to be unstable, it was analyzed as the hydrochloride salt. The salt was prepared by dissolution of 85 mg. of the material in 5 ml. of acetone and addition of 2 ml. of 1 *N* hydrogen chloride in acetone. The resulting yellow, granular solid was separated by filtration from the chilled solution and washed with ether; m.p. 246–247.5°.

Anal. Calcd. for $C_{22}H_{24}N_2O_4 \cdot HCl$: C, 63.49; H, 6.06; N, 6.72. Found: C, 63.45; H, 6.11; N, 6.81.

Hydrolysis of X-b to Yield XII.—The semicarbazone (1.62 g.) was dissolved in a mixture of 55 ml. of glacial acetic acid, 18.4 ml. of water and 13.2 ml. of 1.66 *N* aqueous pyruvic acid, and the mixture was heated under nitrogen at 60° for 30 hr. The cooled mixture was filtered through Darco, added to 600 ml. of water and made basic with concentrated ammonium hydroxide with external cooling. The resulting amorphous, yellow precipitate was separated by filtration, washed with water and dried. The product was dissolved in 350 ml. of benzene and the solution was evaporated to 200 ml. and poured onto a column of 80 g. of Florisil. The column was washed with an additional 250 ml. of benzene, which was discarded, then eluted with 400 ml. of ether to produce 0.09 g. of crude XI, m.p. 234.5–236°. Elution with 1000 ml. of ethyl acetate afforded 0.83 g. of crude, crystalline XII. After washing with ether and recrystallization from methanol the 0.54 g. of pure product had m.p. 209–211°, $[\alpha]^{25}\text{D}$ $+31°$. The infrared spectrum showed twin carbonyl absorptions at 1680 and 1715 cm.$^{-1}$ but only a very faint peak in the 3-iso region at 2750 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36; OCH_3, 16.32. Found: C, 69.13; H, 6.18; N, 7.14; OCH_3, 16.81.

Methyl 3-Iso-18-ketoreserpate.—The ketone was first obtained inadvertently in an effort to effect an elimination of the type experienced in the reductive aminations. When a mixture of 6.18 g. of ketone, 60 ml. of triethylamine, 150 ml. of absolute ethanol and 3 g. of 10% palladium–charcoal was stirred with hydrogen at atmospheric pressure and room temperature for 3 days, an apparent uptake of 375 ml. of hydrogen was observed. Filtration and evaporation *in vacuo* produced in one case 2.7 g. of crystalline 3-iso compound directly. In another reaction the residual froth from the ethanol could not be crystallized until it had been triturated with water. Further recrystallizations from 95% ethanol afforded white needles which gradually lost solvent from about 140° to 170°. On drying at 140° the solvated product became amorphous. It had $[\alpha]^{24}\text{D}$ $-18°$.

The infrared spectrum of a chloroform solution showed a broad carbonyl absorption at 1720–1740 cm.$^{-1}$ and "3-iso" bands at 2750 and 2800 cm.$^{-1}$. No elimination product was isolated from these reactions.

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79; OCH_3, 22.57. Found: C, 67.24; H, 6.97; N, 7.02; OCH_3, 23.05.

Although similar C-3 epimerizations with other reserpine derivatives have been observed under these conditions[14] the reaction was not altogether reproducible with the ketone, and in some apparently identical cases starting material was recovered virtually quantitatively. For this reason the 3-iso derivative was preferably prepared by potassium dichromate oxidation to the dehydro derivative[1] followed by catalytic reduction. In this process 4.12 g. of ketone (II) was dissolved in a mixture of 80 ml. of acetic acid and 160 ml. of water after which a solution of 1.6 g. of potassium dichromate in 80 ml. of water was added over a period of 15 min. The solution, which darkened at once, was stirred at room temperature for 1 hr., then chilled and made alkaline with concentrated ammonium hydroxide. The product was extracted into methylene chloride and the dried extract was immediately evaporated *in vacuo*. The residue was dissolved in 120 ml. of absolute ethanol containing 1.65 g. of 10% palladium–charcoal (previously saturated with hydrogen). Hydrogenation was carried out at room temperature and atmospheric pressure for 21 hr., during which period the apparent hydrogen uptake corresponded to 105%. After filtration and evaporation the residue was triturated with petroleum ether, then recrystallized from 95% ethanol to yield 2.16 g. of pure iso ketone. This was identical with the compound obtained previously as shown by paper chromatographic and other criteria. Material from the mother liquor consisted of a mixture of products which was not investigated further.

