[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. V.[1] The Synthesis of the Isomeric Solanidanones

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Received October 31, 1960

The lithium aluminum hydride–aluminum chloride reduction of solasodine affords a new C-22 isomeric diol which can be converted into C-25D, solanidan-3-one, by reduction to the dihydrodiol, oxidation to the carbinol amine, and reduction.

The reduction of tomatidine (I) yields a pair of C-22 epimeric dihydrotomatidines (IIIA and IIIB) which by oxidative cyclization and subsequent reduction have been converted into the respective C-22 isomeric C-25L solanidan-3-ones (VI and VII).[3]

The reduction of solasodine (II), on the other hand, either catalytically (hydrogen–platinum oxide–acetic acid[4] or with lithium aluminum hydride[5] has so far yielded only one (VA or IVA) of the two possible C-22 isomers. The dihydrodiol A (VA), thus obtained in the above catalytic reduction or from the reduction of IVA, has likewise been converted into an isomeric C-25D, solanidan-3-one (VIII)[6].

Recently we have investigated the aluminum chloride catalyzed lithium aluminum hydride reduction[7] of solasodine and have found that this procedure yields the hitherto unobtainable C-25D, C-22 isomeric diol B (IVB) in about 14% yield. The major product (76%) in this reduction is the known dihydrosolasodenol[5] (IVA) obtained exclusively in the conventional lithium aluminum hydride reduction of solasodine. For comprison purposes the yields of the 3,16-diols obtained from tomatidine and solasodine by the various reduction methods are tabulated in Table I. The new isomeric diol B (IVB) can be acetylated under usual conditions (pyridine–acetic anbydride, room temperature, sixteen hours) to yield the *O,N*-diacetyl derivative, IVa, leaving the 16-hydroxyl function unacetylated. This behavior is analogous to that observed in the case of dihydrotomatidine "B" (IIIB),[8] the corresponding diol from tomatidine, and is attributed to the shielding effect of ring F in the side chain (see IIIB or IVB). Oxidation with

TABLE I

	Dihydrotomatidine A (IIIA), % (M.P. 194.5–195.5°)	Dihydrotomatidine B (IIIB), % (M.P. 230–233°)
Lithium aluminum hydride	80	10[8]
Lithium aluminum hydride-aluminum chloride	18	70[7]
Catalytic reduction (Pt-HOAc)	35–45	30–35[8]
	Dihydrosolasodenol A (IVA), % (M.P. 261–265°)	Dihydrosolasodenol B (IVB), % (M.P. 221–225°)
Lithium aluminum hydride	87	1[8]
Lithium aluminum hydride-aluminum chloride	76	14
Catalytic reduction (Pt-HOAc)	85–90 (5,6-dihydrosolasodanol, VA)	

Kiliani's reagent[9] in acetone converts IVa to the 16-oxo derivative IVb. The reduction of the Δ^5 bond in diol IVB affords the new C-22 isomeric 5,6-dihydrodiol VB which like its parent compound fails to acetylate at C_{16}. The oxidation of VB with Kiliani's reagent followed by reduction (palladium-charcoal, ethyl acetate) of the carbinolamine leads to the formation of a new C-25D, C-22 isomeric solanidan-3-one (IX). Thus the preparation of IX completes the set of the four possible C-22 and C-25 isomers of solanidan-3-ones.[10,11] The properties of these isomers and the derived alcohols are summarized in Table II.

One may rationalize the formation of the predominant diol A by envisaging a mechanism such as proposed by Gaylord[15,16] for cleavage of the —N—C—O— grouping, with an attack occurring from the top of C_{22} with attendant inversion.

(1) For previous papers of this series see *J. Org. Chem.*, **25**, 783, 786, 789, 1962 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956).

(4) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939).

(5) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

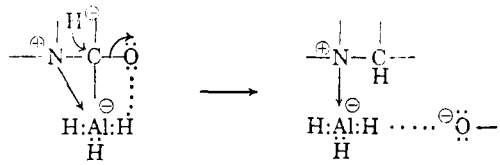
(6) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).

(7) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960). We are grateful to Professor Pettit for informing us of this procedure prior to publication.

