Alkaloids from *Solanum congestiflorum*[1]

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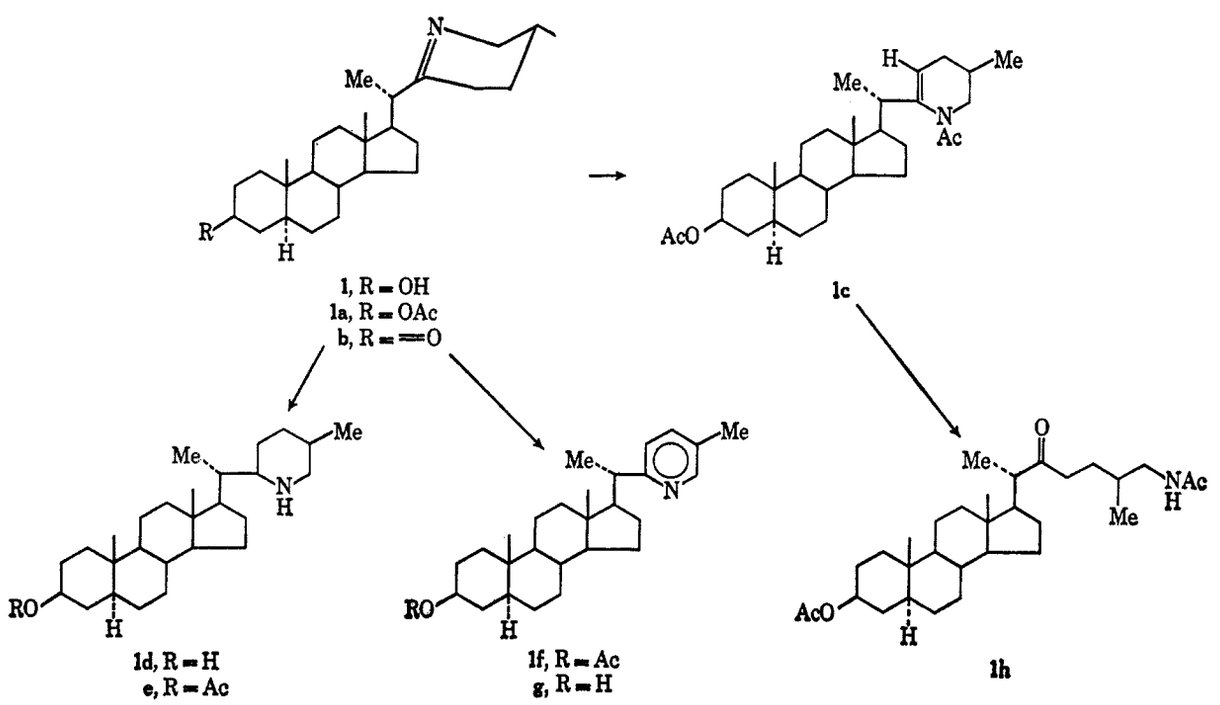
Four steroidal alkaloids, namely, solacongestidine, solafloridine, and 23-oxo- and 24-oxosolacongestidine, were isolated from *Solanum congestiflorum* Dun. DC. Solacongestidine is (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol and solafloridine is the 3β,16α-diol of the same basic moiety.

Solanum congestiflorum Dun. DC., commonly known as Natri, and collected in the environs of Santiago, Chile, afforded after acidic hydrolysis and extensive chromatography four new steroidal alkaloids which we named solacongestidine (**1**), solafloridine (**2**), and 23-oxo- (**3**) and 24-oxosolacongestidine (**4**).

Solacongestidine (**1**) (Scheme I) possesses the formulation $C_{27}H_{45}NO$ with two tertiary and two secondary methyls in the nmr spectrum, a pattern typical of the solanum-type steroidal alkaloids. In the infrared spectrum, absorption bands at 2.78, 3.00 and 6.05 μ are observed. The first two bands are due to the hydroxyl group as shown by its ready conversion into O-monoacetate **1a** ($\lambda_{max}^{CHCl_3}$ 5.78 μ), prepared by shaking **1** in a mixture of acetic and hydrochloric acid. This hydroxyl is easily oxidized with chromic acid to a ketone, **1b**, which causes a larger paramagnetic shift (0.20 ppm) on the 19-methyl signal than on the 18-methyl (0.03 ppm), an observation indicative of a 3-ketone function in the steroid moiety. The infrared absorption at 6.05 μ is ascribed to a C=N moiety[3] which can be converted into an acetylenamine functionality (**1c**) by acetylation in the conventional manner with acetic anhydride–pyridine. This is also supported by the appearance of an olefinic proton in the nmr spectrum of **1c**. In addition, the 18-, 21- and 27-methyl signals in **1** are subjected to paramagnetic shifts of 0.03–0.19 ppm while the 19-methyl resonance appears unperturbed (*cf.* cholestanol).[4] This perturbation can be attributed to the effect of the C=N chromophore being in close proximity to these methyl functions.

Either catalytic hydrogenation or lithium aluminum hydride reduction of **1** adds 1 mol of hydrogen to the alkamine to afford the secondary amine, dihydrosolacongestidine (**1d**) along with its stereoisomers. The melting points of **1d** and its O-monoacetate, **1e**, are in agreement with those described in the literature.[5] In addition, dehydrogenation of monoacetate **1a**, with palladium–charcoal produces the β-picolyl derivative, **1f**, possibly contaminated by its C-20 stereoisomer. The mass spectra of **1** and its dihydro derivative, **1d**, afford further evidence that the site of unsaturation is located in a piperidine side chain, for the spectrum of

SCHEME I



(1) Portions of the paper were presented at the XIth Pacific Science Congress, Tokyo, Japan, Aug 21–30, 1966.

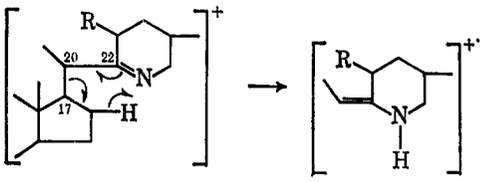
(2) Visiting scientists: Y. Sato (1964-1966), H. Kaneko (1963–1964), E. Bianchi (1963–1964), and H. Kataoka (1966–1968).

(3) E. Bianchi, C. Djerassi, H. Budzikiewicz, and Y. Sato, *J. Org. Chem.*, **30**, 754 (1965).

(4) Nmr of cholestanol in $CDCl_3$ δ 0.87 (21-, 26-, 27-*sec*-CH_3), 0.80 (19-CH_3), 0.65 (18-CH_3), 3.55 ppm (3α-H).

