N-Methylsolasodine

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Displacement reactions of pseudodiosgenin 27-*p*-toluenesulfonate have been studied to assess rearrangement proclivity. Acid-catalyzed cyclization of the 27-methylaminofurostene derivative prepared by displacement with methylamine has given an N-methylsolasodine different from a metastable tertiary amine possessing the N-methylsolasodine skeletal structure produced by alkaline treatment of a tetrahydropyridine methiodide obtained from 3β,16β-diacetoxy-27-chloro-25α-cholest-5-en-22-one. Probable conformations of the isomers have been assigned.

Synthesis of the azaoxaspirane[1] steroid alkaloids solasodine, tomatidine, and 5β-tomatidine from pseudosapogenins hinged upon selective preparation of intermediate 27-*p*-toluenesulfonate esters.[4] Isolation of the mono esters as crystalline entities proved unnecessary with ring-B saturated genins since tosylation with 2 equiv of *p*-toluenesulfonyl chloride in pyridine at 0°, followed by displacement with sodium iodide in butanone and chromatography on alumina, gave the 27-iodides in 40% over-all yields with pseudoneotigogenin, the precursor of tomatidine, and with pseudosarsasapogenin, the precursor of 5β-tomatidine.[4] Pseudodiosgenin 27-*p*-toluenesulfonate (**1**) (Scheme I), the precursor of solasodine, however, was isolated in nicely crystalline form in 80% yield after selective hydrolysis of the 3β-homoallylic ester function of crystalline pseudodiosgenin 3β,27-di-*p*-toluenesulfonate in refluxing aqueous acetone.[5] The convenience of preparation, superb properties, and usefulness of **1** encouraged further exploration of its chemistry.

In a study of direct exposure with amines, the 27-*p*-toluenesulfonate failed to react with ammonia or with benzylamine under any of the conditions chosen. With methylamine, on the other hand, it readily responded.[6] Dropwise addition of 11 *N* aqueous methylamine to a refluxing ethanolic solution of **1** during several hours gave 75% of the 27-methylaminofurostene **2**.

Acid-catalyzed cyclization of **2** to N-methylsolasodine (**3**), patterned on the straightforward synthesis of N-methyl-5β-tomatidine,[4] next was attempted. The results seemed puzzling since crystalline material isolated in only 20–40% yields melted abnormally low over a range from 115°, with intermediate partial or complete resolidification before final melting near 160°, $[\alpha]$ −58°. Modification of conditions in numerous repetitions,[7] together with painstaking chromatography and fractional crystallization of salts, failed to provide a sharply melting product. Consideration of possible inauthenticity of **2** then led to an investigation of the behavior of **1** under conditions of solvolysis, culminating in discovery of participation of the ring-E dihydrofuranoid olefinic bond in a solvolytic ring closure furnishing a novel, hexacyclic hemiketal.[8]

Meanwhile, a provisional preparation of N-methylsolasodine (**3**), previously described,[9] was repeated. Gentle alkaline treatment of the methiodide **4** had given[9] the unsaturated tertiary amine **5**, which, upon basic hydrolysis of both 3β- and 16β-acetoxyl groups, afforded a product of doubtful homogeneity, mp 156–162/176–180°.[10] When **4**[11] now was allowed to react with refluxing aqueous methanolic 1 *N* potassium hydroxide during 30 min,[12] recrystallization from isopropyl alcohol gave 65% of apparently homogeneous prisms, mp 180–185°, $[\alpha]$ −20°.

When alkaline treatment of **4** was carried out during several hours, however, the isolated amine was identical in crystal habit, melting range, and infrared spectrum with the lower melting cyclization product from **2**. Moreover, crystals recovered from mother liquors of the prisms of mp 180–185° were identical with the product melting at 115–160°. Protracted exposure of the higher melting substance in refluxing ethanol alone, in the absence of acid or base, led to gradual conversion to the lower melting form. Both compounds crystallized especially well from isopropyl alcohol.

On acetylation with acetic anhydride in pyridine at 25° both amines furnished the same 3β-acetate as plates melting at 170°–180°, $[\alpha]$ −40°. Hydrolysis of the 3β-acetate with 2% aqueous methanolic potassium bicarbonate at 25° gave the 3β-ol melting at 115–160°.

The infrared spectra of the amines, while departing widely in individual band positions, were characterized in both cases by rich fingerprint regions typical of azaoxaspiranes; neither spectrum showed absorption in the 5.9–6.1-μ segment attributable to enol ether

(1) The expression azaoxaspirane, derived from *Chemical Abstracts*, usage,[2] was introduced,[3] not as a basis for systematic nomenclature but as a functional group term to replace the inaccurate and cacophonous "spiroaminoketal."

(2) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed, American Chemical Society, Washington, D. C., 1960, pp 138–181.

(3) F. C. Uhle and F. Sallmann, *J. Am. Chem. Soc.*, **82**, 1190 (1960).

(4) F. C. Uhle, *ibid.*, **83**, 1460 (1961).

(5) F. C. Uhle, *J. Org. Chem.*, **27**, 2797 (1962).

(6) Basicity of the amines may be controlling: ammonia, pK_a = 9.21; benzylamine, pK_a = 9.34; methylamine, pK_a = 10.62. Values are from H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(7) For details see Experimental Section. A reasonably strong acid environment is required to promote addition of the 27-amino function to the 20(22)-furostene enol ether olefinic bond; **2** may be recovered unchanged from solution in dilute acetic acid. Comparatively retarded amino addition, as opposed to more ready hydroxyl addition, offers little chance of preparing cyclopseudosapogenin ring-F nitrogen analogs.

(8) F. C. Uhle, *Tetrahedron Letters*, No. 42, 3099 (1964); *J. Org. Chem.*, **31**, 4193 (1966).