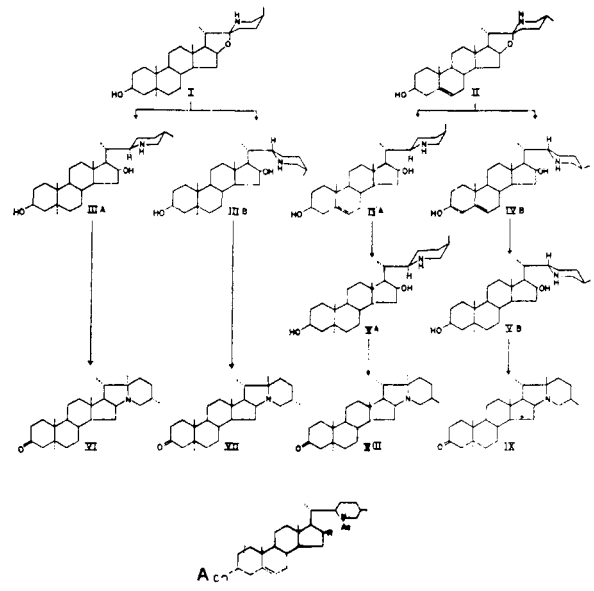
(8) Upon re-examination of the lithium aluminum hydride reduction of solasodine, we have found a very small amount (*ca.* 1%) of the isomeric dihydrosolasodenol (IVB) present. The major component IVA amounted to 87%. In the catalytic reduction (platinum oxide–acetic acid) we were unable to isolate any C-22 isomeric 5,6-dihydrosolasodanol (VB). In these reductions the yields generally ranged from 85 to 90%.

TABLE II

		M.P., °	$[\alpha]^{20}_{D}$(CHCl$_3$)
C-25L,22-isosolanidan-3-one	(VI)[13]	206–208	+32
C-25L,22-isosolanidan-3β-ol		198–203[14]	+12
Solanidan-3-one	(VII)	192–195 (210–213)	+43.5
Solanidan-3β-ol		217–219	+27
C-25D,22-isosolanidan-3-one	(VIII)	146–147	+49
C-25D,22-isosolanidan-3β-ol		154–157	+27
C-25D,solanidan-3-one	(IX)	156–158	+55
C-25D,solanidan-3β-ol		189–194	+40



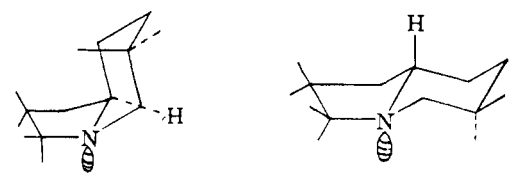
The resulting diol A (or dihydrodiol) will then possess structure IVA (or VA) with its hydrogen at C_{22} projected downward and in the subsequent cyclization to C_{22} isosolanidan-3-one, (VIII), be oriented to the rear, as shown conformationally in



IVa. R = —OH
IVb. R = =O

Figure 1

X. The epimeric dihydrodiol *B* having structure VB would by cyclization lead to solanidan-3-one (IX) of conformation XI.



X XI

Support for the above structure is reinforced by the appearance in the infrared spectra of a distinct band of medium intensity at 3.6 μ[17] in the solanidane derivatives. This is attributed to a system bearing a lone pair of electrons on the nitrogen atom trans to an adjacent tertiary C—H bond. All of the derivatives of the solanidane series (C-25D and C-25L) examined so far exhibit this absorption band while the corresponding C-22 iso compounds lack this prominent band.[18] An unequivocal confirmation of the configuration at C_{22} must, however, await further studies.

EXPERIMENTAL[19]

Reduction of solasodine. (a) *With lithium aluminum hydride.* A solution of solasodine (270 mg.) in ether (50 ml.) was added with stirring to a mixture of lithium aluminum hydride (0.9 g.) and ether (50 ml.) while the reaction mixture was cooled in an ice bath. The stirring of the mixture was continued for 1 hr. followed by a 2-hr. period of refluxing. The excess reagent was decomposed by the cautious addition

(9) A solution of 53 g. of chromium trioxide and 80 g. of sulfuric acid in 400 g. of water.