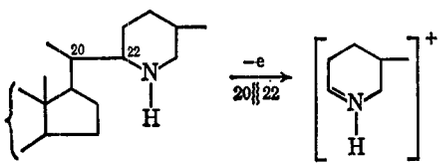
(5) K. Schreiber and G. Adam, *Tetrahedron*, **20**, 1707 (1964).

1, aside from the molecular ion peak (*m/e* 399), shows two prominent peaks at *m/e* 111 (111.1049, $C_7H_{13}N$) and 125, the latter of which can be ascribed the structure A arising from the rupture of the C_{17}–C_{20} bond.[3]



A ($C_8H_{15}N$, *m/e* 125), R = H
C ($C_8H_{13}NO$, *m/e* 139), R = =O

The spectra of dihydrosolacongestidine (**1d**) on the other hand yields a prominent fragment at *m/e* 98 (structure B) ascribable to the fragmentation scheme as shown.[3]



B ($C_6H_{12}N$, *m/e* 98)

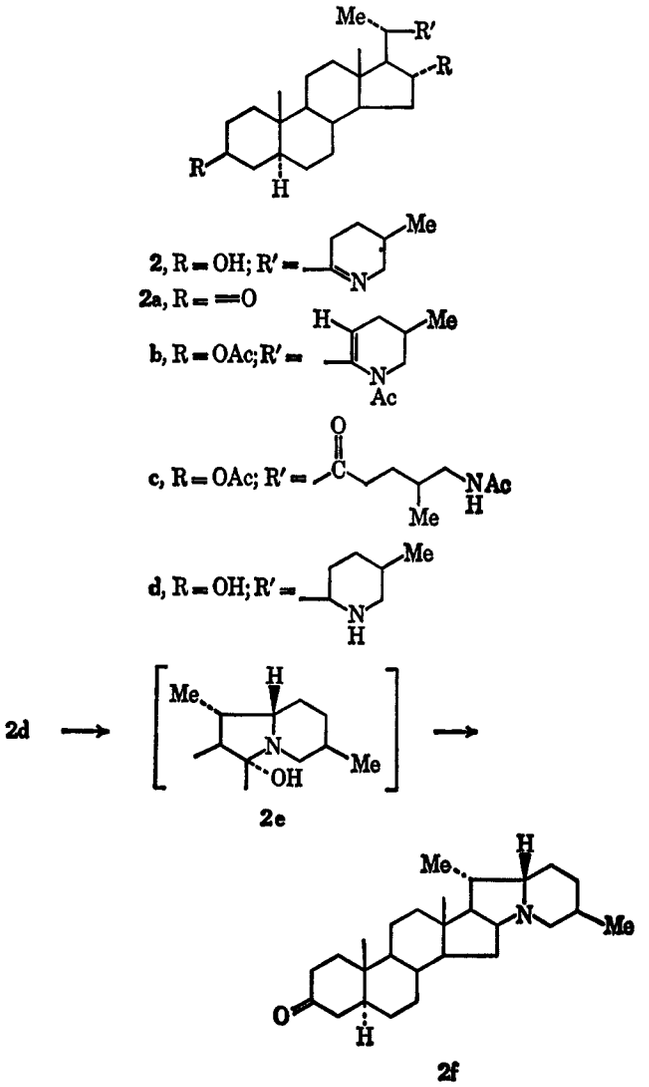
That the site of unsaturation is, indeed, located in the piperidine ring was affirmed by hydrolysis of the O,N-diacetate, **1c**, with hydrochloric acid in acetic acid which lead to the opening of the side-chain ring to yield an acetylamino ketone, **1h**, characteristic of a Δ^2-tetrahydropyridine function.[6]

The fragmentation pattern of 1, its physical data, and the spectral and chemical behavior thus gleaned, were reminiscent of 5,6-dihydrodeoxotomatillidine obtained from the Wolff–Kishner reduction of dihydrotomatillidine, a steroidal alkaloid obtained from *Solanum tomatillo*[3] indigenous to Chile. This was, indeed, found to be the case when the products derived from the two species were compared. In confirmation, it was also found that solacongestidine agreed in properties with a synthetic specimen of (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol[5] prepared in an unambiguous manner.

It is of some interest to note that recently the Δ^5 C-25 epimer (25*S*) of **1** named Verazine have been isolated from a subspecies of Veratrum album.[7] These steroidal alkaloids with a piperideine side chain ($\Delta^{22(N)}$) are of considerable interest since they can be viewed as potential intermediates in the biosynthesis of a number of steroidal alkaloids of the solasodine, solanidine, jerveratrum and ceveratrum type.[8]

Solafloridine (**2**) (Scheme II), the minor component in the plant, analyzes for the formulation $C_{27}H_{45}NO_2$ and possesses an ultraviolet spectrum similar to that of solacongestidine (**1**). Its infrared and nmr spectra indicate the presence of an extra hydroxyl group. Oxidation of **2** with chromic acid afforded a diketone, **2a**, one of which indicated a six-membered-ring and the other a five-membered-ring carbonyl as judged from the infrared data. The alkamine formed by acetylation an amorphous O,O,N-triacetyl derivative (**2b**) which displayed an enamine acetate functionality in the ultraviolet and infrared spectra as well as in the nmr spectrum. It was hydrolyzed, like solacongestidine O,N-diacetate (**1c**), by hydrochloric acid in acetic acid to yield an amorphous ω-acetylamino ketone (**2c**).

SCHEME II



The mass spectrum of the alkamine showed the characteristic ion peak at *m/e* 125 for fragment A while dihydro derivative **2d** had an *m/e* 98 peak for methylpiperidine ion B, as in dihydrosolacongestidine (**1d**). These results indicate that the extra hydroxyl function is very probably located on the steroidal portion of the molecule since a hydroxyl moiety on the piperidine side chain has been shown to afford a fragment of *m/e* 114, an increment of 16 over the methylpiperidine peak of *m/e* 98, corresponding to a hydroxyl group.

The location of the hydroxyl function on the steroid ring in solafloridine (**2**) was shown to be at C-16 by its conversion into (22*S*:25*R*)-solanidan-3-one (**2** → **2d** → **2e** → **2f**), a known isomeric solanidanone.[9] The α orientation is assigned to the hydroxylic function

(6) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **25**, 786 (1960), and papers cited therein.

(7) G. Adam, K. Schreiber, J. Tomko, and A. Vassova, *Tetrahedron*, **23**, 167 (1967).