The phenylhydrazone was prepared by refluxing a mixture of 0.76 g. of ketone, 0.22 g. of phenylhydrazine, 40 ml. of absolute ethanol and 4 drops of acetic acid under nitrogen for 1 hr. The solvent was removed, the residue was dissolved in methylene chloride and washed with sodium carbonate solution and with brine, then dried and evaporated. Dissolution of the dirty froth in minimum methanol, chilling and scratching produced crystalline phenylhydrazone. The rather unstable material was purified by recrystallizations from the same solvent. Like other derivatives of the 3-iso ketone, it was solvated. The compound softened at about 155° and melted at approximately 170–180°.

Anal. Calcd. for $C_{29}H_{34}N_4O_4 \cdot {}^1/_2\ H_2O$: C, 68.08; H, 6.90; N, 10.95; OCH_3, 18.20. Found: C, 68.13; H, 6.99; N, 10.82; OCH_3, 18.65.

The semicarbazone was prepared by the usual method. After recrystallization from methanol–methylene chloride the white needles, obtained in 54% yield, melted at 230–234°. The analytical sample of the solvated derivative melted at 234–235°, $[\alpha]^{25}\mathrm{D}$ −110°.

Anal. Calcd. for $C_{24}H_{31}N_5O_5 \cdot {}^1/_2\ H_2O$: C, 60.23; H, 6.74; N, 14.64. Found: C, 60.04; H, 6.77; N, 15.05.

Reaction of Methyl 3-Iso-18-ketoreserpate with Sodium Methoxide.—A mixture of 0.82 g. of the ketone, 0.05 g. of sodium methoxide (Matheson) and 85 ml. of anhydrous methanol was refluxed in a nitrogen atmosphere for 3.5 hr., then slowly distilled at atmospheric pressure. About 70 ml. of solvent was removed in 80 min. after which the slurry was cooled and the solid was removed and washed with methanol. The 0.47 g. of yellow crystals had m.p. 214–225°. Concentration of the filtrate afforded, after acidification, an acidic material which was not investigated further. The crystalline solid, according to paper chromatographic assay, contained about 60% product and 30% unchanged starting material. Recrystallization from isopropyl alcohol afforded 0.27 g. (35%) of product, m.p. 232–234°. The analytical sample, prepared by further recrystallizations from the same solvent and from methanol had m.p. 235–236.5°, $[\alpha]^{25}\mathrm{D}$ −247°. The infrared spectrum was identical with that of the product from the semicarbazone hydrolysis (XI). The ultraviolet spectrum showed maxima at 228 mμ (ϵ = 43,000) and 296–299 mμ (ϵ = 6250) and a minimum at 281 mμ (ϵ = 4200).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.23; H, 6.31; N, 7.43.

Reaction of the Methyl 3-Iso-18-ketoreserpate Semicarbazone with Sodium Methoxide.—To a solution of 10 mg. of sodium in 2 ml. of anhydrous methanol was added 0.1 g. of the 3-isosemicarbazone and the solution was warmed under nitrogen to dissolve the solid, then allowed to stand at room temperature for 3 days. Evaporation to dryness *in vacuo* followed by trituration of the residue with ether yielded 0.11 g. of solid. This was dissolved in 2 ml. of methanol and the solution was added to 30 ml. of ice-water. The resulting waxy solid (0.03 g.) was recrystallized from 95% ethanol. Because of a shortage of material it was not possible to prepare an analytically pure sample. The twice-recrystallized material on qualitative ultraviolet analysis showed an absorption maximum at 298 mμ, as did the 3-normal isomer of X-b. The infrared spectrum (Nujol) showed carbonyl absorption at 1700 cm.$^{-1}$, and was in other respects similar to the spectrum of the 3-normal isomer.

Anal. Calcd. for $C_{23}H_{27}N_5O_4$: OCH_3, 14.20. Found: OCH_3, 13.34.

Hydrolysis of 3-Iso Form of X-b.—In the first of these hydrolyses an elimination reaction was carried out as above except that the mixture was first refluxed for 1 hr., then allowed to stand at room temperature for 1 day. After evaporation of the methanol the crude product (0.09 g.) was used directly in the hydrolysis. It was added to 1.3 ml. of water, 4 ml. of glacial acetic acid and 1 ml. of 1.66 *N* aqueous pyruvic acid and the solution was heated at 70° for 40 hr., kept at room temperature for 55 hr., then worked up as in the reaction with the 3-normal isomer of X-b (*vide supra*). In one reaction the only product isolated consisted of a few milligrams of crude material, m.p. 209–211°. Sufficient product was not obtained for full characterization, but paper chromatographic comparison in several solvent systems indicated that this was identical with the 3-normal ketone (XII).