(10) A report [F. C. Uhle and F. Sallmann, *J. Am. Chem. Soc.*, **82**, 1190 (1960)] of the synthesis through another route of 22,25-isosolanidine, its dihydro and dihydrooxo derivatives appeared recently. Since the physical constants of their dihydro and dihydrooxo derivatives were not in agreement with our data, a thorough study of these compounds was made. By subjecting their dihydrooxo isosolanidine to gas chromatography,[12] it was found that its chromatogram was resolved into two peaks despite the fact that the compound possessed a sharp melting point (m.p. 164–166°). In contrast, all of our solanidan-3-ones indicated homogeneity of by possessing uniform single peaks. Comparison of the infrared spectra of the various isomers led us to conclude that Uhle and Sallman's so-called dihydrooxoiso derivative was in fact a mixture of C-25L solanidan-3-one (m.p. 192–195°, VII) and C-25D, solanidan-3-one (m.p. 156–158°, IX). A synthetic mixture (1:1) confirmed the above observations. It agreed in all respects (m.p., mixture melting point, infrared spectrum, gas chromatography, and optical rotation) with the properties of the compound prepared by the above authors. A synthetic mixture of the alcohols derived from VII and IX also agreed in infrared spectra with their so-called dihydro 22,25-isosolanidine. Apparently epimerization occurs during the course of their cyclization.

(11) A comprehensive gas chromatographic survey of these isomers and various other derivatives of solasodine and tomatidine is scheduled to appear shortly in a communication to this journal.

(12) See Acknowledgment.

(13) The term "iso" is used to designate epimers having an opposite configuration at C-22 from that of solanidine of natural origin.

(14) Erroneously reported 213–216° in ref. (3).

(15) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, New York, p. 816 (1956).

(16) Alternatively, coördination with the oxygen atom is conceivable. See W. Gerrard *et al.*, *J. Chem. Soc.*, 2144 (1960).

(17) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957).

(18) A weak band of less prominence appears at 3.6 μ in some of the C-22 iso compounds derived from tomatidine when taken in carbon disulfide.

of moist ether. After the addition of excess sodium hydroxide solution (2*N*), the ethereal layer was removed and the aqueous layer repeatedly extracted with methylene chloride containing 0.5% of methanol. The residue from the combined extracts was subjected to chromatography over alumina (Grade II). The fraction eluted with ether-methanol (0.5%) yielded 230 mg. of dihydrosolasodine A (IVA) and a subsequent eluate (5% methanol in ether) afforded 8 mg. of substance presumed to be a mixture of diols A (IVA) and B (IVB) as judged from its infrared spectrum.

(b) *With lithium aluminum hydride–aluminum trichloride.* Anhydrous aluminum trichloride (17 g.) in ether (150 ml.) was added to a mixture of lithium aluminum hydride (5 g.) and ether (150 ml.) while cooling in an ice bath. A solution of solasodine (1.25 g.) in ether (180 ml.) was then added dropwise with stirring to the above reducing agent over a period of 30 min. After an additional hour of stirring (ice bath), the mixture was refluxed for 2 hr. The reaction mixture was then worked up as in the manner described above. The ethereal layer and the combined methylene chloride extracts yielded 1.14 g. of crude product. Crystallization from methanol give 0.806 g. of dihydrosolasodine A^5 (IVA) of m.p. 257–262°. The mother liquor was concentrated to dryness and chromatographed over alumina (Grade II, 20 g.). A further crop (141 mg.) of diol A was obtained from the ether-methanol (1%) eluate (total yield 76%). The later fractions of the chromatography (5% methanol in ether) yielded 172 mg. (14%) of the C_{22} isomeric diol B (IVB) which crystallized as plates from aqueous methanol and melted at 218–222°. An analytical sample melted at 221–225°, $[\alpha]_D^{20}$ −51° (chloroform).

Anal. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.86; H, 11.05; N, 3.62.

Reduction of isomeric dihydro-Δ⁵-solasoden-3β-ol (IVB) *to dihydrosolasodan-3β-ol* (VB). Dihydrosolasodenol B (IVB, 182 mg.) was dissolved in 8 ml. of glacial acetic acid and reduced over 60 mg. of platinum dioxide. One mole equivalent of hydrogen was absorbed over a period of 2 hr. After removal of the catalyst, the filtrate was made alkaline with dilute sodium hydroxide solution and the precipitate crystallized from aqueous acetone. The dihydrodiol (VB, 164 mg.) crystallized as needles, m.p. 197–203°. The analytical specimen melted at 200–205°, $[\alpha]_D^{20}$ +10° (chloroform).

Anal. Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34; N, 3.35. Found: C, 77.88; H, 11.43; N, 3.09.

The *O,N*-diacetyl derivative of VB, *i.e.*, *N*-acetyldihydrosolasodan-3β-ol acetate, was prepared in the usual manner with acetic anhydride and pyridine. It melted at 228–232° and possessed strong infrared absorption bands (carbon disulfide) at 2.97μ (OH) and at 5.76, 8.06μ (OAc).

