The compound can also be obtained from the lithium aluminum hydride reduction of the ketone, A-V. Oxidation of the above, A-VI, with Kiliani's reagent yields A-V.

Solanidan-3-one (B-V) and Solanidan-3β-ol (B-VI).—Dihydrotomatidine B (140 mg.) was dissolved in acetic acid (1.0 cc.) and acetone (35 cc.) and oxidized with Kiliani's reagent. The oxidation product was collected by filtration and dried. It was then redissolved in dry benzene and filtered from insoluble matter. After removal of the benzene the semicrystalline residue was crystallized from benzene–hexane to form needles which melted at 138–143°. The compound seemed to be unstable and attempts at further purification led to some decomposition. A satisfactory analysis could not be obtained. Usually the compound was directly reduced to solanidan-3-one.

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.40; H, 10.48. Found: C, 79.33; H, 10.47.

The oxidation product, presumably the carbinolamine, was reduced with 10% palladium-on-charcoal in ethyl acetate as in the previous case (A-V) and hexagonal platelets (methanol–acetone) of m.p. 192–195°, $[\alpha]^{20}D$ +43.5° ($CHCl_3$) were obtained, identical in respect to m.p., mixture m.p. and infrared spectrum with a specimen prepared from the oxidation of solanidan-3β-ol. However, upon introduction of an authentic sample[28] of m.p. 210–213°[29] into the laboratory, the m.p.'s of previous samples having m.p. 192–195° now rose to 210–213° when recrystallized. The infrared spectrum of the higher melting compound was likewise identical with that of the lower melting species.

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.55; H, 10.98.

The lithium aluminum hydride reduction of the above ketone, B-V, yielded the known solanidan-3β-ol (B-VI), m.p. 217–219°, identical in all respects with an authentic sample.

If the reduction of the oxidized intermediate is carried out with lithium aluminum hydride in place of catalytic reduction (palladium in ethyl acetate), a good yield of solanidan-3β-ol (B-VI) is directly obtained.

Semicarbazone of Solanidan-3-one.—The compound was prepared as in the preparation of the iso derivative. Needles were obtained which charred[30] but did not melt.

Acknowledgments.—We are greatly indebted to Dr. Erich Mosettig for the kind interest and guidance shown in this work and to Professor Vercellone, Milan, for his exceedingly generous contribution of tomatidine without which this work would have been impossible.

(28) We are indebted to Professor Prelog, Zurich, for a sample of solanidan-3-one of m.p. 210–213°.

(29) H. Rochelmeyer, *Arch. Pharm.*, **277**, 340 (1939), reported m.p. 214°; V. Prelog and S. Szpilfogel,[9] reported 210–212°. $[\alpha]^{17}D$ +45.8° (+2°).

(30) H. Rochelmeyer, *ibid.*, reported a m.p. of 237°, but did not give any analytical values for the compound.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

New Dihydro Derivatives of Tomatidine and Solasodine[1]

BY YOSHIO SATO AND H. GEORGE LATHAM, JR.

RECEIVED JANUARY 3, 1956

The catalytic reduction of N-acetylated derivatives of tomatidine and solasodine leads to new dihydro derivatives resulting from the opening of the F ring. These compounds have been partially synthesized from the appropriate sapogenins.

The catalytic (platinum oxide–acetic acid) or lithium aluminum hydride reduction of tomatidine (I) yields two isomeric dihydro derivatives[2] which presumably result from the opening of ring E, *i.e.*, cleavage of the C_{22}–O bond, to give the C_{22}-isomeric 3,16-diols. The catalytic reduction of solasodine (II)[3] has so far yielded only a single tetrahydrosolasodine, a 3,16-diol, also derived from the opening of ring E.

In the course of our studies of the reduction of steroidal alkaloids and their derivatives, we have encountered some new dihydro derivatives which result from the opening of ring F, *i.e.*, cleavage of the C_{22}–N bond. Thus the catalytic reduction (platinum oxide–acetic acid) of N,O-diacetyltomatidine (Ia)[4] and N,O-diacetylsolasodine (IIa)[5] leads to N-acetyldihydrotomatidine acetate (III) and N-acetyltetrahydrosolasodine acetate (IV). These (III and IV), upon saponification with methanolic potassium hydroxide, afford N-acetyldihydrotomatidine (IIIa) and N-acetyltetrahydrosolasodine (IVa), respectively.