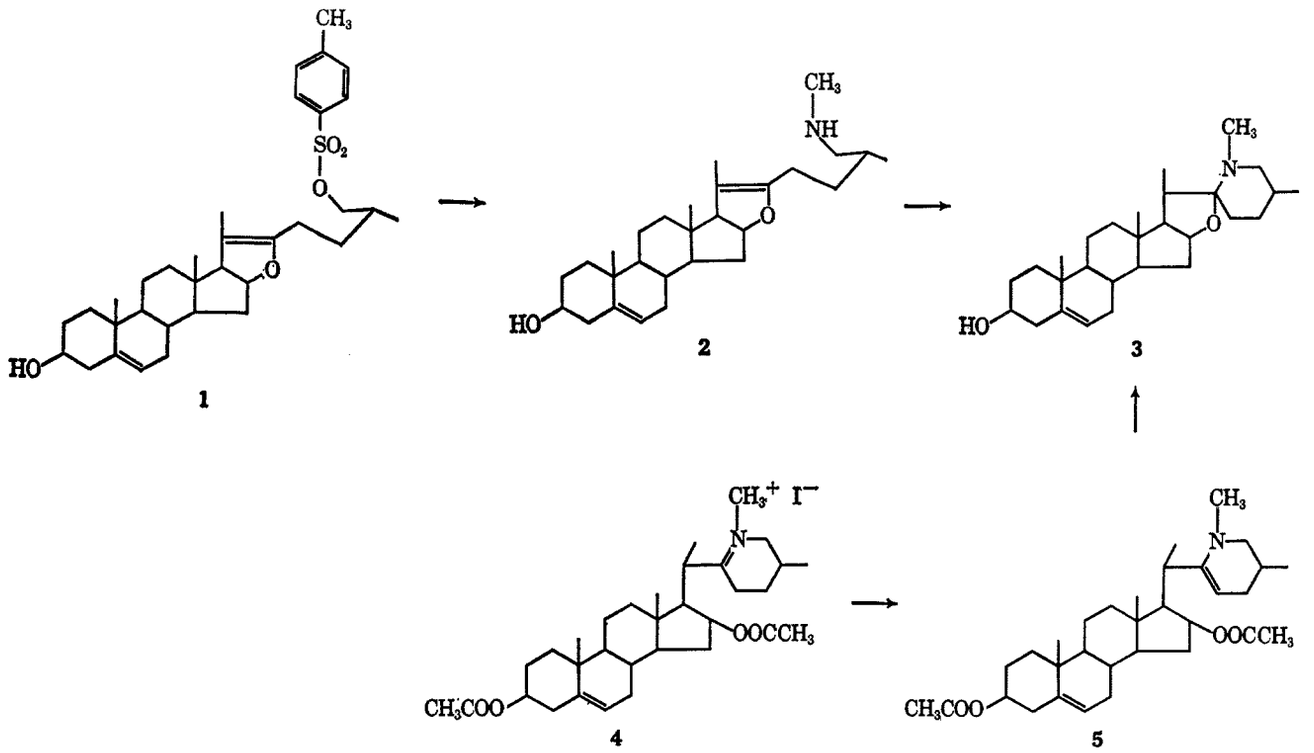
(9) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *ibid.*, **22**, 1496 (1957). The source of the starting methiodide **4** was the tetrahydropyridine derivative from acetolysis of solasodine with acetic anhydride in the presence of zinc chloride.

(10) Attempts to methylate solasodine with methyl iodide failed;[9] *cf.* L. H. Briggs, R. P. Newbold, and N. E. Stace, *J. Chem. Soc.*, 3 (1942). Clarke–Eschweiler methylation likewise gave inconclusive results.[9] In this laboratory, treatment of 5β-tomatidine with formaldehyde and refluxing formic acid furnished a tertiary amine not identical with the N-methyl-5β-tomatidine prepared by acid-catalyzed cyclization of the 27-methylaminofurostene synthesized from pseudosarsasapogenin.

(11) The compound used was prepared from 3β,16β-diacetoxy-27-chloro-25α-cholest-5-en-22-one: F. C. Uhle, *J. Org. Chem.*, **27**, 656 (1962).

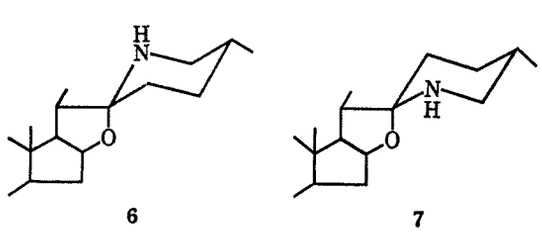
(12) Fairly vigorous alkaline treatment is needed for hydrolysis of the hindered 16β-acetoxyl function.

SCHEME I



or enamine functions.[13] On vapor phase chromatography, both substances gave single peaks with identical retention times.[14] The nuclear magnetic resonance spectra in deuteriochloroform, as well as in benzene, differed in slight alterations in the chemical shifts of the signals associated with the C-18, C-21, and C-26 methyl groups.[14] The spectra of the two forms in deuterioacetic acid were identical. The mass spectra were closely similar with prominent peaks at 427.[14] All of the physical data thus appears to buttress the impression that the compounds are conformational isomers.

Evidence from optical rotatory dispersion measurements,[15] as well as from nuclear magnetic resonance spectroscopy,[16] infers that solasodine itself is represented by conformation **6**, while tomatidine, epimeric



6 **7**

at C-25, is represented by **7**, with the C-26 methyl group equatorially disposed in both alkaloids and in their congeners. Demonstrably, reactions at the nitrogen atom are more readily accommodated in the tomatidine (**7**) than in the solasodine (**6**) series. While 3β-N-diacetyltomatidine is easily prepared,[17] for example, N-acylation of solasodine appears remarkably sluggish since a 3β-acetate of the secondary amine can be detected as the initial product.[18] Forced acetylation leads to amide formation accompanied by as much as 50% scission of ring E.[19] Again, tomatidine is promptly nitrosated in excellent yield while solasodine under the same conditions gives only low conversion to an N-nitroso derivative.[15] Differences in behavior of the two groups have been observed on lithium aluminum hydride reduction,[20] catalytic hydrogenation,[20] reaction with N-bromosuccinimide,[21] and pK determination.[21]

N-Methyltomatidine is smoothly prepared by alkaline treatment of a methiodide related to **4**;[22] an equally stable N-methyl-5β-tomatidine is produced by acid-catalyzed cyclization of the pseudosarsasapogenin counterpart of **2**.[4] Anomaly experienced in preparation of N-methylsolasodine thus appears in harmony with other comparative findings. Presumably, interactions with the *cis* C-21 methyl group exert the destabilizing influence in the solasodine series.

