(B).—Hydrolysis of 128 mg of hymenoxynin in the manner described in the previous section using ethanolic HCl and work-up in the usual fashion furnished, after recrystallization from petroleum ether, the ethoxy derivative **15b** which had mp 73–75°; $[\alpha]_D$ −94.1° ($CHCl_3$, c 0.85); nmr signals at 4.77 m (H-8), 4.12 (H-4), 3.35–4 c (3 protons, H-3a and CH_3CH_2O–), 3.0 m (H-3_b), 1.22 t (J = 7 Hz, CH_3CH_2O–), 1.15 (J = 5 Hz,) and 1.08 d (J = 5.5 Hz, C-10 and C-11 methyl), and 1.06 ppm (C-5 methyl).

This substance was identical in all respects with the less polar material obtained by hydrogenation of anhydrohymenolide (10).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.69; H, 9.52; O, 21.59. Found: C, 68.80; H, 9.45; O, 21.66.

Registry No.—**2**, 16983-23-6; **3**, 25062-22-0; **4a**, 25062-24-2; **4b**, 25062-25-3; **5a**, 25062-26-4; **5b**, 25062-27-5; **6**, 25080-56-2; **7**, 25062-28-6; **8a**, 25062-29-7; **8b**, 25062-30-0; **9**, 25062-31-1; **10**, 25062-32-2; **11**, 25062-33-3; **14a**, 25062-34-4; **14b**, 25062-35-5; **15a**, 25062-36-6; **15b**, 25062-37-7; **15c**, 25062-38-8; **16**, 25080-57-3; **17**, 25062-23-1; **18**, 25062-40-2.

Conversion of Solasodine to Solafloridine and Dihydrosolacongestidine Acetate

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Received December 29, 1969

The two major steroidal alkaloids, solafloridine and solacongestidine, isolable from *Solanum congestiflorum* have been synthesized from solasodine. In the conversion acetylsolasodine is reduced to 3-acetyltetrahydrosolasodine, converted to the N-carbobenzoxy derivative, and oxidized to the 3-acetyl-16-oxo-N-carbobenzoxy compound. Sodium–propanol reduction affords the desired 16α epimer, dihydrosolafloridine, convertible to solafloridine by dehydrohalogenation of the N-chloro derivative. Thioketalization of the 3-acetyl-16-oxo-N-carbobenzoxy compound followed by Raney nickel reduction yields dihydrosolacongestidine acetate.

In a recent publication,[2] the isolation and structure proof of the steroidal alkaloids, solacongestidine (I) and solafloridine (II), from *Solanum congestiflorum* were reported. Owing to the time-consuming, laborious procedure involved in isolation and poor yield of the alkaloids from the plant, an alternate source was sought for these compounds when a demand for more alkamine, particularly solafloridine (II), arose for other projects.

Starting from solasodine[3] (III), a readily available steroidal alkaloid having the correct stereochemical configuration, the conversion was achieved in the following manner. O-acetylsolasodine[4] (IV) prepared from the reaction of solasodine (III) with acetic acid containing *p*-toluenesulfonic acid was reduced with sodium borohydride to O-acetyldihydrosolasodine (V) and in turn reduced catalytically (Pd–C) to O-acetyltetrahydrosolasodine[5] (VI). Conversion of VI to the N-carbobenzoxy-3-acetyl derivative (VII) with carbobenzoxy chloride and oxidation with Kiliani's reagent[6] in acetone to the 16-oxo compound (VIII) followed by reduction with sodium–2-propanol afforded the 16α-hydroxyl bearing dihydrosolafloridine[2] (IX) in good yields. A somewhat lesser yield was obtained by reduction with lithium–ammonia. This was accounted for by the recovery of considerable deacetylated starting material, VIIIa.[7] Compound IX, thus prepared, agreed in properties (melting point, mixture melting point, ir) with that obtained from the reduction of the natural product. The pathway outlined above, we believe, is an improvement over the published partial synthetic procedure[8] since the stereochemistry at C-20 and C-25 is unaffected throughout these reactions. The yield of the N-carbobenzoxy compound (VII) is diminished somewhat by the formation of a by-product assigned the structure XII either formed by the interaction of VI with some phosgene liberated during the reaction or ring closure of the debenzyloxy product of VII with the C_{16}–OH function.[9] The structure of XII was confirmed by its synthesis from the reaction of VI with phosgene. It should be noted in passing that the sodium borohydride reduction of the 16-oxo compound VIII afforded only the 16β-hydroxy isomer, VII, as expected.