In another experiment the reaction with sodium methoxide was carried out on a 0.2-g. scale. Evaporation yielded a crude residue, 0.12 g. of which was again used directly in the hydrolysis. In this case the mixture was heated at 70° for 15 hr., kept at room temperature for 3 days, then heated for an additional 25 hr. The solution was filtered through Darco, added to water and made basic with ammonia, after which the oily product was extracted into methylene chloride. Evaporation yielded 0.03 g. of dark powder which was largely the 3-iso olefinic ketone (XI) as shown by paper chromatographic comparison with the pure material.

Reaction of Methyl Ketoreserpate with Sodium Methoxide.—A mixture of 8.24 g. of ketone, 0.54 g. of sodium methoxide (Matheson) and 1000 ml. of methanol was stirred until the ketone dissolved, then distilled slowly at atmospheric pressure. The color gradually changed to a yellow. After about 750 ml. of solvent had been distilled (1 hr.) the product began to separate. A total of approximately 800 ml. of methanol was removed, after which the slurry was chilled and the yellow solid was separated by filtration and washed with methanol. The yield was 4.18 g., m.p. 223–226°. Darco treatment of a methylene chloride solution followed by recrystallization from methanol–methylene chloride and processing of the mother liquor afforded 3.78 g. (50%) of the new unsaturated keto ester (XIII) m.p. 229–230°. The analytical sample, prepared by further recrystallizations and having the same melting point, was obtained in the form of yellow needles, $[\alpha]^{25}\mathrm{D}$ +113°. The ultraviolet spectrum (ethanol) exhibited maxima at 228 mμ (ϵ = 46,700) and at 296 mμ (ϵ = 6330), a shoulder at 259 mμ (ϵ = 8300) and a minimum at 280 mμ (ϵ = 4370). The infrared spectrum ($CHCl_3$) showed "3-iso" bands at 2750 and 2820 cm.$^{-1}$ and carbonyl absorptions at 1680 and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.21; H, 6.50; N, 7.17.

Treatment of XIII with Acid.—The desmethoxy ketone (0.76 g.) was heated with a mixture of 30 ml. of glacial acetic acid, 10 ml. of water and 7.2 ml. of 1.66 *N* aqueous pyruvic acid at 70° for 40 hr. as in the hydrolysis of X-b. After keeping the solution a further 24 hr. at room temperature it was filtered through Darco and diluted to 300 ml. with water, then chilled and made alkaline with ammonium hydroxide. The resulting precipitate was separated by filtration and washed with water; wt. 0.64 g., m.p. 175–185°. Paper chromatography and thin-layer chromatography on silica gel indicated that this substance was essentially pure unchanged starting material. One recrystallization from methanol–methylene chloride afforded XIII, m.p. 220–222°.

Reaction of XII with Sodium Methoxide.—The 3-normal ketone (0.1 g.) was dissolved in 15 ml. of dry methanol and 0.01 g. of sodium methoxide (Matheson) was added. The methanol was slowly distilled at atmospheric pressure until the volume of the residue was 2–3 ml. After chilling, the product was separated by filtration, washed with methanol and recrystallized from methanol-methylene chloride to afford 0.04 g. of pure XIII, m.p.

231–233°, $[\alpha]^{25}_{\rm D}$ +111°. The identity of the material with the methyl ketoreserpate–sodium methoxide product was demonstrated by mixture melting point determination and by comparison of infrared spectra and paper chromatograms.

