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

Chemistry of Dihydrotomatidines[1]

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The reduction of tomatidine yields isomeric diols. Acetylation and partial hydrolysis of these dihydro derivatives lead to the isomeric N-acetyldiols and subsequent oxidation affords the N-acetyldiketones. Direct oxidation of the diols followed by reduction leads to the isomeric solanidan-3-ones. The dihydrotomatidines are therefore regarded as C_{22} epimers. Some evidence for the assignment of a definite spatial orientation for the diols and solanidanones is discussed.

The isolation of degradation products, Δ^{16}-allopregnen-3β-ol-20-one,[2] tigogenin lactone[3] and 2-methyl-5-ethylpyridine[4] has led to a postulated and generally accepted formulation for tomatidine.[3,5] The recent elegant synthesis by Uhle and Moore[6] has confirmed this structure with its attendant spiro-aminoketal side chain (I'). With the establishment of the 16,22-epoxy structure in the molecule, one can, with some assurance, regard the hydrogenation as involving a rupture of this ether linkage to give the 3,16-dihydroxy derivatives.

Fontaine, *et al.*,[7] had previously reported the reduction of tomatidine with lithium aluminum hydride to a dihydro derivative of m.p. 194–195° and assumed that in this reduction an oxide ring was opened with the formation of a hydroxyl group. Kuhn, *et al.*, also reported the catalytic hydrogenation (platinum oxide, glacial acetic acid) of tomatidine to a diol and in two separate publications[3,4] gave m.p.'s of 202° and 221° for dihydrotomatidine without any comment as to the difference in these values.

Our studies of the catalytic reduction of tomatidine (I') have resulted in the isolation not only of the above diol A of m.p. 194–195° but also of a hitherto unreported isomeric diol B of m.p. 230–233° in good yields. The latter was also obtained by the lithium aluminum hydride reduction but in much smaller yields.

The diol A was acetylated in the usual manner with pyridine and acetic anhydride to afford the known amorphous O,O',N-triacetyldihydro derivative, A-I,[7] while diol B treated in the same manner yielded a crystalline O,N-diacetyldihydro derivative, B-I, m.p. 227–229°. Hydrolysis of the respective acetylated derivatives with methanolic potassium hydroxide led to two isomeric N-acetyldiols, A-II, m.p. 258–261°, and B-II, m.p. 230–234°. Oxidation of A-II and B-II with Kiliani's reagent[8] yielded the isomeric diketones, A-III (m.p. 199–203°, $[\alpha]^{20}D$ −96° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.77 μ, C_{16}-ketone; 5.83 μ, C_3-ketone; 6.15 μ, N-acetyl band) and B-III (m.p. 195–198°, $[\alpha]^{20}D$ −133°; $\lambda_{max}^{CHCl_3}$ 5.77 μ, C_{16}-ketone; 5.83 μ, C_3-ketone; 6.15 μ, N-acetyl band). A 16-keto-N-acetyldihydro derivative, B-IV, has also been obtained by the oxidation of the diacetyldihydro derivative, B-I, and subsequent alkaline hydrolysis of the C_3-acetoxy group ($\lambda_{max}^{CHCl_3}$ 2.77 μ, 3-OH; 5.77 μ, C_{16}-ketone; 6.15 μ, N-acetyl band).

Furthermore, when diol B is oxidized with Kiliani's reagent and subsequently reduced in the presence of palladium–charcoal, it is converted into the known solanidan-3-one, B-V,[9] which can be further reduced to the known solanidan-3β-ol, B-VI, whereas the identical reactions applied to diol A lead to a new isomeric solanidan-3-one, A-V,[10,11] and thence to the isomeric solanidan-3β-ol, A-VI, with lithium aluminum hydride.

Kuhn, *et al.*,[12] have previously reported the conversion of their dihydrotomatidine (m.p. 202°) into demissidine (solanidan-3β-ol) in a similar manner (chromium trioxide oxidation followed by platinum–methanol reduction). We have repeated the conversion following their procedure with our dihydrotomatidine A of m.p. 194–195° but have obtained only the iso derivative, A-VI, (iso(C_{22})-solanidan-3β-ol). This was subsequently oxidized to the ketone, A-V, which proved to be identical with the product obtained *via* our procedure. From these results it now appears that Kuhn, *et al.*,[12] were dealing with a mixture from which they inadvertently obtained the transformation product (solanidan-3β-ol) derived from the high melting (230–233°) dihydrotomatidine B.