Finally dihydrosolafloridine (IX) was converted to solafloridine (II) by dehydrohalogenation of the N-chloro compound in the manner reported by Schreiber and Adam.[8]

The N-carbobenzoxy-16-oxo compound (VIII) served as a convenient starting point for the preparation of dihydrosolacongestidine acetate (XI). This was accomplished by thioketalization of VIII with ethanedithiol which yielded the crystalline thioketal X. Desulfurization of the thioketal moiety with Raney nickel led to concomitant elimination of the N-carbobenzoxy function to afford the desired dihydrosolacongestidine acetate[2] (XI). Compound XI exhibited properties (melting point, mixture melting point, ir, mass spectrum) indistinguishable from those derived from solacongestidine. The compound like dihydrosolafloridine

(1) Visiting Scientists: G. Kusano (1969–present) and N. Aimi (1968–1969).

(2) Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, *J. Org. Chem.*, **34**, 1577 (1969).

(3) For a general review, see K. Schreiber in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, Chapter 1.

(4) We are indebted to Dr. J. A. Beisler of this laboratory for working out this procedure. H. Rochelmeyer, *Arch. Pharm.* (Weinheim), **277**, 329 (1939), report mp 193–194°.

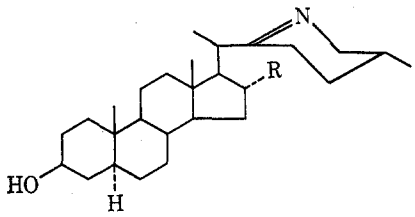
(5) Compound VI can also be prepared in somewhat reduced yields by the direct catalytic reduction (PtO_2–HAc) of O-acetylsolasodine (IV).

(6) H. Kiliani, *Ber.*, **46**, 676 (1913). A solution of 53 g of chromium trioxide and 80 g of concentrated sulfuric acid in 400 g of water was used.

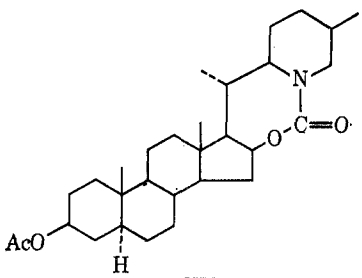
(7) In two runs the yield of the deacetylated starting material, VIIIa, was approximately the same. Perhaps the insolubility of the compound prevents its further participation in the reaction. We intend to study this reaction further.

(8) K. Schreiber and G. Adam, *Justus Liebigs Ann. Chem.*, **666**, 176 (1963).

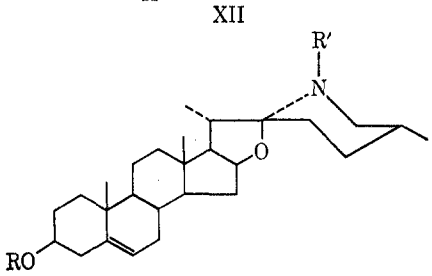
(9) It was suggested by one of the referees that formation of XII could have resulted from the attack of 16β-OH on the carbonyl function of the carbobenzoxy group of VII followed by loss of the benzyloxy ion. However, we had observed that in the repeat runs, vigorous agitation or stirring of the reaction flask resulted in negligible yields of XII. Hence, it was thought that in the earlier runs, due to insufficient agitation of the immiscible phase, neutralization was incomplete, and the resulting local acidic conditions led to prior debenzyloxylation.