Although the infrared data indicated (λ_{max}^{chlf} 2.89 and 3.00 μ, NH; 5.98, 6.60 μ, HN—C(=O)—CH_3) that the hydrogenation of the compounds (Ia, IIa) had probably led to a scission of the C–N bond, the proof was shown by the unambiguous syntheses of IIIb and IVb from the appropriate sapogenins. Prior to the synthesis,[6] IIIa and IVa were reduced with lithium aluminum hydride to the corresponding N-ethyl derivatives, IIIb and IVb. The amino alcohol 26-N-ethyldihydrotomatidine was prepared by the catalytic reduction of neotigogenin acetate[7] to dihydroneotigogenin acetate (V), tosylation of the latter in the usual manner to the 26-O-tosyl derivative Va followed by iodination with sodium iodide in methyl ethyl ketone to the 26-deoxy-26-iodo derivative Vb, amination of Vb with ethylamine in the presence of anhydrous potassium carbonate and hydrolytic

(1) A preliminary account of this work was presented before the Gordon Research Conferences, AAAS, Chemistry of Steroids and Related Natural Products, New Hampton, New Hampshire, August 22–26, 1955.

(2) Y. Sato and H. G. Latham, Jr., *Chemistry and Industry*, 444 (1955).

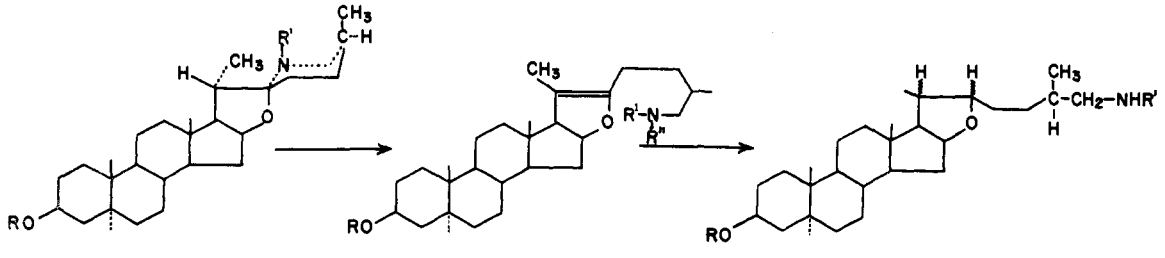
(3) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939); L. H. Briggs, R. P. Newbold and N. E. Stace, *J. Chem. Soc.*, 3 (1942).

(4) T. D. Fontaine, J. S. Ard and R. M. Ma, THIS JOURNAL, **73**, 878 (1951).

(5) L. H. Briggs and T. O'Shea, *J. Chem. Soc.*, 1654 (1952).

(6) With a view of synthesizing IIIa and IVa directly, amination of Vb with liquid ammonia was attempted. However, no tangible product could be isolated.

(7) The authors are indebted to Dr. Callow of the National Institute for Medical Research, London, for a generous gift of neotigogenin acetate.