(8) K. Schreiber "The Alkaloids," Vol. X, Academic Press, New York, N. Y., 1968, pp 115–125.

(9) E. Höhne, K. Schreiber, H. Ripperger, and H.-H. Worch, *Tetrahedron*, **22**, 673 (1966), and papers cited therein.

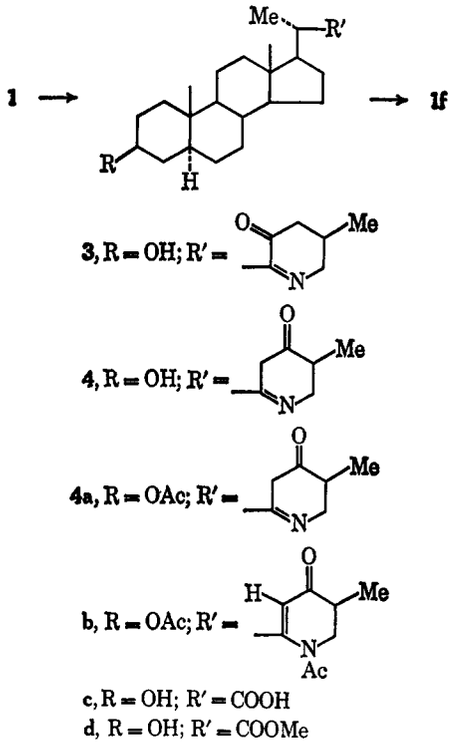
at C-16 in **2** since dihydrosolafloridine (**2d**) does not possess physical constants in agreement with the known isomeric tetrahydrosolasodine[10] having a 16β-hydroxyl moiety. Solafloridine also failed to cyclize to the spiroamino ketal base (dihydrosolasodine) when submitted to refluxing in alcoholic base. This is consistent with the observations of Schreiber and Adam,[11] who have also found that a 16α-hydroxy- in contrast to 16β-hydroxy-$\Delta^{22(N)}$-22,26-imino-5α-cholestene does not cyclize. Finally, the infrared spectra of our alkamine (**2**) and the dihydro derivative (**2d**) were found to be in agreement with the synthetic specimens.[12]

The 23- and 24-oxosolacongestidines are two oxygenated alkaloids which occur in minor amounts and persistently accompany solacongestidine during its isolation. Although it probably exists in the plant *per se*, there appears to be some augmentation during the work-up of solacongestidine.

The structure of 23-oxosolacongestidine (**3**) (Scheme III) was deduced principally from spectral data. It displays in the infrared spectrum characteristic absorption bands at 5.86 and 6.13 μ, and a series of ultraviolet absorption maxima at *ca.* 210 mμ (log ϵ 3.72), 267 (2.52), 277 (2.45) and 405 (1.83).[13] The mass spectrum shows a fairly strong peak at *m/e* 139 representing a fragment $C_8H_{13}NO$ (C) which is an increment of 14 over the corresponding peak, *m/e* 125 (A), in solacongestidine (**1**). Wolff–Kishner reduction of compound **3** affords **1** which can be oxidized with manganese dioxide or selenium dioxide to a mixture of the 23- and 24-oxo compounds (**3**, **4**). An interesting feature of the 23-oxo compound (**3**) is that it readily suffers aromatization into 3β-acetoxy-20-[2-(5-methylpyridyl)]-5α-pregnane (**1f**) by refluxing briefly in acetic anhydride. Although the aromatization is unique in the case of a Δ^1-piperidone-3, an analogy can be found in the conversion of 1,2,3,4-tetrahydro-1-oxoquinolizium bromide into a quinolizium salt by boiling acetic anhydride.[14]

24-Oxosolacongestidine (**4**) (Scheme III) possesses infrared absorption bands at 5.92 and 6.19 μ. In the ultraviolet spectrum (ethanol) it absorbs at *ca.* 211 and 270 mμ (log ϵ 3.66 and 2.32). The nmr spectrum reveals no olefinic proton. Upon acetylation (acetic anhydride–pyridine) for 3 hr at room temperature, the predominant product proved to be the 3β-acetate (**4a**) of **4** whereas prolongation of the acetylation period for 14 hr or boiling in acetic anhydride for 1 hr afforded principally the O,N-diacetate (**4b**). The latter displayed infrared spectrum bands for an enamine acetate system conjugated to a carbonyl function [5.81 (OAc), 5.94, 6.04, 6.30 μ (AcNC=CC=O)] and an appropriate ultraviolet absorption spectrum [222 and 275 mμ (log ϵ 3.75 and 3.60)]. The nmr spectrum also indicated the

SCHEME III



c, R = OH; R' = COOH
d, R = OH; R' = COOMe

presence of an olefinic proton at 5.97 ppm (doublet, J = 3 cps).

The oxygenated enamine system of **4** appears to be very unstable to alkaline condition. Its ultraviolet absorption changes significantly in 3% potassium hydroxide–methanol solution at room temperature within 1 day.[15] During 4 hr of heating in 1% potassium hydroxide–methanol at 130° (bath temperature), **4** is completely changed, and an acidic product identified as 3β-hydroxybisnorallocholanic acid (**4c**) was isolated. Although the spectra of the acid and its methyl ester (**4d**) were identical with authentic samples, the melting points were somewhat lower. We believe this is due to slight contamination by the C-20 isomer. The alkaline and neutral products are still unidentified. The degradation can be visualized as the alkali-catalyzed fission of a β-diketone formed by hydrolysis of the Schiff base type of bond in the piperideine side chain.

Experimental Section[16]

Hydrolysis of the Glycosides.[17]—A solution of 10 g of the crude glycosides in 120 ml of 90% aqueous MeOH and 6 ml of concentrated HCl was refluxed for 2 hr, concentrated to a small

(10) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1469 (1957).

(11) K. Schreiber and G. Adam, *Ann. Chem.* **166**, 176 (1963).

(12) We are grateful to Professor K. Schreiber of the Deutsche Akademie der Wissenschaften zu Berlin, Institut für Biochemie der Pflanzen, D. D. R., for providing us the spectra of these compounds. Schreiber and Adam[11] have reported mp 168–170°, $[\alpha]^{26}D$ +114.8°, for their product (**2**).

(13) K. Schreiber and H. Ripperger [*Chem. Ber.*, **96**, 3094 (1963)] report for (25*R*)-3β,16β-diacetoxy-22,26-imino-5α-cholest-22(N)-en-23-one the following spectral data: ir 5.75 (OAc), 5.87 (ketone), 6.11 μ (C=N); λ_{max} 228 (3.30), 397 mμ (1.97).