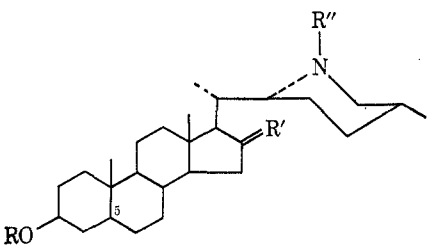
I (solacongestidine), R = H
II (solafloridine), R = OH



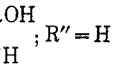
XII



III, (solasodine), R = R′ = H
IV, R = Ac, R′ = H



V (Δ^5), R = Ac; R′ =  ; R″ = H

VI ($C_5\alpha$), R = Ac; R′ =  ; R″ = H

VII ($C_5\alpha$), R = Ac; R′ =  ; R″ = CbO*

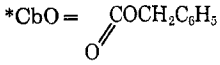
VIII ($C_5\alpha$), R = Ac; R′ = O; R″ = CbO

VIIIa ($C_5\alpha$), R = H; R′ = O; R″ = CbO

IX ($C_5\alpha$), R = H; R′ =  ; R″ = H

X ($C_5\alpha$), R = Ac; R′ =  ; R″ = CbO

XI ($C_5\alpha$), R = Ac; R′ = H_2; R″ = H

*CbO = 

(IX) is convertible to the azomethine, solacongestidine (I), in the manner described above.[10]

Thus, the conversion of solasodine to these alkaloids not only offers additional proof for the correctness of the ascribed stereochemistry and structure of these compounds but also demonstrates the utility of solasodine as a convenient starting material for their preparation.

(10) K. Schreiber and G. Adam, *Tetrahedron*, **20**, 1707 (1964).

Experimental Section[11]

O-Acetylsolasodine (IV).—*p*-Toluenesulfonic acid (12.73 g) was added portionwise to a solution of solasodine (11.95 g, 0.029 mol) in 650 ml of acetic acid while stirring at room temperature. After 2 hr a further batch of *p*-TsOH (4.25 g) was added to the reaction mixture and allowed to stand for 50 hr. The reaction product was then poured into a 1% NaCl solution (3 l.). After standing overnight the precipitate was filtered, dissolved in $CHCl_3$, and washed successively with 2% NaOH solution and water. The $CHCl_3$ extract yielded leaflets (10.99 g) from ethyl acetate: mp 189–190°[4]; $[\alpha]^{20}D$ −112.7° (*c* 1.81, $CHCl_3$); ir ($CHCl_3$) 3400 (NH), 1726 cm^{-1} (C=O).

Anal. Calcd for $C_{29}H_{45}NO_3$: C, 76.44; H, 9.95; N, 3.07. Found: C, 76.51; H, 9.65; N, 3.10.

O-Acetyldihydrosolasodine (V).—O-Acetylsolasodine (10.586 g, 0.023 mol) was dissolved in 550 ml of MeOH–CH_2Cl_2 (5:1) and to the solution was added 3.84 g (0.1 mol) of $NaBH_4$ while cooling. After stirring for 1 hr, ice water was added to the reaction mixture and the aqueous phase extracted twice with CH_2Cl_2. After removal of the solvent from the combined extracts, the residue crystallized as leaflets (9.251 g) from ethyl acetate: mp 211.5–213°; $[\alpha]^{20}D$ −67.13° (*c* 1.08, $CHCl_3$); ir (Nujol) 3280 (NH, OH), 1734 (C=O).

Anal. Calcd for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 75.76; H, 10.22; N, 3.28.

The mother liquor yielded a second crop (0.230 g) of V and starting material, IV (0.267 g), upon chromatography on silica gel.

O-Acetyltetrahydrosolasodine (VI).—To a suspension of 1.20 g of prereduced Pd–C (10%) catalyst in 400 ml of acetic acid was added a solution of V (9.12 g, 0.02 mol) in 100 ml of acetic acid. After the absorption of 520 ml of hydrogen in 10 hr, the uptake virtually ceased, but the hydrogenation was continued for another 10 hr. The catalyst was then removed by filtration and the filtrate was poured into 2 l. of a 2% NaCl solution.