I, R,R'=H

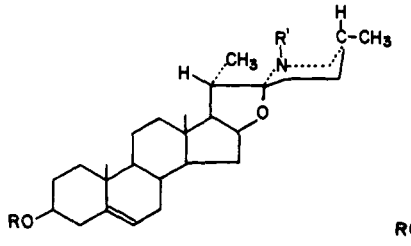
Ia, R,R'=Ac

VI, R,R',R"=Ac

VIa, R,R'=H R"=Ac

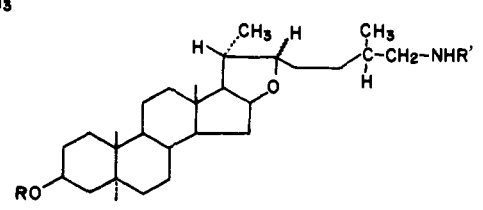
VII, R=H R'=Ac

VIIa, R=H R'=C_2H_5



II, R,R'=H

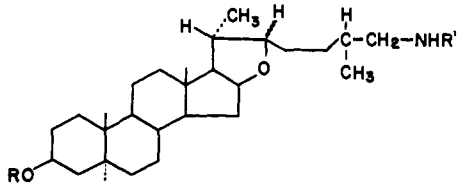
IIa, R,R'=Ac



III, R,R'=Ac

IIIa, R=H, R'=Ac

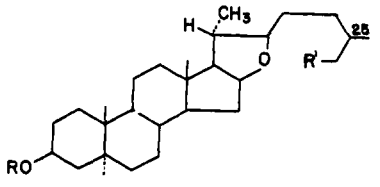
IIIb, R=H, R'=Et



IV, R,R'=Ac

IVa, R=H, R'=Ac

IVb, R=H, R'=Et



V,V'(C25 epimer), R=Ac, R'=OH

Va,V'a(C25 epimer), R=Ac, R'=OTs

Vb,V'b(C25 epimer), R=Ac, R'=I

removal of the 3-acetyl group. The product, 26-deoxy-26-N-ethyldihydroneotigogenin, agreed in all properties with substance IIIb derived from N,O-diacetyltomatidine (Ia).

The compound 26-deoxy-26-N-ethyldihydrotigogenin was synthesized in a similar manner from tigogenin acetate (dihydrotigogenin acetate (V') → dihydrotigogenin-26-tosylate (V'a) → 26-deoxy-26-iododihydrotigogenin acetate (V'b) → 26-deoxy-26-N-ethyldihydrotigogenin). The synthesis proceeded smoothly and the product proved to be identical with the derivative IVb obtained from N,O-diacetylsolasodine (IIa). It is interesting to note that the infrared spectra (in chloroform or carbon disulfide) of the corresponding reduced derivatives of N-acetyltomatidine and N-acetylsolasodine were indistinguishable. This phenomenon[8] was previously observed for the various epimeric dihydrosapogenins. However, the spectra of the Nujol mulls were different.

This synthesis constitutes another example of the conversion of steroidal sapogenins into derivatives of steroidal alkaloids and corroborates the work of Uhle[9] and Uhle and Moore[10] in their transformation of the appropriate pseudosapogenins into solasodine and tomatidine.

In view of the recent discussions concerning the isomerism at C_{22} in the steroidal sapogenins,[11] it was of some interest for us to prepare other isomers of substance IIIb. Accordingly the so-called unsaturated triacetyltomatidine (VI)[12] was hydrolyzed to the unsaturated N-acetyltomatidine (VIa), catalytically hydrogenated to the isomeric

(8) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **77**, 641 (1955).

(9) F. C. Uhle, *ibid.*, **75**, 2280 (1953).

(10) F. C. Uhle and J. A. Moore, *ibid.*, **76**, 6412 (1954).

(11) I. Scheer, R. B. Kostic and E. Mosettig, *ibid.*, **75**, 4871 (1953); M. E. Wall and S. Serota, *ibid.*, **76**, 2850 (1954); J. B. Ziegler, W. E. Rosen and A. C. Shabica, *ibid.*, **76**, 3865 (1954); M. E. Wall, S. Serota and C. R. Eddy, *ibid.*, **77**, 1230 (1955); R. K. Callow and V. H. T. James, *Chemistry and Industry*, 691 (1954); D. H. W. Dickson, J. Elks, R. M. Evans, A. G. Long, I. F. Oughton and J. E. Page, *ibid.*, 692 (1954); D. A. H. Taylor, *ibid.*, 1066 (1954).

(12) Y. Sato, A. Katz and E. Mosettig, THIS JOURNAL, **73**, 880 (1951).

N-acetyldihydrotomatidine (VII) and finally reduced with lithium aluminum hydride to the isomeric 26-N-ethyldihydrotomatidine (VIIa). As expected, the physical properties (including infrared spectrum) of this isomer were different from IIIb.