The above described conversion of dihydrotomatidines A and B into the isomeric N-acetyldiols (A-II, B-II) and N-acetyldiketones (A-III, B-III) and furthermore into the isomeric solanidanones (A-V, B-V) can best be explained by postulating for the two series of dihydrotomatidine and solanidine derivatives a C_{22}-isomerism.[13]

Moreover we would like to assign tentatively to the hydrogen at C_{22} for the low melting dihydro-

(1) A preliminary account of portions of this work was published in *Chemistry and Industry*, 444 (1955).

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

(3) R. Kuhn and I. Löw, *Chem. Ber.*, **85**, 416 (1952).

(4) R. Kuhn, I. Löw and H. Trischmann, *ibid.*, **86**, 372 (1953).

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

(6) F. C. Uhle and J. A. Moore, THIS JOURNAL, **76**, 6412 (1954).

(7) T. D. Fontaine, J. S. Ard and R. M. Ma, *ibid.*, **73**, 878 (1951).

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

(9) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944).

(10) To avoid confusion with the solanidane derivatives, we would like to apply the prefix iso (C_{22}) to this series of compounds, *e.g.*, iso-(C_{22})-solanidan-3-one, iso(C_{22})-solanidan-3β-ol.

(11) A. Soltys, *Ber.*, **66**, 762 (1933), claims to have obtained a compound from the Hofmann degradation of solanidine to which he applies the term iso-solanidine, but later workers have been unable to reproduce his results.

(12) R. Kuhn, I. Löw and H. Trischmann, *Angew. Chem.*, **64**, 397 (1952).

(13) The authors are aware of the fact that in the dihydrotomatidines isomerization at C_{16}, concomitantly with C_{22}, is also possible but in the hydrogenation of tomatidine it seems very unlikely that the bond between C_{16} and oxygen would be involved to alter the configuration at C_{16}.