After standing overnight the precipitate was filtered, washed with water, and dissolved in methanol. Sufficient 5% $NaHCO_3$ solution was added to the methanol until the solution was basic and the compound was taken up in ethyl acetate. Concentration of the solvent afforded 8.460 g of needles: mp 184–185°; $[\alpha]^{20}D$ −15.0° (*c* 1.02, $CHCl_3$); ir ($CHCl_3$) broad band centered at 3100 (OH, NH), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{29}H_{49}NO_3$: C, 75.77; H, 10.74; N, 3.05. Found: C, 75.58; H, 10.82; N, 3.37.

N-Carbobenzoxy-O-acetyltetrahydrosolasodine (VII).—O-Acetyltetrahydrosolasodine (VI, 1.3792 g, 0.032 mol) was dissolved in 150 ml of benzene by warming. After cooling to room temperature 70 ml of $NaHCO_3$ (5%) solution and 1 g (0.6 mol) of carbobenzoxy chloride were added successively to the reaction mixture with occasional shaking. After 4 hr another 0.5-g batch of carbobenzoxychloride was added to the reaction mixture and allowed to stand overnight. The benzene layer was separated, washed repeatedly with water, dried (Na_2SO_4), and concentrated to dryness. The residue upon chromatography on a silicic acid column and elution with benzene–ethyl acetate (10:1) yielded a colorless syrup (1.5 g) which was resubmitted to silicic acid chromatography. The benzene–ethyl acetate (2:1) eluate crystallized as needles (0.9096 g) from *n*-hexane–benzene (10:1): mp 127–129°; $[\alpha]^{20}D$ −12.9° (*c* 1.95, $CHCl_3$); ir (Nujol) 3498 (OH), 1738 (C=O), 1677 (NC=O), 1251 cm^{-1} (COC).

Anal. Calcd for $C_{37}H_{55}NO_5$: C, 74.83; H, 9.34; N, 2.36. Found: C, 74.83; H, 9.09; N, 2.46.

In the above reaction considerable amount of insoluble matter collects at the organic and aqueous interphase. This was collected and crystallized from methanol as needles, XII (235 mg): mp 312–315° with partial sublimation at 280–290°; $[\alpha]^{20}D$ −138.9° (*c* 0.83, $CHCl_3$); ir (Nujol) 1731 (C=O), 1692

(11) Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this laboratory. Infrared spectra were obtained with a Model 421 Perkin-Elmer spectrophotometer. Optical rotations were obtained in a 1-dm tube with a Model 141 Perkin-Elmer polarimeter. Nmr spectra were determined on the Model A-60 Varian Associates spectrometer, using $CDCl_3$ as solvent with tetramethylsilane as internal standard and described in δ values (TMS, 0.0 ppm). The mass spectra in these experiments have been measured with a Hitachi Perkin-Elmer RMU-7 spectrometer. Tlc plates were precoated with silica gel G and purchased from Analtech, Inc., Wilmington, Del.

(OC=O); mass spectrum 485 (M^+, $C_{30}H_{47}O_4N$), 344, 329, 276, 274, 269.

Anal. Calcd for $C_{30}H_{47}NO_4$: C, 74.18; H, 9.75; N, 2.88. Found: C, 74.33; H, 9.75; N, 3.15.

Synthesis of Compound XII.—To a solution of O-acetyltetrahydrosolasodine (VI, 195 mg) in 20 ml of ethyl acetate was added 20 ml of 5% $NaHCO_3$ solution; the mixture was shaken. To the mixture was then added 2 ml (0.534 g) of a phosgene–benzene solution with vigorous agitation. After standing overnight, the volatile components were removed *in vacuo* and the residue crystallized from methanol as needles (57.5 mg), mp >300°. The compound exhibited an ir spectrum identical with the spectrum of XII isolated above.