This reduction (VIa → VII) is parallel to that of the conversion of pseudosapogenins[13] into dihydropseudosapogenins in the sapogenin field.

Acknowledgment.—The authors are deeply indebted to Dr. Erich Mosettig of this Institute for his kind interest and guidance shown during the course of this work.

Experimental[14]

N-Acetyldihydrotomatidine Acetate (III) and N-Acetyldihydrotomatidine (IIIa).—N,O-Diacetyltomatidine[4] (0.515 g.) was dissolved in 9 cc. of glacial acetic acid and reduced in the presence of 0.083 g. of Adams catalyst. After the uptake of 1 mole of hydrogen, the reduction ceased. The product, even after chromatography, gave only a semi-crystalline mass, m.p. 65–80°; λ_{max}^{chlf} 2.90, 3.01 μ (N–H); 5.78 μ (acetoxy); 5.98, 6.61 μ (NH–acetyl) and hence was hydrolyzed with 2% methanolic potassium hydroxide to the crystalline alcohol. Upon chromatography over alumina and elution with benzene–ether (1:1), large needles of m.p. 176–178° were obtained from acetone–hexane; λ_{max}^{chlf} 2.78 μ (free hydroxyl); 2.91, 3.01 μ (N–H); 5.99, 6.60 μ (NH–acetyl).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.74. Found: C, 75.85; H, 10.45.

A compound of m.p. 208–214° was also obtained, albeit in lesser yield, from this chromatography. It has been set aside for later study.

Lithium Aluminum Hydride Reduction of N-Acetyldihydrotomatidine (IIIa) to 26-N-Ethyldihydrotomatidine (IIIb).—To 4 g. of lithium aluminum hydride in 100 cc. of dry tetrahydrofuran was added dropwise 0.46 g. of IIIa in 50 cc. of tetrahydrofuran during the period of 20 minutes. Gentle refluxing was maintained for an additional 2.5 hours. After cautious decomposition of the excess lithium aluminum hydride with ice-water, the reaction mixture was repeatedly extracted with ether. The ethereal extract yielded 0.380 g. of semi-crystalline residue. Crystallization from ether gave crystals of m.p. 112–115°. Further purification by chromatography over alumina and elution with 0.5% methanol in ether afforded blade-like crystals of m.p. 115.5–117.5°, $[\alpha]^{20}D$ +6° (chlf.).

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53. Found: C, 78.17; H, 11.75.

Dihydroneotigogenin Acetate (V).—One and one-half grams of neotigogenin acetate was dissolved in 60 cc. of acetic acid and reduced with 400 mg. of Adams catalyst. The compound consumed slightly over 1 mole of hydrogen. It was chromatographed on neutral alumina and the fraction eluted with 1% methanol in ether yielded 1.2 g. of dihydroneotigogenin acetate, m.p. 107–111°. Recrystallization from dilute acetone gave needles of m.p. 112–113.5°.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.91; H, 10.57.

The 26-Tosylate of Dihydroneotigogenin Acetate (Va).—To a solution of 1.212 g. of V in 5 cc. of benzene was added slowly 1.382 g. of *p*-toluenesulfonyl chloride in 5 cc. of dry pyridine with cooling. After the solution had stood for 60 hr. at room temperature, it was poured into ice-water with vigorous stirring. After several hours of standing, the mixture was extracted with ether and the ethereal extract washed with 1 *N* hydrochloric acid, 2% sodium bicarbonate solution and water. One and one-half grams of a rather intractable oil was obtained. For analysis a portion of the oil was chromatographed over Florisil. Fractions eluted with benzene–hexane (1:1) and benzene were collected.

Anal. Calcd. for $C_{36}H_{56}O_6S$: C, 70.20; H, 9.00; S, 5.21. Found: C, 70.86; H, 9.24; S, 4.96.