(14) E. E. Glover and G. Jones, *J. Chem. Soc.*, 3021 (1958).

(15) The same phenomenon is observed in the case of dihydrotomatillidine[9] which is provisionally regarded as a C-25 stereoisomer of 24-oxosolacongestidine.

(16) 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). Ultraviolet spectra were recorded with Model 15 Cary spectrophotometer and the absorption data in shortwave regions are uncertain. The mass spectra in these experiments have been measured with an AEI MS-9 spectrometer. Tlc plates were precoated with silica gel G and purchased from Analtech, Inc., Wilmington, Del.

(17) The isolation and characterization of the glycosides will appear in a forthcoming publication.

volume in the rotatory evaporator until a heavy residue was obtained. The residue was triturated with NH_4OH and extracted with $CHCl_3$ to yield 4.5 g of the crude free base. Two major [R_f 0.55 (I), 0.28 (II)] and three minor fractions [R_f 0.73 (III), 0.8 (IV), 0.4] were separated on tlc (CH_2Cl_2–AcOEt–MeOH, 2:2:1). Each component could be crudely separated on a larger scale by using columns of 100 parts of silica gel (0.05–0.2 mm) with the solvent system of benzene–AcOEt–MeOH (12:12:5). More chromatography and recrystallization were required for further refinement.

Solacongestidine (I).—The fraction of R_f 0.55 was recrystallized quickly from either Me_2CO, EtOAc, Et_2O or aqueous MeOH, preferably in an oxygen-free atmosphere, to yield rods melting at 169–174°: $[\alpha]^{20}D$ +35.6° (*c* 1.6, $CHCl_3$); mass spectrum 399 (M^+, $C_{27}H_{45}NO$), 384, 164, 151, 125 (strong, $C_8H_{15}N$), 111 (strong, $C_7H_{13}N$); mass spectrum of the trimethylsilyl ether 471 (M^+) 456, 151, 125, 121, 111; $\lambda_{max}^{CHCl_3}$ 2.78, 3.00 (OH), 6.05 (C=N), 6.25, 9.75 μ (C–O); λ_{max}^{EtOH} 239 mμ (ϵ 360), end absorption $\lambda^{EtOH-HCl}$ 222 mμ (ϵ 1560); nmr 0.69 (18-CH_3), 0.81 (19-CH_3), 0.90 (d, J = 6 cps, 3 H), 1.06 (d, J = 7 cps, 3 H), 2.14 (OH), 2.95 (26α-H), 3–4 ppm (26β-H and 3α-H), no olefinic proton; ORD (*c* 0.047, EtOH) $[\alpha]_{300}$ +233°, $[\alpha]_{260}$ +891° (peak), $[\alpha]_{228.5}$ +222° (trough), $[\alpha]_{210}$ +947°.

Anal. Calcd for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N, 3.51. Found: C, 81.08; H, 11.17; N, 3.40. (The specimen for analysis was dried at 110° for 20 hr.) The compound was identical (mixture melting point and ir) with a specimen derived from dihydrotomatillidine, and with a synthetic specimen of (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol.

Chromic Acid Oxidation of Solacongestidine.—To a solution of 120 mg of **1** in 25 ml of Me_2CO was added 0.8 ml of Kiliani's reagent[18] at 5–10°. After the reaction mixture was allowed to stand *ca.* 0.5 hr at room temperature, 2 ml of *i*-PrOH was added to destroy the excess oxidant. The reaction mixture was brought to dryness at room temperature *in vacuo*, and dissolved in a slight amount of water. The aqueous solution was made alkaline with K_2CO_3, and extracted with Et_2O. The crystalline residue which amounted to about 110 mg was subjected to tlc (benzene–AcOEt–MeOH, 3:3:1). A band at R_f 0.5 was extracted with MeOH–AcOEt to yield 45 mg of pale yellow flakes melting at 134–142° (**1b**). Recrystallization from AcOEt gave a product of mp 139–142°; $[\alpha]^{20}D$ +51° (*c* 0.19, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.87 (C=O), 6.06 μ (C=N), no OH band; nmr 0.72 (18-CH_3), 0.91 (d, J = 6 cps, *sec*-CH_3), 1.01 (19-CH_3), 1.08 ppm (d, J = 7 cps, *sec*-CH_3), no olefinic proton; mass spectrum 397 (M^+, $C_{27}H_{43}NO$), 382, 125, 111.

Acetylation of Solacongestidine with Acetic Anhydride–Pyridine.—A mixture of 306 mg of 1, 3 ml of anhydrous pyridine and 3 ml of Ac_2O was allowed to stand at room temperature (22–23°) for 19 hr. It was poured into ice–water to afford a white powder (348 mg), which when twice crystallized from MeOH gave crystals melting at 156–158° (**1c**, 171 mg): $\lambda_{max}^{CHCl_3}$ 5.78 (ester C=O), 5.99 and 6.09 μ (–C=CNAc); nmr 0.67 (18-CH_3), 0.82 (19-CH_3), 0.93 (d, J = 6 cps, *sec*-CH_3), 1.12 (d, J = 7 cps, *sec*-CH_3), 2.02 (OAc), 2.15 (NAc), 3.38 (26-H), 4.7 (m, 3α-H), 5.2 (olefinic proton); mass spectrum 483 (M^+, $C_{31}H_{45}NO_3$), 468, 441, 440, 426, 423 (M^+ – 60) 185, 167, 166, 152, 143, 125, 111; λ_{max}^{EtOH} 235 mμ (log ϵ 3.90).

3β-Acetoxy-26-acetylamino-5α-cholestan-22-one (Ih).—A solution of 130 mg of **1c**, 0.6 ml of 4 *N* HCl in 3 ml of acetic acid was allowed to stand for 1 hr at room temperature. After addition of water and neutralization with $NaHCO_3$, it was extracted with $CHCl_3$. The organic layer yielded 149 mg of solid, which was purified by tlc and recrystallized from MeOH to afford rods (**1h**) melting at 138–140°: nmr 0.67 (18-CH_3), 0.82 (19-CH_3), 0.88 (d, J = *ca.* 6 cps, *sec*-CH_3) 1.07 (d, J = 7 cps, *sec*-CH_3), 1.97 and 1.99 (2Ac), 3.06 (t, J = 5.5 cps, C_{26}-H_2).