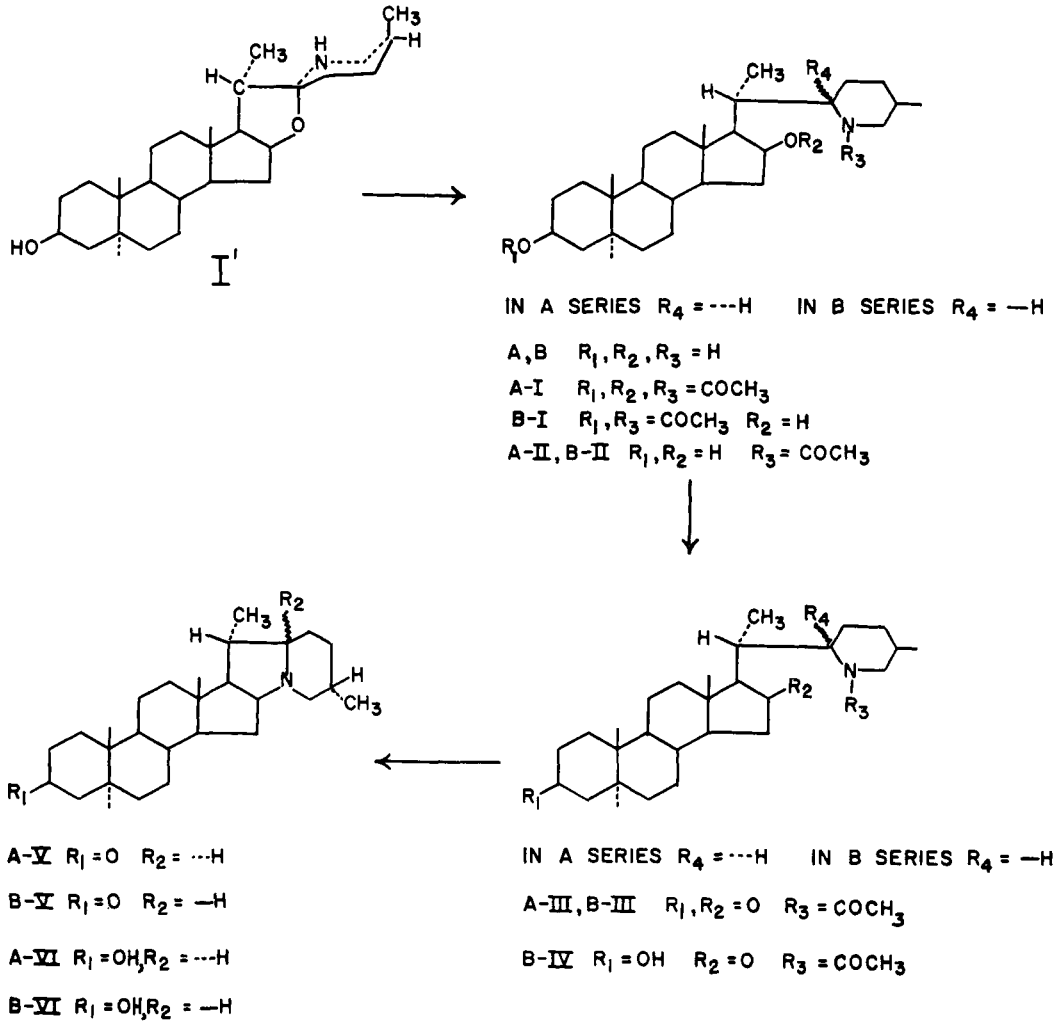

CHART 1

tomatidine A an α-orientation[14] (in reference to C_{18}-CH_3 when the piperidine ring is rotated about the C_{20}-C_{22} axis until the amino nitrogen is brought nearest to C_{16}). This assignment is based upon the consideration that if the apparently stereospecific lithium aluminum hydride reduction[15] of tomatidine is accompanied by inversion and involves the attack of the hydride ion upon carbon atom 22 from the rear of the C_{22}–O bond farthest away from the oxygen at C_{16}, the entering hydrogen would have an α-orientation[16] according to the above convention. The cyclization of the resulting dihydrotomatidine A leads then to the formation of isosolanidan-3-one. Under the same treatment the high-melting dihydro derivative, B, possessing the oppositely β-oriented C_{22} hydrogen, results in the formation of the known solanidan-3-one.

From the above considerations regarding the C_{22}-hydrogen and adopting the configurational propositions already advanced for other centers, *i.e.*, C_{20}[17] and C_{25},[18] solanidan-3-one would most likely possess structure B-V[19,20] and its C_{22}-isomer, A-V.

As a pathway for the formation of solanidanones from dihydrotomatidine, we would like to suggest the probable steps as shown in Chart 2.

In this scheme dihydrotomatidine (I) undergoes facile ring closure to a carbinolamine (VII)[22] when

(14) This assignment does not conform strictly to conventional terminology. Another expression would be the use of *cis–trans* isomers with respect to C_{25}-methyl, *i.e.*, *cis* for α and *trans* for β.

(15) L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949); N. G. Gaylord, *Experientia*, X, 351 (1954).

(16) The behavior of the isomeric diols toward acetylation can perhaps be explained on this basis. In model studies the β-oriented dihydrotomatidine, B, seems to offer more steric interference toward acetylation than the α-oriented dihydro compound, A.

(17) M. E. Wall, C. R. Eddy and S. R. Serota, THIS JOURNAL, **76**, 2849 (1954); M. E. Wall and S. R. Serota, *ibid.*, **76**, 2850 (1954); J. B. Ziegler, W. F. Rosen and A. C. Shabica, *ibid.*, **76**, 3865 (1954).