In attempting to assign conformations to the N-methylsolasodine isomers, the C-21 methyl group has

(13) All of the chemical observations reported could be explained by assuming the metastable compound of mp 180–185° to be the 3β,16β-diol of **5**, and by postulating cycloaddition to N-methylsolasodine (**3**, **9**) to be abnormally slow in alkaline media. This possibility appears excluded by all of the physical measurements, however, most convincingly by absence of enamine infrared absorption near 6.1 μ and by the absence from the nuclear magnetic resonance spectrum of signals in the olefinic proton region other than the signal at 5.35 ppm due to the C-6 hydrogen.

(14) The vapor phase chromatogram, nuclear magnetic resonance, and mass spectral determinations were carried out by Dr. R. J. Highet to whom the author is greatly indebted for generous help and counsel.

(15) P. M. Boll and B. Sjöberg, *Acta Chem. Scand.*, **17**, 1176 (1963).

(16) P. M. Boll and W. von Philipsborn, *ibid.*, **19**, 1365 (1965).

(17) T. D. Fontaine, J. S. Ard, and R. M. Ma, *J. Am. Chem. Soc.*, **73**, 878 (1951).

(18) L. H. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray, and R. N. Seelye, *J. Chem. Soc.*, 3013 (1950).

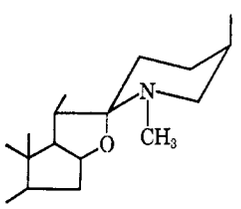
(19) Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, **25**, 783 (1960); Y. Sato and N. Ikekawa, *ibid.*, **25**, 786 (1960).

(20) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146, 3150 (1956); Y. Sato and N. Ikekawa, *J. Org. Chem.*, **26**, 1945 (1961).

(21) L. Toldy, *Acta Chem. Acad. Sci. Hung.*, **16**, 403 (1958); *Chem. Abstr.*, **54**, 5718 (1960); P. M. Boll, *Acta Chem. Scand.*, **14**, 783 (1960).

(22) Y. Sato, H. G. Latham, Jr., and N. Ikekawa, *J. Org. Chem.*, **25**, 1962 (1960).

been allotted the β configuration[23] in both compounds since the nuclear magnetic resonance spectrum of neither shows the relationship of the C-19 and C-18 signals characteristic of the cyclopseudosapogenins.[24] Secondly, equatorial orientation of the N-methyl group in both substances has been assumed. Although piperidine derivatives have been studied only recently by the methods of conformational analysis,[25] current information is interpreted as showing a pronounced preference of the methyl group of N-methylpiperidine itself for the equatorial position.[26] Finally, the customary ring-F chair forms have been proposed. These qualifications limit possible structures for the two isomers to an N-methylisosolasodine **8** and an N-methylsolasodine **9**.



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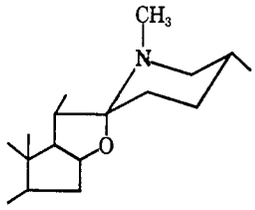

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Unfortunately, neither the chemical facts nor the physical measurements permit a firm decision. Examination of models suggests interaction of the *cis* C-21 methyl and N-methyl groups of **9** to be severe. On the other hand, the uniform C-26 methyl equatorial orientation of the naturally occurring alkaloids, contrasted with abundant C-26 methyl axial forms throughout the sapogenin family, appears to implicate some still undefined determinant rendering an axial C-26 methyl group peculiarly adverse in the nitrogen analogs.

Striving to estimate the relative magnitudes of these opposing effects has inclined to the view that the metastable tertiary amine produced by brief alkaline treatment of the methiodide **4** is represented by the N-methylisosolasodine formulation **8**. On acid treatment, or on prolonged exposure in alkaline medium, this compound is transformed, presumably by ring fission and reclosure, to the N-methylsolasodine **9** of mp 115–160°. According to this belief, the metastable **8**, despite the unfavorable axial disposition of its C-26 methyl group, is capable of isolation and of existence in solution when not unduly challenged, because a restraint to generation of the conformer **9** characteristic of solasodine itself becomes manifest when a methyl group has been fixed to the nitrogen atom.

The nuclear magnetic resonance spectra of the isomers appear to support this opinion (Table I). The proximity of the N-methyl to the C-21 methyl group of **9** would be expected to induce a downfield shift of the C-21 signal relative to that seen in the spectrum of solasodine or of **8**. On the other hand, the N-methyl group of **8** might be expected to cause a less pronounced downfield shift of the signal resulting from the fairly closely situated C-18 angular methyl group. The lower field position of the axial C-26 signal in the spectrum of **8** is consistent with observations from the spiroketal sapogenins whose axial C-26 signals are seen at lower field relative to equatorial C-26 signals with $\Delta\delta$ of about 0.2 ppm.[27] However, the reading of the spectra of **8** and of **9** summarized in Table I arbitrarily assigns the secondary methyl signal at higher field in the spectrum of **8** to the C-21 methyl group despite the claim[27] that the C-26 signal of the sapogenins always is observed at higher field relative to the C-21 signal. Hence, since attribution of the secondary methyl doublets, which are in part obscured by the angular methyl signals, is uncertain, and since suitable reference compounds are not available for comparison, the interpretation must be viewed with reserve.