Ring Opening of Methyl Ketoreserpate Oxime.—The oxime (1.07 g.) was dissolved in 25 ml. of dry methylene chloride and 0.53 g. of phosphorus pentachloride in the same volume of solvent was added at room temperature. The solution became orange-red and a transient precipitate formed, which however, largely dissolved on standing for 18 hr. The solution was washed with cold 5% sodium carbonate solution, with water and with brine, then dried and evaporated *in vacuo*. The residue was extracted several times with boiling ether. Evaporation of the extracts yielded 0.86 g. of yellow-orange solid, which, by paper chromatographic assay, was 80–90% enol–ether. The product was quite unstable, particularly in polar solvents. Although it could be obtained crystalline from isopropyl alcohol or other alcohols, serious decomposition took place in solution and the crystals were usually obtained with an off-white color. The analytical sample, prepared by recrystallizations from isopropyl alcohol and Darco treatment of ether solutions, melted at about 191–193°, $[\alpha]^{25}_{\rm D}$ −31°. The infrared curve (Nujol) showed a carbonyl band at 1705 cm.,$^{-1}$ a strong absorption at 1645 cm.$^{-1}$ with a shoulder at 1635 cm.$^{-1}$, and nitrile absorption at 2250 cm.$^{-1}$. No absorption in the "3-iso" region was noted below 2850 cm.$^{-1}$ ($CHCl_3$). Further evidence for the β-configuration of the C-3 hydrogen was obtained from the n.m.r. spectrum ($CDCl_3$). The equatorial C_3H signal was observed at 4.31 p.p.m.

Anal. Calcd. for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26; OCH_3, 22.74. Found: C, 67.71, 67.40; H, 6.89, 6.69; N, 10.47; OCH_3, 22.58.

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Study of the Reactions in the Zinc Chloride–Benzaldehyde–Glucose System[1]

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A chromatographic method of analysis was used to study the kinetic and equilibrium properties of the zinc chloride–benzaldehyde–glucose system. 1,2-*O*-Benzylidene-D-glucofuranose was not found to be a product of the system under the conditions employed (liquid phase at 30°). The benzylidenation reactions were found to be consecutive. That is, glucose reacts to give 4,6-*O*-benzylidene-α-D-glucopyranose which then reacts to yield 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose. The equilibrium yields of 4,6-benzylideneglucose and 1,2:4,6-dibenzylideneglucose were both linear functions of the concentration of zinc chloride. This fact is shown to be in accord with the expected behavior of zinc chloride (a Lewis acid) in the presence of benzaldehyde and the water which is produced by the reactions (both Lewis bases). The calculated free energies of the reactions which produce the benzylideneglucoses were used to estimate that the difference in free energy between a five- and a six-membered acetal ring is about 1500 cal./mole.

A method was devised for analyzing for the sugar and sugar-containing species of the zinc chloride–benzaldehyde–glucose system. It involved a chromatographic separation of the various species using a water-saturated isobutyl alcohol solvent and methanol prewashed paper. Subsequently, glucose was determined using the well known technique of Somogyi[2] and the benzylideneglucoses were determined using their color reaction with anthrone.

Studies of the liquid phase of the system at 30 ± 0.2° using the above-mentioned method of analysis indicated that the chemical reactions taking place conformed to the following equilibria:

$$2\ G + ZnCl_2(C_6H_5CHO)_2 \rightleftarrows 2\ M + ZnCl_2(H_2O)_2 \qquad (1)$$

$$2\ M + ZnCl_2(C_6H_5CHO)_2 \rightleftarrows 2\ D + ZnCl_2(H_2O)_2 \qquad (2)$$

where G = glucose; M = 4,6-*O*-benzylidene-α-D-glucopyranose; and D = 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose. The formulas $ZnCl_2$ $(C_6H_5CHO)_2$ and $ZnCl_2(H_2O)_2$ were used to represent Lewis acid-base adducts between zinc chloride, benzaldehyde, and water.

Although 1,2-*O*-benzylidene-D-glucofuranose (I) has been prepared using this system,[3] none was found in this work. I, when added to a zinc chloride solution in benzaldehyde is rapidly converted to D. This information, coupled with the known stability of fused five-membered ring acetals such as I toward hydrolysis,[4] leads to the speculation that I, as prepared by Sowden and Kuenne,[3] might have been the product of a mild hydrolysis of D. If so, the hydrolysis would have to be accompanied by a change from the pyranose to the furanose form.

Reported yields of G, M, and D from the system[3,5,6] are variable. The preparations of Sowden and Kuenne,[3] Zervas,[5] and Wood, Diehl, and Fletcher[6] involved reaction times of 20, 24, and 4 hours, respectively. The data presented in Fig. 1 show that, at these times, the system has not yet come to equilibrium. The yields obtained are therefore dependent upon all factors which affect reaction rates in a two-phase system. Some of these are: glucose particle size, temperature, zinc chloride concentration, and efficiency of agitation. Failure to control carefully any such variable would cause different yields. Also, the previously mentioned preparations involved quenching the reactions by adding water. This could possibly give rise to hydrolyzing conditions which would reduce the yields.

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