Acetylation of Solacongestidine with Acetic–Hydrochloric Acid Mixture.—A solution of 64 mg of **1**, 20 ml of AcOH and 0.4 ml of concentrated HCl was shaken at room temperature for 25 hr, poured into ice–water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The organic layer yielded 65 mg of solid, which was submitted for purification by tlc (*n*-heptane–AcOEt, 13:7). The main band at R_f 0.24 on the tlc plate was extracted with mixture of MeOH and $CHCl_3$ to afford 47 mg of the monoacetate. Two recrystallizations from Me_2CO gave needles (**1a**): mp 185–195°; mass spectrum 441 (M^+, $C_{29}H_{47}NO_2$), 426 (M^+ – 15), 164, 151, 125, 111 (strong); nmr 0.68 (18-CH_3), 0.82 (19-CH_3), 0.92 (d, J = 6 cps, *sec*-CH_3), 1.07 (d, J = 7 cps, *sec*-CH_3), 2.01 (OAc), 4.7 (m, 3α-H); $\lambda_{max}^{CHCl_3}$ 5.78 (OAc), 6.05 μ (C=N).

Dehydrogenation of Solacongestidine O-Monoacetate.—A mixture of 250 mg of **1a** and 250 mg of 5% Pd–C in 10 ml of isoquinoline was heated at 240–250° for 4 hr under a nitrogen atmosphere. The reaction mixture was concentrated to a small volume, and extraction of the residue with $CHCl_3$ afforded 347 mg of a brownish oily mass. The separation of the product with the solvent system, cyclohexane–AcOEt (3:1), on tlc provided 0.17 g of oil (R_f 0.75), which still consisted of two components. Further chromatography on alumina[19] and elution with benzene–petroleum ether (bp 30–60°) (1:1) afforded a crystalline mass which crystallized from acetone as needles of mp 164–166° (**1f**); mass spectrum 437 (M^+), 422, 121, 120; λ_{max}^{KBr} 5.79 (OAc), 6.27, 6.39, 6.74, 8.05, 9.77, 12.07 μ (pyridine ring); nmr 0.78 (18-CH_3), 0.83 (19-CH_3), 1.28 (d, J = 7 cps, *sec*-CH_3), 2.01 (OAc), 2.29 ($C_{5'}$-CH_3), 4.67 (3α-H), 6.98 (d, $J_{3',4'}$ = 8 cps, $C_{3'}$-H), 7.40 (q, $J_{3',4'}$ = 8 cps, $J_{4',6'}$ = 2 cps, $C_{4'}$-H), 8.33 ($C_{6'}$-H).

Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.58; H, 9.90; N, 3.20. Found: C, 79.51; H, 9.68; N, 3.47.

Hydrolysis of the Dehydrogenation Product.—A mixture of 36 mg of the dehydrogenation product (**1f**), 3 ml of saturated $KHCO_3$–MeOH and 1 drop of water was refluxed for 2 hr under N_2. The solvent was removed. The white precipitate which formed on dilution of the residue in ice–water was collected, washed with water and twice recrystallized from acetone. It gave 12 mg of hexagonal plates (**1g**): mp 261–262°; λ_{max}^{KBr} 2.92 (OH), 6.26, 6.39, 6.74, 9.71 μ.

Anal. Calcd for $C_{27}H_{41}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.87; H, 10.20; N, 3.43.

This product was identical with the compound of mp 254–256° (**1g**) derived from 23-oxosolacongestidine (**3**) by Ac_2O treatment and hydrolysis. There was no melting point depression on admixture and the ir spectra were in good agreement.

Manganese Dioxide Oxidation of Solacongestidine.—A solution of 82 mg of 1 in 8 ml of $CHCl_3$ was stirred with 0.8 g of active MnO_2[20] at room temperature for 4 hr until the starting material was no longer detectable on tlc (benzene–AcOEt, 1:1). The inorganic material was filtered off and washed with $CHCl_3$. The combined $CHCl_3$ solution yielded 87 mg of solid, which was absorbed on 1 g of Al_2O_3 and placed on a column of 5 g of Al_2O_3 (grade 1). Elution with 1% MeOH–Et_2O furnished 75 mg of crude crystals. Recrystallization from MeOH–Me_2CO gave pale yellow needles (**3**), mp 198–208°, which were identical with 23-oxosolacongestidine (**3**) in every respect (mixture melting point, uv, ir, nmr, mass spectrum). Tlc revealed the presence of a small amount of 24-oxosolacongestidine (**4**) in the mother liquor.

Selenious Acid Oxidation of Solacongestidine.—1 (200 mg) was added to a mixture of 55 mg of freshly sublimated SeO_2, 10 ml of *p*-dioxane and 5 drops of water. The mixture was warmed at 70° for 3 hr, cooled, filtered, and evaporated to dryness. The residue was chromatographed on 10 g of Al_2O_3 (grade I) into three fractions: 1 (1% MeOH–Et_2O), 16 mg of nearly pure compound, mp 135–155°, proved to be identical with **4**; **2** (the same solvent), 72 mg of mixture of **3** and **4**, mp 130–198°; 3 (2% MeOH–Et_2O), 14 mg of crystals, mp 180–194°. Recrystallization from MeOH–Me_2CO gave pale yellow needles, mp 190–205°, identical with alkamine **3**.

Hydrogenation of Solacongestidine.—Alkamine 1 (100 mg) was dissolved in 6 ml of AcOH and hydrogenated over 72 mg of PtO_2 catalyst under atmospheric pressure. After about 25 min, the absorption ceased with the uptake of 1 mol equiv of H_2 (22.1 ml, 21°). The catalyst was removed and the AcOH solution evaporated to dryness *in vacuo*. The residue was made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract provided 110 mg of white powder, which was separated

(18) A solution of 53 g of chromium trioxide and 80 g of sulfuric acid in 400 g of water (118 mg of CrO_3/ml).

(19) The other component, which emerged first from the glpc column, could not be crystallized. However, it appeared to be a C-20 isomer having a similar nmr pattern: 0.67 (18-CH_3) 0.73 (19-CH_3), 1.19 (d, J = 7 cps, *sec*-CH_3), 2.01 (OAc), 2.29 ($C_{5'}$-CH_3), 4.67 (3α-H), 7.0 (d, J = 8 cps, $C_{3'}$-H), 7.40 (q, $C_{4'}$-H), 8.30 ($C_{6'}$-H).