TABLE I

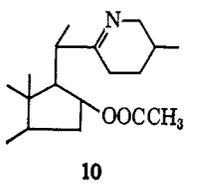
NUCLEAR MAGNETIC RESONANCE SPECTRA (60 Mc)[a]

	In deuteriochloroform			In benzene	
	8	**9**	Solasodine[b]	**8**	**9**
C-19	1.02	1.03	1.02	0.93	0.93
C-18	0.87	0.80	0.82	0.83	0.79
C-21	0.96	1.18	0.94	1.04	1.21
C-26	1.07	0.95	0.85	1.19	0.97
NCH_3	2.36	2.35		2.48	2.42

[a] Parts per million relative to TMS = 0. [b] Reference 16.

The broad melting range of **9** need not arouse suspicion of inhomogeneity since other substances derived from pseudodiosgenin exhibit similar double melting points with a prefatory low phase, followed by resolidification to distinctive, tiny needle clusters which melt finally at higher temperatures. Pseudodiosgenin 27-iodide (**13**) and the corresponding 27-phthalimido derivative (**12**) are noteworthy in this respect. Moreover, the melting point of the 3β-acetate derived from both N-methylsolasodine isomers is normal in character and range.

Treatment of the tetrahydropyridine derivative **10** with aqueous methanolic 1 *N* potassium hydroxide, employing conditions exactly duplicating those used with its methiodide **4** in preparation of **8**, afforded 31% of solasodine (**6**). The mother liquor concentrate gave



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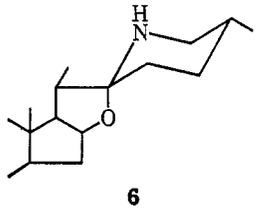

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an infrared spectrum which showed fully developed hydroxyl, ester, and azomethine bands, demonstrating incomplete hydrolysis of the 16β-acetoxy function under these circumstances. The 31% yield of solasodine, compared with the 65% yield of **8**, paradoxically appears to connote less hindrance of the 16β-acetoxyl group in the methylated compound. Perhaps the tendency to minimize interaction of the C-21 and N-

(23) Directed to the rear; for terminology, see L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p 819. The convention of numbering the substituted member of the side-chain-terminal methyl groups C-27 and the unsubstituted C-26 has been adopted, consisted with previous practice.

(24) W. E. Rosen, J. B. Ziegler, A. C. Shabica, and J. N. Shoolery, *J. Am. Chem. Soc.*, **81**, 1687 (1959).

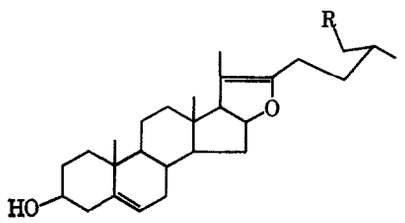
(25) E. L. Eliel, N. L. Allinger, S. A. Angyal, and G. B. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 244.

(26) N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.*, **87**, 1227 (1965); N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *ibid.*, **87**, 1232 (1965); M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963); N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (London), 1903 (1963); T. M. Monyehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

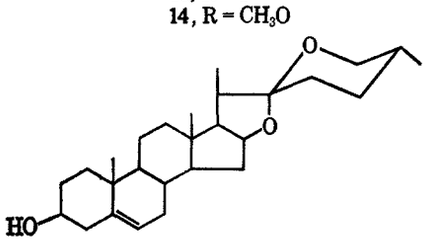
(27) J. P. Kutney, *Steroids*, **2**, 225 (1963).

methyl groups of **5** governs a spatial arrangement of the Δ^2-N-methylpiperidine ring which impedes access to the 16β ester function less than does the tetrahydropyridine ring of **10**.

Treatment of pseudodiosgenin 27-*p*-toluenesulfonate (**1**) with potassium acetate in refluxing ethanol gave the 27-acetoxy derivative **11**. Alkaline hydrolysis of **11**, followed by acidification, afforded diosgenin (**15**), confirming absence of rearrangement through a 1,2-hydrogen migration in displacement reactions of **1**. With potassium phthalimide in dimethylformamide, **1** gave the 27-phthalimido derivative **12** first prepared[4] from pseudodiosgenin 27-iodide (**13**). When **1** was allowed to react with potassium hydroxide in refluxing



11, R = CH_3COO
12, R = $C_6H_4(CO)_2N$
13, R = I
14, R = CH_3O



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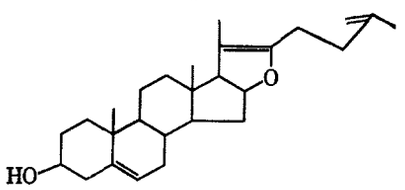

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methanol, 88% of pseudodiosgenin 27-methyl ether (**14**) was produced.[28] With pseudodiosgenin 27-iodide (**13**), however, methanolic potassium hydroxide furnished 94% of the elimination product **16**.[29]

Experimental Section[30]

3β-Hydroxy-27-methylamino-25α, 5,20(22)-furostadiene (2).—A mixture of 569 mg (0.001 mole) of pseudodiosgenin 27-*p*-toluenesulfonate (**1**),[5,8,31] 5 ml of 11 *N* aqueous methylamine, and 25 ml of ethanol was heated under reflux. When dissolution was complete (5 min) 50 ml of 11 *N* aqueous methylamine was added dropwise during 2.5 hr at reflux temperature. After 20 hr at 0°, the precipitate was collected by filtration, washed with water, dried, and dissolved in 15 ml of methanol. The methanolic solution was filtered by gravity to remove a vexing trace of opalescent suspension. The filtrate was concentrated to give a residue which was recrystallized from 5 ml of methanol to afford 320 mg (74%) of long needles, mp 149–156°, [α] −30°, infrared spectrum: 5.92 μ (m) (enol ether).