26-Deoxy-26-iododihydroneotigogenin Acetate (Vb).—To 1.086 g. of Va in 25 cc. of methyl ethyl ketone was added 1.88 g. of sodium iodide and the mixture refluxed in the steam-bath for 16 hr. The insoluble salts were removed by filtration and the methyl ethyl ketone taken off *in vacuo*. The crude residue was partitioned between chloroform and water and the organic layer washed thoroughly with sodium thiosulfate and water. After drying and removal of chloroform *in vacuo*, 1.323 g. of oily iodo derivative was obtained.

Anal. Calcd. for $C_{29}H_{47}O_3I$: C, 61.04; H, 8.30; I, 22.24. Found: C, 60.94; H, 8.51; I, 22.32.

The iodo alcohol of Vb was prepared by refluxing Vb with dilute hydrochloric acid in methanol. The compound crystallized as needles from hexane, m.p. 120–122°. The compound is sensitive and attempts at purification have so far failed to give satisfactory analytical values.

26-Deoxy-26-N-ethyldihydroneotigogenin (IIIb).—A stoppered flask containing 1.295 g. of Vb, 25 cc. of ethylamine and 0.1 g. of anhydrous potassium carbonate was placed in the refrigerator (5°) overnight. It was then opened and allowed to stand at room temperature for 4 hr. Water was added to the residue in the flask and the solution extracted with ether. The extract yielded 0.98 g. of a slightly yellowish oil which was taken up in ether and treated with excess ethereal hydrogen chloride. The precipitate was washed thoroughly with dry ether, dissolved in 30 cc. of methanolic potassium hydroxide (2%) and refluxed for 75 minutes. When the solution was partially concentrated and allowed to crystallize, crystals (0.620 g.) of the amino alcohol were obtained. Recrystallization from ether–hexane gave crystals of m.p. 111.5–115°. For analysis a portion was purified by chromatography over alumina. Fractions eluted with ether–methanol (0.5, 1%) crystallized from hexane as clusters of blades, m.p. 114–116°. The compound was identical (mixture m.p., infrared spectra, rotation) with 26-N-ethyldihydrotomatidine.

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.40; H, 11.28; N, 3.09.

A 26-N-ethyl-N-acetyl derivative of IIIb was prepared by treating the above compound (IIIb) with excess acetic anhydride and pyridine for 1 hr. at 110–125° and hydrolyzing the resulting oily O,N-diacetyl derivative with 2% methanolic potassium hydroxide to 26-N-ethyl-N-acetyldihydroneotigogenin, m.p. 160–163° (acetone–hexane).

Anal. Calcd. for $C_{31}H_{53}O_3N$: N, 2.87. Found: N, 2.99.

N-Acetyltetrahydrosolasodine Acetate (IV) and N-Acetyltetrahydrosolasodine (IVa).—O,N-Diacetylsolasodine (0.512 g.) was reduced in 15 cc. of glacial acetic acid with Adams catalyst (0.168 g.). The compound consumed 2 moles of hydrogen. When chromatographed over alumina and eluted with benzene and benzene–ether, it crystallized as needles from ether–hexane, m.p. 141–143°; λ_{max}^{chlf} 2.89, 3.00 μ (N–H); 5.80 μ (acetoxy); 5.98, 6.61 μ (NH–acetyl). Usually the compound was directly hydrolyzed (without chromatography) with 2% methanolic potassium hydroxide to the alcohol and then chromatographed over alumina. The ether–methanol (0.5%) eluates yielded rods of m.p. 186–188° from acetone–hexane; λ_{max}^{chlf} 2.77 μ (free hydroxyl); 2.89, 2.99 μ (N–H); 5.98, 6.60 μ (NH–acetyl).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.74. Found: C, 75.69; H, 10.66.

26-N-Ethyltetrahydrosolasodine (IVb).—A solution of 0.16 g. of IVa in 20 cc. of tetrahydrofuran was added dropwise to 1.6 g. of lithium aluminum hydride in 45 cc. of the same solvent and the mixture refluxed for 3 hr. It was worked up as in the previous reduction (IIIb) and the crude substance crystallized twice from acetone–hexane. Clusters of plates of m.p. 139.5–141.5°, $[\alpha]^{20}D$ +5.8° (chlf.), were obtained.