(20) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

on tlc (CH_2Cl_2–AcOEt–MeOH, 3:3:1). A band at R_f 0.5 was extracted with MeOH–$CHCl_3$ and recrystallized from MeOH to yield 11 mg of needles (**1d**): mp 233–236°; mass spectrum 401 (M^+, $C_{27}H_{47}NO$), 400, 386, 165, 164, 125, 111, 98 (very strong, $C_6H_{12}N$).

The reduction of 50.5 mg of **1** with 62 mg of $LiAlH_4$ in Et_2O for 7 hr gave 44 mg of the crude product. It showed four spots on tlc and looked almost the same as in the catalytic hydrogenation of **1**.

The combined crude reaction mixture (187 mg) of several reductions was partially acetylated by stirring in 40 ml of AcOH with 1 ml of concentrated HCl at 23° for 1 day. The product (154 mg) was separated by tlc (CH_2Cl_2–AcOEt–MeOH, 45:45:11). A zone at R_f 0.3–0.5 gave 67 mg of dihydrosolacongestidine O-monoacetate (**1e**): mp 215–217° (Et_2O); $\lambda_{max}^{CHCl_3}$ 5.80 μ (OAc); nmr 0.66 (18-CH_3), 0.82 (19-CH_3), 2.02 (OAc); HCl salt, mp 323–326° (MeOH).

Solafloridine (2).—A crude fraction (R_f 0.28) contaminated with small amounts of R_f 0.73 material was obtained from the silica gel column and converted into its hydrochloride in MeOH. An analytical specimen of solafloridine hydrochloride monohydrate (mp 280–288°) was prepared from aqueous MeOH and dried over P_2O_5 at 80° for 5 hr *in vacuo*.

Anal. Calcd for $C_{27}H_{45}NO_2HCl$: C, 71.72; H, 10.25. Found: C, 71.83; H, 10.05.

Liberation of the free base with K_2CO_3 and rapid crystallization from Me_2CO yielded needles of mp 162–165°.[12] On the other hand, if the compound is allowed to crystallize slowly from a dilute solution, prisms of mp 172–175° were recovered. Their ir spectra ($CHCl_3$) were identical.

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.01; H, 10.91; N, 3.38. Found: C, 78.23; H, 10.77; N, 3.51.

Data follow: $\lambda_{max}^{CHCl_3}$ 2.74, 3.03 (OH), 6.03 μ (C=N); λ_{max}^{EtOH} 240 mμ (ε 260); nmr 0.71 (18-CH_3), 0.80 (19-CH_3), 0.92 (d, J = 7 cps, *sec*-CH_3), 1.03 (d, J = 6.5 cps, *sec*-CH_3), 4.7 ppm (OH), no olefinic proton; mass spectra 415 (M^+, $C_{27}H_{45}NO_2$), 398, 162, 138, 125, 98; $[\alpha]^{20}D$ +122.7° (*c* 1.15, $CHCl_3$).

Acetylation of Solafloridine with Acetic Anhydride–Pyridine.—A solution of 170 mg of **2**, 10 ml of anhydrous pyridine and 7 ml of Ac_2O was kept standing at room temperature (*ca.* 23°) for 46 hr. Work-up in the usual manner gave 203 mg of amorphous material. The product was submitted to tlc (benzene–AcOEt, 2:1) to yield solafloridine triacetate (**2b**, R_f 0.45) but it failed to crystallize: $\lambda_{max}^{CHCl_3}$ 5.79 (strong OAc), 5.99, 6.08 μ (C=CNAc); λ_{max}^{EtOH} 238 mμ (log ε 3.60); nmr 0.7 (18-CH_3), 0.82 (19-CH_3), 0.92 (d, J = 6.5 cps, *sec*-CH_3), 1.07 (d, J = 6 cps, *sec*-CH_3), 1.97 ($C_{16\alpha}$-OAc), 2.02 ($C_{3\beta}$-OAc), 2.15 (NAc), 3.2–3.4 (C_{26}-H), 5.13 (olefinic proton).

Hydrolysis of Solafloridine Triacetate. A.—A solution of 18 mg of **2b**, obtained above, in 5 ml of 10% KOH–MeOH was refluxed for 7 hr, diluted with water, and extracted with $CHCl_3$ to yield 15 mg of oil, which solidified later and possessed the same R_f value as **2** on tlc. In the nmr all methyl signals associated with acetyl groups and the signals of the olefinic proton disappeared.

B.—A mixture of 110 mg of **2b**, 3 ml of AcOH and 0.6 ml of 4 *N* HCl was allowed to stand for 1 hr at room temperature, and then neutralized with excess aqueous $NaHCO_3$. The $CHCl_3$ extract gave 110 mg of oil, which was purified by tlc (AcOEt–MeOH, 15:1). The resulting product **2c**, R_f 0.6, did not crystallize: nmr 0.74 (18-CH_3), 0.82 (19-CH_3), 0.88 (d, J = 7 cps, *sec*-CH_3), 1.10 (d, J = 7 cps, *sec*-CH_3), 1.99, 2.01 and 2.04 ppm (three Ac).

Chromic Acid Oxidation of Solafloridine.—A mixture of 0.1 g of **2**, 100 ml of Me_2CO, and 0.6 ml of Kiliani's reagent was allowed to stand at room temperature and worked up in the same way as in the oxidation of alkamine **1** to produce 113 mg of amorphous substance. It was submitted to tlc (benzene–AcOEt, 11:3), and the band at R_f 0.5 (**2a**) was isolated. The compound possessed ir bands at $\lambda_{max}^{CHCl_3}$ 5.80 (five-membered-ring ketone) and 5.90 μ (six-membered-ring ketone).

Hydrogenation of Solafloridine.—A solution of 772 mg of **2** in 80 ml of EtOH was hydrogenated with 0.5 g of PtO_2 catalyst under 770-mm pressure at 21°. It consumed 1 mol equiv of H_2 in 3 hr. Crystallization of the product from MeOH gave 339 mg of crystals (**2d**) melting at 280–285°. Upon recrystallization its melting point rose to 282–285°: $[\alpha]^{20}D$ +25.9° (*c* 0.424, $CHCl_3$). Ir (Nujol) showed good agreement with the synthetic specimen of (22*S*:25*R*)-22,26-imino-5α-cholestane-3β,16α-diol [lit.[11] mp 285–287°, $[\alpha]^{26}D$ +23.9° (*c* 0.481, $CHCl_3$)]: mass spectrum 417 (M^+, $C_{27}H_{47}NO_2$), 416, 402, 204, 150, 140, 98 (strong).