(18) I. Scheer, R. B. Kostic and E. Mosettig, *ibid.*, **75**, 4871 (1953); V. H. T. James, *Chemistry and Industry*, 1388 (1953); F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(19) These assignments are contingent upon tomatidine having configurational structure I', as proposed by Uhle and Moore.[5]

(20) W. E. Rosen and D. B. Rosen, *Chemistry and Industry*, 1581 (1954), suggest that the C_{22}-hydrogen is β-oriented because isorubijervine[21] which has been correlated with solanidine forms readily a cyclic ammonium salt.

(21) F. L. Weisenborn and D. Burn, THIS JOURNAL, **75**, 259 (1953).

(22) S. Gabriel and J. Colman, *Ber.*, **41**, 518 (1908), have shown that γ- and δ-phthalimidoketones, *i.e.*, $C_6H_4O_2$:N—$(CH_2)_{3-4}$—COR (R, CH_3 or C_6H_5), undergo immediate ring closure to Δ^2-pyrroline or Δ^2-piperidine upon hydrolysis.

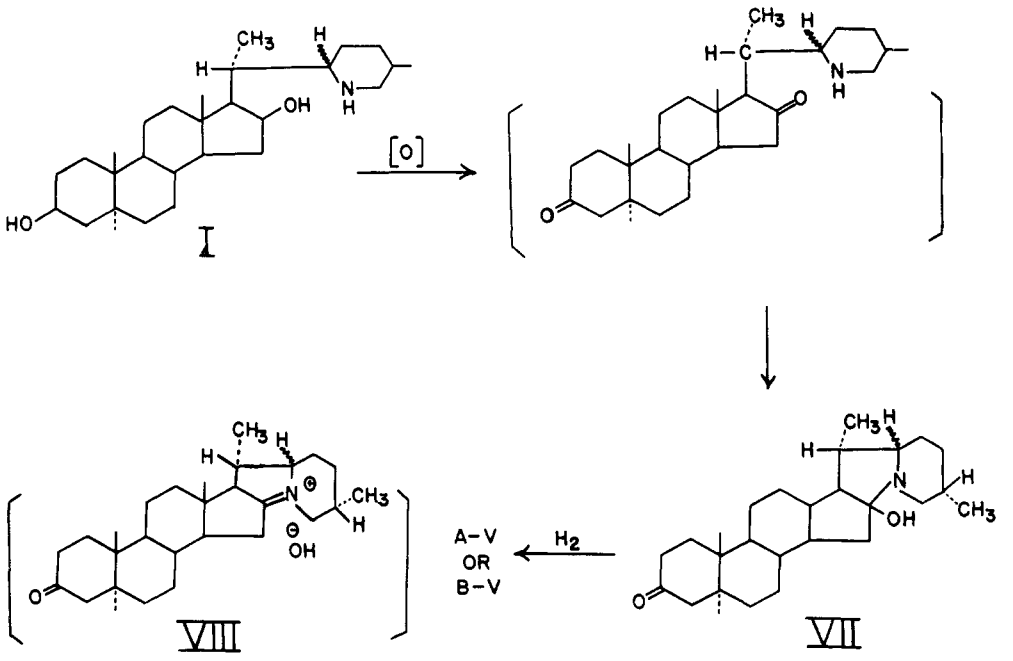

CHART 2

oxidized in the presence of an acid. This is then reduced to the desired solanidan-3-one (A-V or B-V). The carbinolamine (VII) may possibly exist to some extent as an unsaturated ammonium hydroxide (VIII). Support for the carbinolamine structure VII is offered by its analysis and spectral data. The absence of a 16-ketone absorption band in the infrared spectrum excludes a 3,16-bisdehydro derivative as a stable intermediate as Kuhn, *et al.*,[12] have shown ($\lambda_{max}^{CHCl_3}$ 2.74 μ, weak; 5.83 μ,[23] strong; 5.95 μ, inflection; 6.07 μ, weak).

In concluding we wish to report an analogous conversion of dihydrosolasodanol[24] to another isomeric solanidanone (m.p. 146–147°, $[\alpha]^{20}D$ +49°)[25] which should be the C_{25}-epimer[18] of one of the solanidanones obtained from the dihydrotomatidines.