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53. Found: C, 77.98; H, 11.62.

The 26-N-ethyl-N-acetyl derivative prepared as in the manner with IIIb crystallized as clusters of small needles, m.p. 162.5–163.5°, from acetone–hexane.

Anal. Calcd. for $C_{31}H_{53}O_3N$: N, 2.87. Found: N, 3.19.

Dihydrotigogenin-3-acetate (V′).—A solution of 1.2 g. of tigogenin acetate in 50 cc. of acetic acid was reduced with

(13) R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 521 (1940).

(14) All melting points were taken on the Kofler block and are uncorrected. We are indebted to Dr. W. C. Alford and his associates of this Institute for the microanalyses and to Messrs. H. K. Miller and W. M. Jones for the spectrophotometric measurements.

0.4 g. of platinum oxide under atmospheric pressure. Slightly over 1 mole of hydrogen was absorbed. After the removal of the catalyst, the filtrate was poured into ice-water and the precipitate collected and washed thoroughly with water. The crude, dried solid was chromatographed over alumina and the fraction eluted with 5% methanol in ether crystallized from dilute aqueous ethanol, m.p. 70–73°.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.91; H, 10.30.

Dihydrotigogenin-26-tosylate (V'a).—The acetate V' (1.01 g.) was tosylated as in the manner of V. A sample for analysis was chromatographed over Florisil.

Anal. Calcd. for $C_{36}H_{55}O_6S$: C, 70.20; H, 9.00; S, 5.21. Found: C, 70.37; H, 9.28; S, 5.09.

26-Deoxy-26-iododihydrotigogenin Acetate (V'b).—The tosylate V'a (1.15 g.) was iodinated and worked up in the same manner as Vb. A sample was distilled in high vacuum to yield an oil which crystallized from ether–methanol as slightly colored plates, m.p. 66–70°. Repeated crystallizations and chromatography failed to produce an analytically pure specimen.

A crystalline **26-deoxy-26-iododihydrotigogenin** of m.p. 118–122° was prepared by hydrolysis with potassium bicarbonate in methanol. As with Vb, the analysis was unsatisfactory.

26-Deoxy-26-N-ethyldihydrotigogenin (IVb).—A sealed tube containing 0.773 g. of V'b, 5 cc. of ethylamine and anhydrous potassium carbonate (*ca.* 0.1 g.) was allowed to stand at room temperature for 64 hr. After removal of the excess amine, water was added to the tube and the suspension extracted with ether. The ethereal extract yielded 0.794 g. of an oily residue which was hydrolyzed with 2% methanolic potassium hydroxide. Upon partial concentration and addition of water to the solution, 0.613 g. of a slightly colored crystalline mass was obtained. Recrystallization from acetone–hexane yielded white plates of m.p. 139–140.5°, $[\alpha]^{20}D$ +4.3° (chlf.). A mixture melting point with 26-N-ethyltetrahydrosolasodine of m.p. 139.5–141.5° was undepressed. The infrared spectrum (Nujol mull) was identical with the product derived from solasodine.

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.06; H, 11.69; N, 3.03.

The 26-N-ethyl-N-acetyl derivative, prepared as in the previous manner, agreed (m.p., mixture m.p., infrared spectra) with the N-acetylated derivative of the product (IVb) obtained from solasodine.

Hydrolysis of the Unsaturated Triacetyltomatidine[12] (VI) to N-Acetyltomatidine (VIa).—A solution of 1.27 g. of the so-called unsaturated triacetyltomatidine in 35 cc. of 2% methanolic potassium hydroxide was refluxed for 75 minutes. After partial concentration and addition of water 1.0 g. of crystals, m.p. 175–182°, was obtained. Recrystallization from methanol–water yielded plates of m.p. 186–190°; λ_{max}^{chlf} 2.77 μ (free hydroxyl); 2.89, 2.99 μ (N–H); 5.98, 6.61 μ (NH–acetyl).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.25; H, 10.15.