Conversion of Dihydrosolafloridine (2d) into (25*R*)-Isosolanidan-3-one (2f).—To a suspension of 0.2 g of **2d** in 65 ml of Me_2CO and 3 ml of AcOH was added 2.0 ml of Kiliani's solution dropwise in 10 min and stirred for 0.5 hr at room temperature. About 0.5 ml of 10% NaOH was added to the reaction mixture and the greenish precipitate was removed by filtration. The filtrate was diluted with 200 ml of water and made alkaline with aqueous NaOH. The resulting precipitate was collected and thoroughly washed with water. The crude semicrystalline mass (138 mg) which was dried *in vacuo* at room temperature crystallized from MeOH and melted at *ca.* 125°. The carbinolamine possessed the same R_f value as an authentic specimen on tlc (R_f 0.75, AcOEt–CH_2Cl_2–NEt_3, 14:14:3). The oxidation product was hydrogenated with 0.1 g of 10% Pd-C in 12 ml of EtOH under atmospheric pressure. After consuming 1 mol equiv of H_2 in 195 min, the product was worked up in the usual manner to give 138 mg of a mixture. The main component (**2f**) was isolated by tlc (AcOEt–CH_2Cl_2–MeOH, 9:9:2, R_f 0.33), and crystallized from aqueous Me_2CO. Flakes with mp 137–144° were obtained. It showed no depression on admixture with an authentic specimen (mp 146–147°),[10] λ_{max} 5.84 μ (C=O). The spectral pattern was identical with that of an authentic sample.

23-Oxosolacongestidine (3).—A crude fraction from the column chromatography, which was eluted just after 24-oxosolacongestidine (**4**), was further purified on tlc. The band at R_f 0.73 was extracted with $CHCl_3$ and recrystallized from MeOH–Me_2CO to afford pale, yellow needles (**3**) melting unsharply at 213–223° and above 300° with some decomposition.

Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.39; H, 10.55; N, 3.48.

Data follow: λ_{max}^{EtOH} 267, 277, 405 mμ (log ε 2.52, 2.45, 1.83) and *ca.* 210 (3.72); $\lambda_{max}^{CHCl_3}$ 2.73, 2.9 (OH), 5.86, 6.13 (COC=N–); $[\alpha]^{20}D$ +33.0° (*c* 1.1, $CHCl_3$); nmr 0.72 (18-CH_3), 0.80 (19-CH_3), 1.02 (d, J = 5.5 cps, *sec*-CH_3), 1.04 (d, J = 7 cps, *sec*-CH_3); mass spectrum 413 (M^+), 395, 161, 139, 121, 111.

Acetic Anhydride Treatment of 23-Oxosolacongestidine.—A solution of 72 mg of **3** in 8 ml of Ac_2O was refluxed over N_2 for 45 min, diluted with water, made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract yielded 89 mg of an amorphous residue, which was chromatographed on tlc (cyclohexane–AcOEt, 13:7). A band at R_f 0.8 was extracted with $CHCl_3$–MeOH, and the extract crystallized from acetone to furnish 10 mg of needles, mp 159–164°. This was in every respect identical with 3β-acetoxy-20-[2-(5-methylpyridyl)] 5α-pregnane (**1f**) derived from **1a** by Pd-C dehydrogenation: ORD (*c* 0.058, $[\alpha]_{290}$ 0°, $[\alpha]_{282}$ +37.9°, $[\alpha]_{265}$ −145°, $[\alpha]_{255}$ −465°; λ_{max}^{EtOH} 269 mμ (log 3.58), 276 (3.46), end absorption [*ca.* 212 mμ, (log ε = 3.92)].

Hydrolysis of this compound by refluxing in MeOH half-saturated with $KHCO_3$ for 2 hr, and crystallizing from Me_2CO gave needles melting at 254–256° (1 g): $\lambda_{max}^{CHCl_3}$ 2.73 (OH), 6.22 and 6.37 μ (C=N, C=C); λ_{max}^{MeOH} 269 and 276 mμ (log ε 3.51, 3.37); $\lambda_{max}^{0.1\,N\,HCl\text{–}MeOH}$ 272 mμ (log ε 3.85); end absorption [*ca.* 200 mμ (log ε 3.92)].

Wolff–Kishner Reduction of 23-Oxosolacongestidine.—A mixture of 80 mg of 3 in 2 ml of EtOH, 2 ml of diethylene glycol and 0.36 ml of 85% NH_2NH_2–H_2O under N_2 atmosphere was refluxed for 25 min. After addition of 0.2 g of KOH, the mixture was heated for another 35 min until the temperature rose to 190°. The mixture was poured into ice–water and the precipitate was crystallized from Me_2CO to give needles with melting point of 166–170°. The ir spectrum of the compound was superposable with that of solacongestidine (**1**) or dihydrodeoxotomatillidine and the mixture melting point was undepressed.

24-Oxosolacongestidine (4).—The first crystalline fraction eluted from the silica gel column was recrystallized from MeOH. The lusterous, pale yellow plates contained 1 mol of the solvent (MeOH), which was removed at 110° *in vacuo*.

Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.45; H, 10.68; N, 3.27.

Data follow: mp 158–162°; $[\alpha]^{23}D$ +40.9° (*c* 0.8, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.8 (OH), 5.92 (C=O), 6.20 μ (C=N); λ_{max}^{EtOH} 270 mμ (ε 149), 345 (37); end absorption [*ca.* 211 mμ (ε 5540)]; nmr 0.72 (18-CH_3), 0.79 (19-CH_3), 1.01 (d, J = 6.5 cps, *sec*-CH_3), 111 (d, J = 7 cps, *sec*-CH_3); mass spectrum 413 (M^+) 398, 385, 166, 140 (strong), 139, 111; ORD (MeOH) $[\alpha]_{600}$ +56°,

$[\alpha]_{500}$ +77°, $[\alpha]_{375}$ +220° (peak), $[\alpha]_{320}$ +10° (trough), $[\alpha]_{250}$ +505°.

24-Oxosolacongestidine O-Acetate (4a).—A solution of 14 mg of **4**, 0.6 ml of anhydrous pyridine, and 0.45 ml of Ac_2O was allowed to stand at room temperature for 3 hr. To the reaction mixture was added ice–water to decompose excess Ac_2O, and the product was extracted with $CHCl_3$. The $CHCl_3$ extract gave 19 mg of amorphous mixture, which was chromatographed on tlc plates (benzene–AcOEt, 2:1). The substance eluted from the R_f 0.85 band (10 mg) was recrystallized from acetone to give prisms (**4a**): mp 200–203°; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.92 (C=O); mass spectrum 455 (M^+, $C_{29}H_{45}NO_3$), 440, 427, 140, 139, 395, 111; the mass spectrum pattern was almost the same as that of alkamine **4**.