N-Carbobenzoxy-O-acetyl-16-dehydrotetrahydrosolasodine (VIII).—Kiliani's chromic acid reagent (1 ml, 0.0125 mol) was added to a solution of VII (0.7897 g, 0.0013 mol) in 25 ml of acetone while stirring at 0°. Following the addition of the oxidant, the stirring was continued overnight at room temperature. Methanol (10 ml) and $NaHCO_3$ solution (20 ml, 5%) were then added to the reaction mixture and extracted with $CHCl_3$. The residue, after removal of the $CHCl_3$, was submitted to chromatography on a silica gel column. The benzene–ethyl acetate (100:1) eluate yielded lumpy crystals (564 mg) after crystallization from benzene–*n*-hexane (10:1): mp 156–158°; $[\alpha]^{20}D$ −83.3° (*c* 1.59, $CHCl_3$); ir ($CHCl_3$) 1734 (five-membered-ring ketone + acetyl), 1687 cm^{-1} (NCO).

Anal. Calcd for $C_{37}H_{53}NO_5$: C, 75.09; H, 9.03; N, 2.37. Found: C, 75.14; H, 9.08; N, 2.46.

Dihydrosolafloridine (IX). Procedure A.—Compound VIII (506 mg) dissolved in 5 ml of 2-propanol was added dropwise, in the span of 10 min, to 15 ml of boiling toluene containing 0.7 g of sodium metal. After the addition the mixture was refluxed for 3 hr. When cool, a 2 *N* HCl (100 ml) solution was added to the reaction mixture. This resulted in the collection of some insoluble matter between the organic and aqueous interphase. After its removal, the acidic solution was made alkaline with NaOH (aqueous) and extracted with ethyl acetate. The precipitate and the dried extract were combined and chromatographed on alumina. The ethyl acetate–methanol (10:1) eluate gave needles (355 mg) after crystallization from methanol. Tlc of the acetyl derivative indicated the presence of a small amount of the 16β-isomeric tetrahydrosolasodine.[12] Recrystallization of IX from methanol afforded needles: mp 280–284°; $[\alpha]^{20}D$ 24.6° (*c* 0.37, $CHCl_3$); ir (Nujol) broad band, centered at 3300 (OH, NH), 1050 cm^{-1} (CO).

Anal. Calcd for $C_{27}H_{47}NO_2$: C, 77.64; H, 11.34; N, 3.35. Found: C, 77.70; H, 11.05; N, 3.26.

The compound was indistinguishable from the product obtained by the reduction of solafloridine (II).

Procedure B.—Compound VIII (319.5 mg) was dissolved in 5 ml of tetrahydrofuran and added to a solution of 100 mg of lithium in 10 ml of liquid ammonia. After 5 min, 10 ml of absolute ethanol was added dropwise to the reactants. The mixture stood overnight at room temperature. Water was then added to the reaction mixture and the resulting precipitate was filtered. The filtrate was extracted with ethyl acetate and evaporated to dryness. The precipitate and the residue were combined and submitted to chromatography on alumina. Elution with ethyl acetate and crystallization from the same solvent afforded needles, mp 193–195° (110 mg). Elemental analysis and spectra showed it to be the deacetylated product of VIII, *i.e.*, N-carbobenzoxy-16-dehydrotetrahydrosolasodine (VIIIa). VIIIa possesses the following characteristics: $[\alpha]^{20}D$ −86.3° (*c* 0.87, $CHCl_3$); ir (Nujol) 3498 (OH), 1737 (five-membered-ring ketone), 1680 (NCbO), 750 cm^{-1} (monosubstituted benzene); nmr ($CDCl_3$) δ 0.65 (3 H, s, C_{18} H's), 0.87 (3 H, s, C_{19} H's), 3.67 (1 H, m, C_3 H), 5.15 (2 H, OCH_2Ph), 7.38 (5 H, s, Ar H's).

Anal. Calcd for $C_{35}H_{51}NO_4$: C, 76.46; H, 9.35; N, 2.55. Found: C, 76.72; H, 9.32; N, 2.62.

Further elution of the above chromatogram with ethyl acetate–methanol (20:1) yielded the desired dihydrosolafloridine (IX, 117.8 mg), identical in every respect with the sample obtained by procedure A.