Anal. Calcd for $C_{28}H_{45}NO_2$ (427.65): C, 78.63; H, 10.61; N, 3.28. Found: C, 78.69; H, 10.52; N, 3.57.

Acetylation of **2** with acetic anhydride in pyridine at 0°, followed by hydrolysis of the 3β-acetoxy function with dilute aqueous ethanolic potassium hydroxide and recrystallization of the product from a mixture of methanol and ethyl acetate gave the N-acetyl derivative: mp 159–163°; infrared spectrum: 5.90 (m) (enol ether), 6.10 (sh), and 6.15 μ (tertiary amide).

Anal. Calcd for $C_{30}H_{47}NO_3$ (469.68): N, 2.98. Found: N, 3.32.

Treatment of **1** with 15 *N* aqueous ammonia in refluxing ethanol according to a procedure similar to that used for preparation of **2** led only to recovery to unchanged **1**. Treatment of 114 mg (0.0002 mole) of **1** with 1.07 g (0.01 mole) of benzylamine in 3 ml of absolute ethanol at reflux temperature during 3 hr led only to recovery of **1**. Trituration of the total product with 10% aqueous acetic acid revealed no acid-soluble material.

N-Methylsolasodine (9).—A mixture of 172 mg (0.0004 mole) of 3β-hydroxy-27-methylamino-25α,5,20(22)-furostadiene (**2**), 4 ml of 1 *N* aqueous hydrochloric acid, and 4 ml of methanol was heated under reflux during 2 hr (dissolution complete after 0.5 hr). The mixture was diluted with 5 ml of methanol and was made basic with 300 mg of potassium hydroxide. After 15 min at reflux temperature, the solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal phase was dried and chromatographed over 4.8 g of aluminum oxide to give 85 mg of product eluting with ether and 60 mg with 5% methanol in ether. The ether eluate was crystallized from isopropyl alcohol to afford 35 mg (20%) of rods, mp 115°, followed by partial resolidification to characteristic clusters of tiny needles which melted finally near 160°; [α] −58°; infrared spectrum: 6.85 (s), 6.9 (s), 7.0 (m), 7.1 (w), 7.25 (s), 7.35 (m), 7.55 (w), 7.65 (w), 7.95 (m), 8.0 (w), 8.1 (w), 8.25 (w), 8.45 (m), 8.65 (m), 8.80 (m), 8.85 (m), 9.0 (m), 9.2 (m), 9.45 (s), 9.65 (m), 9.8 (s), 9.9 (s), 10.1 (w), 10.25 (s), 10.4 (s), 10.6 (w), 10.9 (w), 11.05 (w), 11.1 (m), 11.35 (s), 11.6 (s), 11.95 (m), 12.3 (w), 12.55 (m), 12.8 (m), 13.6 (w), 14.0 (w), and 14.2 (w) μ. On a 1% SE-30 vapor phase chromatography column the compound gave a single peak with retention time of 6.2 min (cholesterol, 2.8 min); on a 1% QF-1 column, retention time of the single peak was 5.55 min (cholesterol, 2.4 min);[14] the mass spectrum showed prominent peaks at 127, 128, 152, and 427.[14]

Fifteen cyclization attempts were run with concentrations of hydrochloric acid ranging from 0.1 to 1 *N* during periods of 15 min to 24 hr in refluxing aqueous methanol. These experiments failed to indicate a trend although 0.5 *N* HCl during 2 hr consistently gave 20–40% of characteristic crystalline material. After 15 min with 0.1 *N* HCl, no product was isolated. Acetone, methanol, and isopropyl alcohol were used as crystallizing solvents; the latter appeared preferable. Tedious, repetitive chromatography on alumina, as well as fractional crystallization of hydrochlorides and of picrates failed to alter the product. Occasionally, the lower component of the double melting point is not seen. For example, a specimen, which melted at 115–155°, on a later repetition taken slowly showed the rods to rearrange into tiny needle clusters, without visible prefatory melting, as the temperature of the hot stage was elevated, with eventual melting at 153–160°. The same sample on a third repetition melted at 125–150°. The rate of heating appears in part to govern the actual values observed. The melting behavior of the compound thus resembles that of pseudodiosgenin 27-iodide (**13**) and of the corresponding 27-phthalimido derivative (**12**).[4,5] On a few occasions more sharply melting products were secured, *e.g.*, needles of mp 142–147 or 147–152°. Attempts to correlate melting

(28) *Cf.* P. Veeravagu, R. T. Arnold, and E. W. Eigenmann [*J. Am. Chem. Soc.*, **86**, 3072 (1964)], who found that in competitive elimination-substitution reactions, primary alkyl bromides predominantly undergo elimination with potassium *t*-butoxide in anhydrous *t*-butyl alcohol while the corresponding tosylates afford good yields of substitution products.

(29) For preparation of related terminal methylene unsaturated compounds, see Y. Sato, H. G. Latham, Jr., and I. Scheer, *J. Org. Chem.*, **21**, 689 (1956); M. J. Thompson, I. Scheer, and E. Mosettig, *J. Am. Chem. Soc.*, **81**, 5225 (1959).

(30) Melting points were observed on a calibrated micro hot stage and are corrected. Ethereal solutions were dried over anhydrous magnesium sulfate. Concentrations were carried out under diminished pressure with a rotating evaporator. Woelm nonalkaline alumina was used for chromatography. Infrared spectra were recorded from potassium bromide disks with a Perkin-Elmer spectrophotometer, Model 137. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Rotations were measured in chloroform at 25° by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(31) For comments on preparation of pseudodiosgenin with pyridine hydrochloride in acetic anhydride, see F. C. Uhle, *J. Org. Chem.*, **30**, 3915 (1965).

range with reaction conditions, chromatographic fraction, or mode of crystallization, however, proved bewildering. Infrared spectra of all products were virtually identical.