Experimental[26]

Dihydrotomatidine A and B.—Crystalline tomatidine, m.p. 206–208° (1.033 g.), was dissolved in 15 cc. of glacial acetic acid (distilled over chromium trioxide) with slight warming and reduced over 463 mg. of platinum oxide catalyst. Slightly over 1 mole of hydrogen was consumed. After removal of the catalyst and addition of water and methanol to the filtrate, it was made alkaline with ammonia gas and the copious precipitate collected. The dried substance (0.986 g.) was dissolved in 30 cc. of chloroform–benzene (1:4) and placed on 30 g. of neutral alumina for chromatography. Elution with 1–2% methanol in ether gave dihydrotomatidine of m.p. 190–193°. Recrystallization from benzene–hexane gave rods of m.p. 194.5–195.5°, $[\alpha]^{20}D$ −19 ± 2° ($CHCl_3$). In general yields ranged from 35–45%.

Anal. Calcd. for $C_{27}H_{49}O_2N$: C, 77.64; H, 11.34. Found: C, 77.44; H, 11.17.

Elution with 5% CH_3OH in ether afforded dihydrotomatidine of m.p. 230–233°, rectangular plates from dilute methanol, $[\alpha]^{20}D$ +14° (CH_3OH).[27] Yields have averaged 30–35%.

Anal. Calcd. for $C_{27}H_{49}O_2N$: C, 77.64; H, 11.34. Found: C, 77.31; H, 11.46.

On several occasions elution with 50% methanol in ether gave a few mg. of an unidentified high melting substance (m.p. 270–300° dec.).

Hydrogenation over platinum oxide in ethanol or ethanol–triethylamine led to a preponderance of low melting dihydro, A (*ca.* 8:1), while hydrogenation in an acidic medium (ethanol–methanol–hydrochloric acid) increased the production of the high melting dihydro, B (*ca.* 1:1).

Lithium Aluminum Hydride Reduction of Tomatidine.—Four grams of tomatidine was dissolved in 1000 cc. of dry ether by slight warming. The solution was cooled and 6 g. of lithium aluminum hydride was added in small chunks at a rate to maintain moderate refluxing. The reaction mixture was refluxed for 4 hr., and then the excess reagent was decomposed with the cautious addition of ice-water. After the addition of excess sodium hydroxide (1 *N*) the ethereal layer was separated and the aqueous layer repeatedly extracted with ether. The combined ethereal extract yielded 3.5 g. of crude substance which gave 3.2 g. of the low melting and 0.3 g. of the high melting derivative upon chromatography. In several runs the yields of the high melting compound averaged about 10%.

N,O,O'-Triacetyldihydrotomatidine (A-I).[7]—The dihydrotomatidine A was treated in the usual manner with pyridine and acetic anhydride at room temperature overnight. Attempts at chromatography failed to yield a crystalline compound, $[\alpha]^{20}D$ +2.9° ($CHCl_3$).

(23) This is obviously due to the 3-ketone absorption. The infrared spectrum of the product from an analogous oxidation of dihydrosolasodane (only 16-hydroxyl present) shows no carbonyl absorption band.

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

(25) To be published in a forthcoming publication.

(26) All melting points were taken on the Kofler block and are uncorrected. Infrared spectra were determined on a Perkin–Elmer double beam spectrophotometer by Mrs. Phyllis B. Smeltzer, Mrs. Alma L. Hayden and Mr. H. K. Miller. Microanalyses were performed by the Analytical Service Laboratory under the direction of Dr. William C. Alford.

(27) Rotations taken in chloroform gave non-reproducible results. Studies are under way to investigate this behavior.

Anal. Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82. Found: C, 72.46; H, 9.95.

N-Acetyldihydrotomatidine (A-II).—N,O,O'-Triacetyldihydrotomatidine, A-I (960 mg.), was dissolved in 40 cc. of 2% methanolic potassium hydroxide and refluxed for 1 hr. Upon concentration and addition of water a crystalline substance was obtained (728 mg.). Chromatography of this substance gave crystals (338 mg.) of m.p. 256–259°, $[\alpha]^{20}D$ +13.5° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.74. Found: C, 75.57; H, 10.76.