Sodium Borohydride Reduction of VIII.—Compound VIII (110.5 mg) was dissolved in 10 ml of a solution of MeOH–CH_2Cl_2 (5:1) by warming. After cooling to room temperature, $NaBH_4$ (108.9 mg) was added with stirring to the solution and allowed to stand for 30 min. The reaction mixture was then poured into 50 ml of 5% $NaHCO_3$ solution and extracted with ethyl acetate. The residue obtained from the extract was chromatographed on silica gel. The benzene–ethyl acetate (10:1) eluate gave colorless needles (90 mg) after crystallization from hexane–benzene (10:1), mp 125–127°. The compound exhibited properties indistinguishable from authentic VII.

Preparation of Solafloridine (II).—The conversion of dihydrosolafloridine (IX) to solafloridine (II) was carried out essentially in the manner described by Schreiber and Adam.[8] Compound IX (223.5 mg) was dissolved in 25 ml of CH_2Cl_2 by warming. After the solution was cooled in an ice–salt water bath, the N-chlorosuccinimide (158.3 mg) in 10 ml of CH_2Cl_2 was added to it and the mixture allowed to stand for 1 hr. Removal of the solvent and chromatography of the residue on a silica gel column afforded the N-chlorodihydrosolafloridine (benzene–ethyl acetate eluate, 1:1) which crystallized as needles from ethanol (222 mg), mp 254–256° (lit.[8] mp *ca.* 280° dec).

Anal. Calcd for $C_{27}H_{46}NO_2Cl$: C, 71.73; H, 10.26; N, 3.09. Found: C, 71.57; H, 10.50; N, 3.00.

To a solution of sodium methylate prepared from the interaction of 70 ml of absolute methanol and 700 mg of sodium was added 401 mg of the above prepared N-chlorodihydro compound and refluxed for 2 hr in a N_2 atmosphere. The methanol was then removed *in vacuo* and water was added to the residue. The ethyl acetate extract after chromatography on alumina and elution with ethyl acetate yielded needles after two recrystallizations from ethyl acetate (79.8 mg): mp 163–164°; $[\alpha]^{20}D$ 116.0° (*c* 0.63, $CHCl_3$) [lit.[8] mp 168–170°; $[\alpha]^{20}D$ 114.8° (*c* 0.248)]. The properties (melting point, mixture melting point, and ir) of the compound were in agreement with a specimen of solafloridine[2] obtained from the natural source.

N-Carbobenzoxy-O-acetyl-16-dehydrotetrahydrosolasodine Ethylene Dithioketal (X).—Ethanedithiol (0.4 ml) and BF_3 etherate (0.4 ml) were added to a HAc (5 ml) solution of the ketone VIII (176 mg), and the reaction mixture was kept at room temperature for 3 hr with stirring. The reaction product after the usual work-up was obtained as a syrup which was submitted to chromatography over silica gel. The desired thioketal X was eluted with benzene–chloroform (3:7) and crystallized from ethanol–acetone (1:1) as needles: mp 144–146°; ir (Nujol) 1250, 1740 (OAc), 1700 cm^{-1} (NCbO).

Anal. Calcd for $C_{39}H_{57}NO_4S_2$: C, 70.13; H, 8.60; N, 2.10. Found: C, 70.41; H, 8.57; N, 2.13.

Dihydrosolacongestidine Acetate (XI).—The thioketal X (38 mg) was dissolved in absolute ethanol (10 ml) and a large excess of Raney nickel[13] suspended in ethanol was added to it. After the mixture was refluxed for 2 hr, the catalyst was filtered off and washed with chloroform. The combined catalyst washings and the filtrate yielded 19 mg of a residue which when crystallized from ether gave needles of mp 212–215°. The compound, XI, exhibited properties (melting point, mixture melting point, and ir) which were in agreement with dihydrosolacongestidine acetate[2] derived from solacongestidine of natural origin.

Registry No.—II, 2385-18-4; III, 126-17-0; IV, 6159-99-5; V, 24694-69-7; VI, 24694-70-0; VII, 24694-71-1; VIII, 24694-72-2; VIIIa, 24694-73-3; IX, 24674-74-4; X, 24694-75-5; XI, 19374-54-0; XII, 24694-77-7; N-chlorodihydrosolafloridine, 24694-78-8.

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

(13) No. 28 from W. R. Grace and Co., Baltimore, Md.