In attempted conversion to a methiodide, a mixture of 43 mg (0.0001 mole) of **9**, 2 ml of acetone, and 2 ml of methyl iodide was kept at 25° during 20 hr; a crystalline precipitate had formed. The mixture was concentrated to give a residue which was triturated with acetone to afford 50 mg (88%), mp 200–240°. Two recrystallizations from a mixture of methanol and acetone gave 15 mg: mp 245–250°; infrared spectrum: 6.8, 6.9, 7.2, 7.3, 8.4, 8.6, 9.1, 9.45, 9.8, 9.9, 10.3, 10.5, 11.2, 11.4, 11.9, and 12.3 μ. Two recrystallizations of the mother liquors from methanol–acetone afforded 10 mg: mp 225–235°; infrared spectrum: 3.7, 6.85, 7.0, 7.15, 7.25, 7.4, 7.8, 8.0, 9.1, 9.4, 9.7, 10.2, 10.5, 10.95, 11.9, 12.3, and 12.45 μ. The methiodides were not studied further.

N-Methylisosolasodine (8).—A mixture of 160 mg (0.00025 mole) of 3β,16β-diacetoxy-25α-22(27)-imino-5,22-(N)-cholestadiene methiodide (**4**)[9,11] (prepared from 3β,16β-diacetoxy-27-chloro-25α-cholest-5-en-22-one),[11] 560 mg (0.01 mole) of potassium hydroxide, 1 ml of water, and 9 ml of ethanol was heated under reflux during 2 hr. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal solution was dried and concentrated, affording a remainder which was crystallized from isopropyl alcohol to furnish 80 mg, mp 120–170°. Recrystallization from isopropyl alcohol gave 40 mg (37%) of tiny prisms, mp 175–179°. A third recrystallization from isopropyl alcohol gave 20 mg of the analytical sample, mp 172–176°, [α] −20°. After drying *in vacuo* at 100° during 15 hr, the sample melted at 163–168°; infrared spectrum: 6.8 (s), 6.85 (s), 6.95 (m), 7.2 (m), 7.3 (m), 7.4 (m), 7.5 (m), 7.55 (m), 7.7 (m), 7.8 (m), 7.9 (m), 8.0 (w), 8.15 (w), 8.2 (w), 8.35 (w), 8.6 (m), 8.65 (m), 8.85 (m), 8.95 (m), 9.25 (s), 9.45 (s), 9.7 (w), 9.8 (w), 9.95 (m), 10.1 (w), 10.25 (s), 10.35 (s), 10.45 (w), 10.5 (w), 10.7 (w), 10.85 (w), 11.1 (s), 11.15 (s), 11.4 (m), 11.85 (s), 11.95 (m), 12.05 (w), 12.3 (w), 12.5 (w), 12.9 (m), 13.5 (w), 13.9 (w), and 14.2 (w) μ. On a 1% SE-30 column, the compound gave a single peak with retention time of 6.2 min; on a 1% QF-1 column, retention time of the single peak was 5.55 min.[14] The mass spectrum showed prominent peaks at 127, 128, 152, and 427.[14]

Anal. Calcd for $C_{28}H_{45}NO_2$ (427.65): C, 78.63; H, 10.61; N, 3.28. Found: C, 78.75, H, 10.63; N, 3.30.

Mother liquors from the analytical sample were concentrated and crystallized from isopropyl alcohol to afford 40 mg of rods, mp 110°, followed by partial solidification to needle clusters which melted finally near 160°. The infrared spectrum was identical with that of the product (**9**) from hydrochloric acid catalyzed cyclization of **2**.

A second experiment in which the above quantities had been heated under reflux in aqueous ethanol (1:9) during 30 min gave 60 mg (56%) from isopropyl alcohol, mp 171–181°. Recrystallization afforded 45 mg (42%), mp 179–182°.

A third experiment in which aqueous methanol (1:9) was used as solvent during a 30-min reflux period gave 70 mg (65%) of prisms from isopropyl alcohol, mp 175–185°. Recrystallization afforded 56 mg (52%) of prisms, mp 180–185°. Several repetitions of the third set of conditions demonstrated the melting point and yield to be reproducible. Infrared spectra of the compounds prepared in the three differing runs were identical.

A fourth experiment in which aqueous ethanol (1:9) was used as solvent during 3 hr gave 53 mg (50%) from isopropyl alcohol, mp 115°, followed by partial solidification to needle sheaves with final melting near 160°. Recrystallization gave 25 mg of similar melting point. The infrared spectrum was identical with that of the product (**9**) from acid-catalyzed cyclization of **2**.

N-Methylsolasodine 3β-Acetate (9 3β-Acetate). A. From 8.—A mixture of 43 mg (0.0001 mole) of N-methylisosolasodine (**8**), 1 ml of acetic anhydride, and 2 ml of anhydrous pyridine was kept at 0° during 20 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 30 mg (64%) of tiny plates, mp 170–180°. Recrystallization from dichloromethane–methanol afforded plates: mp 168–180°; [α] −40°; infrared spectrum: 5.78, 8.05 (acetoxy), 6.8, 6.9, 7.2, 7.25, 7.5, 7.8, 8.45, 8.6, 8.8, 9.0, 9.2, 9.4, 9.6, 9.8, 10.05, 10.2, 10.35, 10.5, 11.1, 11.3, 11.45, 11.6, 11.9, 12.2, 12.45, 12.6, and 12.85 μ. On a 1% SE-30 column the acetate gave a single peak with retention time of 8.7 min; on a 1% QF-1 column retention time of the single peak was 7.9 min.[14]

Anal. Calcd for $C_{30}H_{47}NO_3$ (469.68): C, 76.71; H, 10.09; N, 2.98. Found: C, 76.80; H, 10.20; N, 2.98.