Oxidation of N-Acetyldihydrotomatidine A-II to N-Acetyl-3,16-bisdehydrodihydrotomatidine A-III.—The N-acetyldiol, A-II (282 mg.), was dissolved in 90 cc. of acetone by slight warming and divided evenly among three flasks. To each was added dropwise a solution of Kiliani's reagent until a slight excess of oxidant was indicated by the persistence of an orange color. After allowing them to stand at room temperature for 10 minutes, several drops of water were added to each flask to dissolve the flocculent precipitate. This addition caused a simultaneous deposition of greenish oily droplets of chromium salts. The clear solution was carefully removed by filtration from this sediment and made alkaline with dilute sodium hydroxide while cooling. Upon addition of excess water to this turbid solution, a flocculent precipitate appeared. After the mixture was saturated with sodium chloride, it was repeatedly extracted with ether. The combined ethereal solution was evaporated and the semi-crystalline residue (250 mg.) was subjected to chromatography on an alumina column. Elution with 1% methanol in ether afforded 110 mg. of crystalline substance with a double m.p. 179–181° and 193–196°. Recrystallization from ether yielded rods, m.p. 192–196°, $[\alpha]^{20}D$ −88° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.44; H, 9.95. Found: C, 76.64; H, 10.00.

Semicarbazone of N-Acetyl-3,16-bisdehydrodihydrotomatidine (A-III).—This was prepared in the usual manner with semicarbazide hydrochloride and sodium acetate. An amorphous 3-semicarbazone was formed which melted at 213–216°; $\lambda_{max}^{CHCl_3}$ 2.83, 2.93, 5.77, 5.91, 6.18 and 6.40 μ, all strong.

Anal. Calcd. for $C_{30}H_{48}O_3N_4$: N, 10.93. Found: N, 10.82.

O,N-Diacetyldihydrotomatidine (B-I).—To 810 mg. of dihydrotomatidine B dissolved in 12 cc. of dry pyridine was added 4.0 cc. of acetic anhydride and the solution allowed to stand overnight at room temperature. Upon addition of ice-water, 860 mg. of a semicrystalline substance was obtained. Recrystallization from methanol yielded crystals of m.p. 227–229°, $[\alpha]^{20}D$ −10° ($CHCl_3$).

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 74.33; H, 10.53.

N-Acetyldihydrotomatidine (B-II).—A solution of 760 mg. of O,N-diacetyldihydrotomatidine (B-I) in 30 cc. of 2% methanolic potassium hydroxide was refluxed for 1 hr. After concentration and dilution with water, a precipitate was obtained which was collected and washed well with water. The dried product weighed 728 mg. Upon chromatography on neutral alumina and elution with 1% methanol in ether, 560 mg. of B-II of m.p. 229–232° was obtained. Recrystallization from dilute methanol yielded plates of m.p. 232–233.5°, $[\alpha]^{20}D$ −25° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.74. Found: C, 75.98; H, 10.73.

Oxidation of N-Acetyldihydrotomatidine (B-II) to N-Acetyl-3,16-bisdehydrodihydrotomatidine (B-III).—A solution of 150 mg. of N-acetyldihydrotomatidine (B-II) in acetone (20 cc.) was oxidized with dropwise addition of Kiliani's reagent (0.5 cc.) at room temperature. After allowing the mixture to stand for 20 minutes, water was added dropwise to it until the precipitate dissolved The clear solution was then removed from the settled conglomeration of dark, greenish oily droplets by filtration and made alkaline with dilute sodium hydroxide while cooling. The copious precipitate was extracted with ether after the solution was saturated with sodium chloride. The crude substance, after removal of the ether, was chromatographed over alumina. Elution with 1% methanol in ether afforded 97 mg. of crystalline substance which melted at 159–163°, then resolidified to melt at 191–194°. Recrystallization from ether–hexane gave plates with a single m.p. 163–166°, whereas crystallization from dilute acetone yielded plates which melted at 196–198°, $[\alpha]^{20}D$ −146° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.44; H, 9.95. Found: C, 76.52; H, 9.96.