The other component (R_f 0.3) was identified as 24-oxosolacongestidine O,N-diacetate (**4b**). When the reaction time was prolonged for 14 hr, diacetate **4b** was formed predominantly.

24-Oxosolacongestidine O,N-Diacetate (4b).—**4** (90 mg) in 5 ml of Ac_2O was refluxed under N_2 for 1 hr. The reaction mixture, worked up in the conventional way, yielded 0.1 g of powder, which crystallized from Me_2CO to afford 22 mg of prisms (**4b**) of mp 184–187°; λ_{max}^{EtOH} 275 (log ϵ 3.60); end absorption [222 mμ (log ϵ 3.75)]; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.94, 6.04, 6.30 (AcNC=CCO), 9.83 μ (CO).

Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52. Found: C, 74.50; H, 9.43.

Data follow: nmr 0.65 (18-CH_3), 0.79 (19-CH_3), 1.13 (d, J = 6.5 cps, *sec*-CH_3), 1.17 (d, J = 7 cps, *sec*-CH_3), 1.98 (OAc), 2.02 (NAc), 5.97 (d, J = 3 cps, C_{23}-H); mass spectrum 497 (M^+), 455, 454, 152, 140, 124.

Alkali Treatment of 24-Oxosolacongestidine.—A solution of 80 mg of **4** in 5 ml of 1% KOH–MeOH was refluxed at 130° (bath temperature) for 4 hr under N_2. After removal of the solvent, and addition of water, the $CHCl_3$ extract gave about 60 mg of amorphous powder[21] (mainly basic and neutral substances). Extraction of the aqueous layer with $CHCl_3$ after acidification with dilute H_2SO_4 yielded about 28 mg of brown powder (acid part). The acidic fraction was purified by tlc (benzene–AcOEt–MeOH, 15:15:4) to afford crystals (**4c**) of mp 255–265°. Treatment of the acid with CH_2N_2 in MeOH–Et_2O overnight afforded methyl ester[22] **4d**: mp 130–145°; $\lambda_{max}^{CHCl_3}$ 2.79, 2.95 (OH), 5.78 (OAc), 8.66, 9.78, 11.72 μ; mass spectrum 362 (M^+), 347, 329, 233, 215, 165, 147. The acid and the ester proved to be 3β-hydroxybisnorallocholanic acid and its methyl ester by comparison with an authentic sample (tlc, ir, glpc, and mass spectrum).

Registry No.—**1**, 984-82-7; **1a**, 19374-52-8; **1b**, 19374-53-9; **1c**, 19398-17-5; **1d**, 19398-18-6; **1e**, 19374-54-0; **1f**, 19374-55-1; **1g**, 19374-56-2; **1h**, 19374-57-3; **2**, 19374-58-4; 2 HCl, 19374-59-5; **3**, 19374-60-8; **4**, 19374-61-9; **4a**, 19398-19-7; **4b**, 19374-62-0.

(21) From the amorphous fraction, about 5 mg of unidentified crystals were obtained by tlc (benzene–AcOEt–MeOH, 15:15:2, R_f 0.6). Crystallization from MeOH–$CHCl_3$ yielded fine needles of mp 275–280°; mass spectra 411 (M^+, strong), 396, 139, 108; nmr 0.77 (18- and 19-CH_3), 2.05 3.55, 4.30, 6.79 ppm; λ_{max}^{MeOH} 254 mμ (ϵ 990), 299 (2520); λ_{max}^{Nujol} 6.12 (sharp, medium), 7.24, 8.03, 8.68, 10.30 μ.

(22) W. Bergman, D. H. Gould, and E. M. Low, *J. Org. Chem.*, **10**, 570 (1945): 3β-hydroxybisnorallocholanic acid, mp 274–276°; methyl ester, mp 151–152.5°. The same alkali treatment of an authentic specimen lowered its melting point to 240–255° (acid) and 125–140° (methyl ester).

Synthesis of Dihydrothiazines Related to Deacetylcephalosporin Lactones. An Alternate Total Synthesis of Deacetylcephalosporin Lactones

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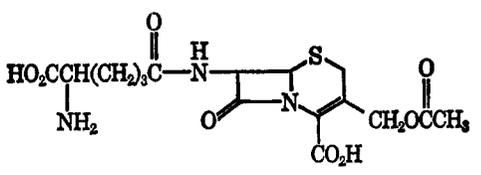
A unique synthesis of dihydrothiazines related to the cephalosporins is based upon the reaction of 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone I with aldehydes to form an imine, followed by acid-catalyzed cyclization with the simultaneous loss of the trityl group. The synthesis has been used to produce a compound [XI, R = $C(CH_3)_3$] which is a known intermediate for the synthesis of deacetylcephalosporin lactones.

The cephalosporin antibiotics are widely recognized as interesting and useful broad spectrum antimicrobial agents. Cephalosporin C was discovered by Abraham



cephalosporin C

and Newton[1] as a result of their studies on the antibiotic components produced by a species of *Cephalosporium* isolated by Brotzu.[2] Classical degradative studies[3] culminated in a tentative structure assignment which received confirmation by X-ray crystallographic studies.[4] Cephalosporin C, the subject of these pioneering studies, was therefore unambiguously assigned its now accepted structure. A recent review[5] has cataloged with clarity and thoroughness the major points of interest in the developing area of cephalosporin antibiotics.

The Squibb Institute has been responsive to the challenge involved in the synthesis of the cephalosporins for some time.[6a] At the present date several approaches of various degrees of success have been described.[6] In common to all of these propositions is the construction of a 1,3-[6H]-dihydrothiazine system. The formation of model 1,3-dihydrothiazines structurally related to cephalosporins has been studied by a number of groups.[6,7]

An approach to cephalosporin synthesis which depended upon the preparation of a deacetylcephalosporin lactone, a type represented by the following

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(4) D. Hodgkin and E. N. Maslen, *ibid.*, **79**, 393 (1901).
(5) E. P. Abraham, *Quart. Rev.* (London), **21**, 231 (1967).

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(7) See, *inter alia*, G. C. Barrett, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 783 (1964); D. M. Greene, A. G. Long, P. J. May, and A. F. Turner, *ibid.*, 766 (1964); A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966); J. C. Sheehan and J. A. Schneider, *ibid.*, **31**, 1635 (1966).