B. From 9.—The ether eluate (65 mg) from chromatographic fractionation of the product from 0.5 *N* hydrochloric acid catalyzed cyclization of 172 mg (0.0004 mole) of **2**, as described above under preparation of **9**, was acetylated with 1 ml of acetic anhydride in 2 ml of pyridine at 0° during 50 hr. The solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration and dissolved in ether. The ethereal solution was dried and concentrated to give a residue which was crystallized from methanol to afford 30 mg, mp 153–173°. Recrystallization from methanol gave 21 mg of plates, mp 170–176°. A third recrystallization from methanol afforded 15 mg of tiny plates, mp 170–180°, whose infrared spectrum was identical with that of the 3β-acetate prepared from **8**.

Anal. Calcd for $C_{30}H_{47}NO_3$ (469.68): C, 76.71; H, 10.09. Found: C, 76.70; H, 10.13.

Hydrolysis of N-Methylsolasodine 3β-Acetate (9 3β-Acetate).—To a mixture of 400 mg of potassium bicarbonate, 6 ml of water and 14 ml of methanol was added 19 mg (0.00004 mole) of **9** 3β-acetate. The solution was stirred magnetically during 10 days. (Hydrolysis was incomplete after 5 days.) The solution was concentrated to give a residue which was diluted with water. The precipitate was collected by filtration, washed with water, and dried. The infrared spectrum of the total product was nearly identical with that of **9**. Recrystallization from isopropyl alcohol gave 4 mg (23%) of rods, mp 105–115°, whose infrared spectrum was identical with that of **9**. Not unexpectedly, isomerization of **8** to **9** appears to take place under acetylation conditions.

Solasodine (6) from 10.—A mixture of 125 mg (0.00025 mole) of 3β,16β-diacetoxy-25α-22(27)-imino-5,22-(N)-cholestadiene (**10**)[9,11,32] (prepared from 3β,16β-diacetoxy-27-chloro-25α-cholest-5-en-22-one),[11] 560 mg (0.01 mole) of potassium hydroxide, 1 ml of water, and 9 ml of methanol was heated under reflux during 30 min. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Two recrystallizations of the residue from acetone afforded 32 mg (31%) of plates, mp 194–198°, whose infrared spectrum was identical with that of solasodine.

The combined mother liquors were allowed to evaporate slowly at 25°, giving a crystalline residue, mp 80–110°, whose infrared spectrum showed fully developed hydroxyl (2.9 μ), acetate (5.8 and 8.05 μ), and azomethine (6.0 μ, m) bands typical of the product arising from hydrolysis of only the 3β-acetoxy function of **10**.

3β-Hydroxy-27-acetoxy-25α-5,20(22)-furostadiene (11).—A mixture of 114 mg (0.0002 mole) of **1**, 382 mg (0.004 mole) of potassium acetate, and 2 ml of absolute ethanol was heated under reflux during 5 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from methanol afforded 55 mg (61%) of needles, mp 90–94°. Additional recrystallizations from methanol gave needles: mp 96–100°; [α] −28°; infrared spectrum: 5.8, 8.05 (acetoxy), and 5.92 μ (m) (enol ether).

Anal. Calcd for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 76.06; H, 9.69.

Diosgenin (15) from 11.—A mixture of 46 mg (0.0001 mole) of 3β-hydroxy-27-acetoxy-25α-5,20(22)-furostadiene (**11**), 100 mg of potassium hydroxide, 0.5 ml of water, and 2 ml of ethanol was heated under reflux during 2 hr. The solution was diluted with 2 ml of water and with 5 ml of ethanol and was acidified with 0.5 ml of aqueous 6 *N* hydrochloric acid. After 15 min at reflux temperature, the mixture was diluted with 5 ml of water and kept at 0° for 20 hr. The precipitate was collected by filtration to give 40 mg (96%) of needles, mp 186–198°. Recrystallization from a mixture of dichloromethane and methanol afforded fine needles, mp 201–203°, whose infrared spectrum was identical with that of diosgenin (**15**), [α] −124°.

3β-Hydroxy-27-phthalimido-25α-5,20(22)-furostadiene (12).—A magnetically stirred mixture of 114 mg (0.0002 mole) of **1**, 148 mg (0.0008 mole) of potassium phthalimide, and 1.5 ml of dimethylformamide was heated at 90° during 22 hr. The solution was diluted with aqueous potassium chloride to give a

(32) Purification of **10** is effected more readily by recrystallization from acetone than from methanol as previously recommended.[9,11]

precipitate which was collected by filtration, washed with water, dried, and recrystallized from isopropyl alcohol to afford 40 mg (37%) of needles, mp 72°, followed by resolidification to needle clusters and final melting at 130–140°. The infrared spectrum was identical with that of the product prepared from pseudodiosgenin 27-iodide (**13**): 5.92 (sh) (enol ether), 5.7 (m), 5.9, 13.8, and 14.0 μ (phthalimide).[4]

3β-Hydroxy-27-methoxy-5,20(22)-furostadiene (Pseudodiosgenin 27-Methyl Ether) (14).—A solution of 228 mg (0.0004 mole) of **1** and 2.5 g of potassium hydroxide in 10 ml of methanol was heated under reflux during 1 hr. The mixture was diluted with water to give a precipitate which was collected by filtration and dissolved in ether. The ethereal solution was washed with water, dried, and concentrated. Crystallization of the residue from methanol gave 150 mg (88%) of needles, mp 117–122°. Recrystallization from acetone afforded glistening plates, mp 128–129°, [α] −34°, infrared spectrum: 5.92 (m) (enol ether) and 9.05 μ (OCH_3).

Anal. Calcd for $C_{28}H_{44}O_3$ (428.63): C, 78.45; H, 10.35. Found: C, 78.49; H, 10.44.