The semicarbazone of N-acetyl-3,16-bisdehydrodihydrotomatidine (B-III) formed crystals of 3-semicarbazone, m.p. 222–225°, $\lambda_{max}^{CHCl_3}$ at 2.83, 2.93, 5.77, 5.91, 6.18 and 6.40 μ, all strong.

Anal. Calcd. for $C_{30}H_{48}O_3N_4$: N, 10.93. Found: N, 10.87.

Oxidation of O,N-Diacetyldihydrotomatidine (B-I) to N-Acetyl-16-dehydrodihydrotomatidine (B-IV).—O,N-Diacetyldihydrotomatidine (150 mg.) was oxidized with Kiliani's reagent and worked up as in the previous experiment. The amorphous residue ($\lambda_{max}^{CHCl_3}$ 5.78 μ, 3-acetoxy and C_{16}-ketone; 6.15 μ N-acetyl) failed to crystallize and was therefore subjected to chromatography. However, no crystalline substance could be obtained.

The combined material was then hydrolyzed by refluxing in 2% methanolic potassium hydroxide for 1 hr. and the resulting semi-crystalline matter chromatographed. Upon elution with 5% methanol in ether, crystals which melted at 256–258° were obtained, $\lambda_{max}^{CHCl_3}$ 2.78 μ (hydroxyl); 5.76 μ (16-ketone); 6.15 μ (N-acetyl).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.01; H, 10.23.

Iso(C_{22})-solanidan-3-one (A-V).—To 140 mg. of dihydrotomatidine A dissolved in 40 cc. of acetone was added dropwise with swirling 0.45 cc. of oxidant. The mixture was worked up as in the previous oxidations but the precipitate was collected by filtration instead of extraction. The dried material was redissolved in hexane and filtered from insoluble matter. The residue, after removal of the hexane, was crystallized from methanol to form needles which seemed to fuse at about 131–135°.

The intermediate (presumably the carbinolamine) is rather unstable and attempts at purification *via* chromatography or sublimation produce a change in the nature of the compound, $\lambda_{max}^{CS_2}$ 2.76 μ (hydroxyl, weak); 5.86 μ (3-ketone, strong); 5.95 μ (weak); 6.07 μ (weak).

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.40; H, 10.48. Found: C, 78.60; H, 10.47.

In a typical run 216 mg. of the oxidized product was dissolved in 10 cc. of ethyl acetate and 1 cc. of methanol and reduced under normal pressure in the presence of 120 mg. of 10% palladium-on-charcoal catalyst. After the uptake of approximately one mole of hydrogen in about 2 hours, the hydrogenation was suspended and the catalyst removed. The filtrate yielded 206 mg. of semi-crystalline substance which was chromatographed over alumina. Elution with benzene–ether (9:1) gave 113 mg. of crystals of m.p. 203–210°. Recrystallization from methanol–acetone yielded needles of m.p. 206–208°, $[\alpha]^{20}D$ +32° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.43; H, 11.02.

Semicarbazone of Iso(C_{22})-solanidan-3-one (A-V).—To 44 mg. of crude ketone in 12 cc. of ethanol was added 64 mg. of semicarbazide hydrochloride and 64 mg. of anhydrous sodium acetate and the solution refluxed for 1.5 hr. It was partially concentrated and made alkaline with dilute sodium carbonate solution. The flocculent precipitate was extracted with chloroform. The residue after removal of the chloroform failed to crystallize from dilute alcohol and only slightly from benzene. The amorphous substance was therefore thoroughly washed with ether and dried. The compound did not melt but charred with browning commencing about 200°.

Anal. Calcd. for $C_{28}H_{46}ON_4$: N, 12.32. Found: N, 12.55.

Iso(C_{22})-solanidan-3β-ol (A-VI).—Dihydrotomatidine A of m.p. 188–192° was treated according to the procedure of Kuhn, *et al.*[12] A semi-crystalline residue was obtained which after recrystallization, sublimation and further crystallization yielded needles of m.p. 213–216°, $[\alpha]^{20}D$ +12° ($CHCl_3$). It formed a digitonide.

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35. Found: C, 80.94; H, 11.45.

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]

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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

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(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.