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 74.33; H, 10.19.

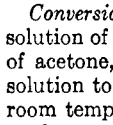
Acetylation of dihydrosolasodenol (IVB) to *N-acetyldihydro-Δ⁵-solasoden-3β-ol acetate* (IVa). IVB (90 mg.) was allowed to stand with pyridine (3 ml.) and acetic anhydride (2 ml.) at room temperature overnight. The product was crystallized from aqueous acetone, plates, m.p. 239–242°, $[\alpha]_D^{20}$ −59° (chloroform), $\lambda_{max}^{CS_2}$ 2.97 μ (OH); 5.75, 8.07μ (3-OAc).

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.85; H, 10.32; N, 3.19.

Oxidation of IVa to IVb. Kiliani's solution (0.08 ml.) was added dropwise to a solution of IVa (50 mg.) in acetone (10 ml.). After 10 min. a few drops of 3*N* sodium hydroxide solution was added to the reactants and the greenish colored sediment removed by filtration. Water was added to the filtrate and the precipitate collected and dried. Chromatography of this crude oxidation product over alumina and elution with 0.5% methanol in ether yielded 35 mg. of the 16-oxo derivative IVb, needles (ether-hexane), m.p. 181–183°, $[\alpha]_D^{20}$ −202° (chloroform), $\lambda_{max}^{CS_2}$ 5.75μ (OAc and C_{16} ketone); 8.07μ (OAc).

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 74.95; H, 9.35.

When the above compound (10 mg., IVb) was refluxed with a solution of 3*N* potassium hydroxide (0.2 ml). and methanol (2 ml.) for 20 min. and the product crystallized from acetone-hexane, needles of m.p. 233–238° were obtained. Its infrared spectrum (chloroform) possessed bands at 2.77, 2.90μ (OH); 5.75μ (5-membered ring ketone); 6.13μ



Conversion of VB to *C-25D, solanidan-3-one* (IX). To a solution of the isomeric dihydrodiol, (VB, 155 mg.) in 20 ml. of acetone, there was added dropwise 0.42 ml. of Kiliani's solution to the mixture and allowed to stand for 10 min. at room temperature. Several drops of water were then added to the contents of the flask and the greenish sediment which settled to the bottom removed by filtration. The filtrate was concentrated to about 5 ml. *in vacuo* and slowly diluted with sodium hydroxide solution. The crystalline substance (needles), which formed, was collected and thoroughly washed with water. The crude dried oxidation product was then hydrogenated over 10% palladium-charcoal in 8 ml. of ethyl acetate. In 70 min., 8 ml. (calcd. 8.5 ml.) of hydrogen was absorbed. When the product was chromatographed over alumina, the ether eluate afforded 100 mg. of C-25D, solanidanone, IX, which crystallized as rods from aqueous acetone or ethyl acetate, m.p. 152–156°. An analytical specimen melted at 156–158°, $[\alpha]_D^{20}$ +55° (chloroform), $\lambda_{max}^{CHCl_3}$ 3.59, 5.83μ. Under gas chromatography only a single uniform band was observed.

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90; N, 3.52. Found: C, 81.73; H, 11.08; N, 3.76.

The *alcohol of* IX, *C-25D, solanidan-3β-ol*, was prepared by the lithium aluminum hydride reduction of IX in ether. The compound was obtained from the 0.2% methanol–ether eluate fraction of the alumina chromatography. It melted at 189–194° (from acetone-hexane), $[\alpha]_D^{20}$ +40° (chloroform).

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35. Found: C, 81.01; H, 11.46.

The *alcohol of* VIII[6], *C-25D, 22-isosolanidan-3β-ol*, was also prepared by the lithium aluminum hydride reduction of VIII. The compound, after chromatography, crystallized as plates from methanol, m.p. 154–157°, $[\alpha]_D^{20}$ +27° (chloroform).

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35; N, 3.51. Found: C, 81.33; H, 11.56; N, 3.81.

Acknowledgment. The authors are deeply indebted to Dr. E. C. Horning and W. J. A. Vanden Heuvel of the National Heart Institute for invaluable aid rendered them in running gas chromatograms of these compounds.

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(19) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this Laboratory under the direction of Mr. Harold G. McCann. The infrared spectra were taken on the Model 21 Perkin Elmer Infrared Spectrometer by Mr. H. K. Miller and Mrs. Anne H. Wright of this Laboratory. "Woelm" neutral alumina grade I was used as absorbent for chromatography unless otherwise noted.