Isomeric N-Acetyldihydrotomatidine (VII).—The unsaturated alcohol VIa (0.92 g.) in 30 cc. of acetic acid was reduced with platinum oxide (0.36 g.) under atmospheric pressure. After an uptake of 1 mole of hydrogen the hydrogenation ceased. The filtrate, after the removal of the catalyst, was poured into ice-water containing excess dilute sodium hydroxide. The precipitate (0.839 g.) was washed thoroughly with water and crystallized from dilute methanol. Needles of m.p. 180–183° were obtained.

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.75. Found: C, 75.69; H, 10.80.

Isomeric 26-N-Ethyldihydrotomatidine (VIIa).—The N-acetyl derivative VII (0.700 g.) was reduced with lithium aluminum hydride as in the previous manner. The semi-crystalline material (0.621 g.) obtained from this reduction was chromatographed on alumina. Elution with 1% methanol–ether afforded the isomeric amino alcohol of m.p. 119–123°. Recrystallization from dilute acetone yielded plates of m.p. 121–123°, $[\alpha]^{20}D$ −3° (chlf.).

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53. Found: C, 77.89; H, 11.27.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE JULIAN LABORATORIES, INC., AND THE GLIDDEN COMPANY]

Sterols. XVI.[1] Cortisone and Analogs. Part 2. 17α,21-Dihydroxy-4-pregnene-3,12,20-trione

BY PERCY L. JULIAN, CHAPPELLE C. COCHRANE,[2] ARTHUR MAGNANI AND WILLIAM J. KARPEL*

RECEIVED OCTOBER 15, 1955

The synthesis of the 12-keto analog of cortisone, namely, 17α,21-dihydroxy-4-pregnene-3,12,20-trione (XV) from 3α,12α-diacetoxypregnan-20-one (I) is described. The 17,21,21-tribromo derivative of I is converted into 3α,12α-diacetoxy-16-pregnen-20-one (III) by treatment with sodium iodide in glacial acetic acid. The 16α,17α-epoxy derivative of III is converted into 3α-acetoxy-17α-hydroxypregnane-12,20-dione (VIIIa) and the latter converted into XV by the well-known procedures of bromination and acetoxylation at C_{21}, followed by introduction of the double bond into ring A. Improvements in several reactions involved in this type of synthesis of cortisone analogs are recorded, including the Raney nickel dehalogenation of vicinal steroid bromohydrins and the oxidation at C_3.

Some years ago when the simpler analogs of cortisone were actively being sought for the first time, we devised a facile synthesis of 17α,21-dihydroxy-4-pregnene-3,12,20-trione (XV) from 3α,12α-diacetoxypregnan-20-one (I). The procedure was in great part made possible by four observations in our laboratories.

(a) Bromination of I with slightly more than 3 moles of bromine yields the corresponding 17,21,-21-tribromo-3α,12α-diacetoxypregnan-20-one (II), isolable pure in good yield.[3]

(b) II on treatment with sodium iodide in boiling glacial acetic acid solution gives 3α,12α-diacetoxy-16-pregnen-20-one (III), likewise in good yield.[3b,3c]

(c) Epoxidation of 16-pregnen-20-ones, like III, with hydrogen peroxide in alkaline medium, followed by opening the 16,17-epoxy ring with hydrogen bromide, and dehalogenation of the resulting bromohydrin with Raney nickel leads generally to 17α-hydroxypregnan-20-ones in yields as high as 90% or better.[1,3b,3c,4]

(d) Bromination of 17α-hydroxypregnan-20-ones,

* This talented young investigator, devoted friend and research assistant to the senior author for twelve years, died on February 12, 1956.

(1) For Sterols XV, see THIS JOURNAL, **77**, 4601 (1955).

(2) The Glidden Company, Chicago, Illinois.

(3) (a) P. L. Julian and W. J. Karpel, THIS JOURNAL, **72**, 362 (1950); (b) P. L. Julian, Abstracts of 118th Meeting, Amer. Chem. Soc., Chicago, September, 1950; (c) P. L. Julian in G. Pincus, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, p. 195.

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