3β-Hydroxy-25α-5,20(22),25(27)-furostatriene (16).—A mixture of 105 mg (0.0002 mole) of pseudodiosgenin 27-iodide (**13**),[4,5,8] 112 mg (0.002 mole) of potassium hydroxide, and 5 ml of methanol was heated under reflux during 50 hr. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal phase was dried and chromatographed over 2.4 g of aluminum oxide. The ether eluate was crystallized from a mixture of dichloromethane and methanol to give 78 mg (94%) of needles, mp 129–136°. Recrystallization from acetone gave long, asbestos-like needles, mp 132–136°, [α] −36°. Although both the 3β-ol and its 3β-acetate appear to crystallize with a mole of tenaceously held water, rendering analyses ambiguous, the infrared spectra give unquestionable evidence for the presence of terminal methylene unsaturation: 2.8, 3.1 (hydroxyl), 5.92 (m) (enol ether), 6.1 (w) (C=C), and 11.25 μ (=CH_2).

Anal. Calcd for $C_{27}H_{40}O_2 \cdot H_2O$ (414.61): C, 78.21; H, 10.21. Found (average of three determinations): C, 78.42; H, 9.84.

Treatment of pseudodiosgenin 27-iodide (**13**) with 25% methanolic potassium hydroxide during 1 hr at reflux temperature gave 82% of the same product.

Acetylation with acetic anhydride in pyridine during 20 hr at 25°, followed by crystallization of the product from a mixture of dichloromethane and methanol gave long needles: mp 126–131°; [α] −45°; infrared spectrum: 5.8, 8.05 (acetate): 5.92 (m) (enol ether), 6.05 (w) (C=C), and 11.25 μ (=CH_2).

Anal. Calcd for $C_{29}H_{42}O_3 \cdot H_2O$ (456.64): C, 76.27; H, 9.71. Found: C, 76.56; H, 9.43.

Clarke–Eschweiler Methylation of 5β-Tomatidine.—A mixture of 86 mg (0.0002 mole) of 5β-tomatidine (mp 207–217°),[4] 0.2 ml of 37% aqueous formaldehyde, and 2 ml of formic acid was heated under reflux during 10 hr. The solution was concentrated to give a residue which was dissolved in 15 ml of 80% aqueous ethanol, made basic with 330 mg of potassium hydroxide and heated under reflux during 1 hr. The mixture was concentrated to give a remainder which was diluted with water and extracted with ether. The ethereal phase was washed with water, dried, and concentrated. A solution of the concentrate in 2 ml of pyridine was acetylated with 0.5 ml of acetic anhydride during 20 hr. The mixture was diluted with aqueous potassium chloride to give a precipitate which was collected, washed with water, and dried. The precipitate was fully soluble in 10% aqueous acetic acid, denoting complete conversion to a tertiary amine. Crystallization from methanol gave 9 mg of kernels: mp 220–255°; infrared spectrum: 5.75, 8.05 (acetate), 9.2, 9.4, 9.75, 10.05, 10.1, 10.2, 10.45, 10.7, 10.8, 11.3, and 11.7 μ. Although this spectrum appears consistent with an N-methylazaoxaspirane formulation, it differs, particularly in the 10–14-μ region, from the spectrum of the N-methyl-5β-tomatidine 3β-acetate (mp 215–217°)[4] prepared by acid-catalyzed cyclization of 3β-hydroxy 27-methylamino-5β,25β-20(22)-furostene synthesized from pseudosarsasapogenin.

Registry No.—**2**, 7648-74-0; **2** N-acetyl derivative, 7648-75-1; **9**, 7604-92-4; **9** methiodide, 7604-93-5; **8**, 7604-94-6; **8** acetate, 7604-95-7; **6**, 126-17-0; **11**, 7604-96-8; **15**, 512-04-9; **12**, 7604-97-9; **13**, 7604-98-0; **14**, 7604-99-1; **16**, 7605-00-7; **16** acetate, 7605-01-8.

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Absolute Configuration of Pulegone Oxide and Piperitenone Dioxide

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The conversion of (−)-pulegone oxide to (−)-(1*R*:3*S*:4*R*)-*trans*-4-hydroxyneomenthol and (+)-(1*R*:3*R*:4*R*)-*cis*-4-hydroxymenthol and of (+)-pulegone oxide to (−)-(1*R*:3*R*:4*S*)-*trans*-4-hydroxyneoisomenthol is described. (−)-Piperitenone dioxide, derived from (+)-piperitenone oxide, has been converted to (+)-(1*S*:3*S*:4*S*)-*cis*-1-*cis*-4-dihydroxyisomenthol. From the absolute configurations of these alcohols, it follows that (−)-pulegone oxide and (+)-pulegone oxide are *trans* and *cis* isomers, respectively, and that (−)-piperitenone dioxide has the *cis*-(1*S*:2*S*:4*S*) configuration.

Reusch and Johnson[1] recently discussed the configuration of the diastereomeric pulegone oxides and concluded that, on the basis of infrared, ultraviolet, nmr, and ORD data, (−)-pulegone oxide, derived from (+)-pulegone, should be assigned the *cis* configuration (**3**) and (+)-pulegone oxide should be given the *trans* structure (**2**).

Djerassi, *et al.*,[2] on the other hand, suggested that this assignment should be reversed in the light of an extensive ORD investigation.

We wish, at this time, to report the determination of the absolute configuration of the pulegone oxides by an unequivocal chemical transformation into known diols of well-defined configuration.[3] (+)-(1*R*)-Pulegone (**1**) was oxidized with 30% hydrogen peroxide in 30% sodium hydroxide solution to a mixture of *cis*- and *trans*-pulegone oxides (mp 43°). Fractional distillation followed by zone-melting purification of the mixture afforded (−)-pulegone oxide (**2**, mp 54°) and (+)-pulegone oxide (**3**, mp 59°).

(1) W. Reusch and C. K. Johnson, *J. Org. Chem.*, **28**, 2557 (1963).

(2) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).

(3) This was briefly described in a preliminary short communication: J. Katsuhara, *Bull. Chem. Soc. Japan*, **39**, 1825 (1966).