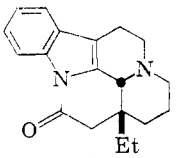
in agreement with their genesis through the pathway XXXVI → XXXIX. *The Mannich-type closure of the rigid nine-membered ring in XXXVIII requires formation of a cis-perhydroisoquinoline system in XXXIX.*[39] Furthermore, the *cis-anti-cis* backbone exhibited by XXI may be the consequence of the Mannich condensation and the subsequent reduction following the path of least steric resistance.

As the above discussion indicates, the prephenic acid hypothesis (and/or the monoterpenoid hypothesis) is able to account for the structure patterns of all indole alkaloids without exception. It will be of interest to watch experimental developments in this field of alkaloid biosynthesis.

(39) In this connection it is of interest that eburnamonine (iv) [M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960)], a Hunteria alkaloid of aspidospermine-like features, possesses the same stereochemistry (unpublished observations of Dr. B. Wickberg presented by the author at the 17th National Organic Chemistry Symposium, Bloomington, Ind., June 25–29, 1961).



iv

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A., MEXICO, D.F.]

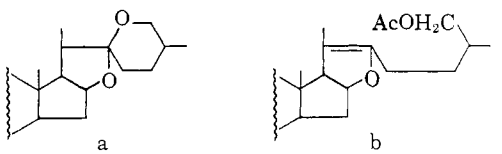
Sapogenins. XLI.[1] A New Reaction of the Spiroketal Side Chain

BY JOHN A. ZDERIC,[2a] LOURDES CERVANTES[2b] AND MARIA TERESA GALVAN[2b]

RECEIVED AUGUST 7, 1961

Treatment of sapogenins with acetic anhydride in the presence of boron trifluoride etherate leads to products for which 23-acetyl-Δ^{22}-furostene type structures are proposed.

The Marker procedure for conversion of sapogenins to 20-keto pregnane derivatives[3] involves as the first step treatment with acetic anhydride at 200°. Under these conditions sapogenins (a) are converted to furostene derivatives (b) and in general the yields are good. Even so, numerous attempts have been made to develop reaction



conditions which would avoid the use of special autoclaves or sealed tube systems required in order to reach the 200° temperature.

The use of octanoic anhydride[4] and pyridine hydrochloride in acetic anhydride[5] have been investigated and found to be satisfactory variants of the original procedure. A study employing Lewis acids in boiling acetic anhydride has also been described,[6] although in these cases the yields of furostene were low.

Recently we noted[7] that either hecogenin ketol diacetate or 11β,12β-dihydroxytigogenin 11β,12β-acetonide acetate undergo normal furostene formation at 200° during periods ranging from 45 to 70 minutes. This stands in contrast to most procedures which employ times of from five to twenty-four hours. Additional examples of compounds capable of undergoing this rapid reaction are 11a-aza-C-homotigogenin,[8] rockogenin and tigogenin.[8]

On the basis of these observations we were led to wonder whether these reactions might not also proceed at less drastic temperatures. After ascertaining that acetic anhydride at its boiling point was without effect, even over prolonged periods of time, the use of boron trifluoride etherate was investigated.

This procedure involved treating the sapogenin in acetic anhydride at room temperature with a weight of boron trifluoride etherate equal to the steroid. Under these conditions a slightly exothermic reaction set in which rapid darkening of the mixture. If prolonged periods of time were employed, only intractable gums could be recovered. On the other hand, after ten- to twenty-minute reaction periods it was possible to isolate a crystalline product in 10 to 45% yield, either by direct crystallization or chromatography. This reaction was found to be applicable to hecogenin ketol diacetate, diosgenin, 3-desoxytigogenin and tigogenin. For the purpose of characterizing the reaction products all further work was carried out on tigogenin (I).

The substance showed unusual spectral properties. The infrared was characterized in the carbonyl region by a strong band at 5.78 μ, a medium in-

(1) Paper XL, A. Bowers, E. Denot, M. B. Sánchez, F. Neumann and C. Djerassi, *J. Chem. Soc.*, 1859 (1961).

(2) (a) Present address: Syntex Institute for Molecular Biology, Palo Alto, Calif. (b) Taken in part from theses presented by L. C. and M.T.G. to the Facultad de Quimica, Universidad Nacional Autónoma de México.

(3) For a general description of method see L. F. Fieser and M. Fieser "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, pp. 549–550.

(4) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

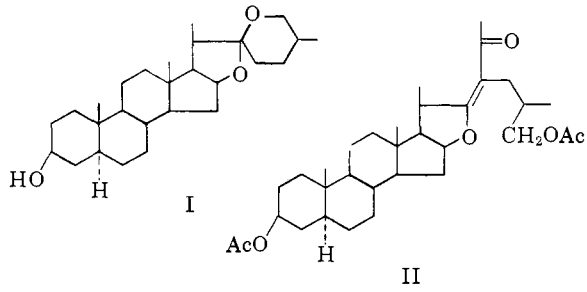
(5) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **76**, 4618 (1954).

(6) D. H. Gould, H. Staeudle and E. B. Hershberg, *ibid.*, **74**, 3685 (1952).

(7) J. A. Zderic, H. Carpio and C. Djerassi, *ibid.*, **82**, 446 (1960).

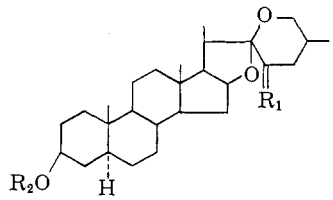
(8) J. A. Zderic, H. Carpio, D. Chávez Limón and A. Ruiz, *J. Org. Chem.*, **26**, 2842 (1961).

tensity and very sharp band at 6.01 μ and a very strong band at 6.36 μ. The ultraviolet spectrum consisted of a single band at 274 mμ with an intensity of log ϵ 4.02.

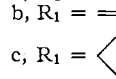
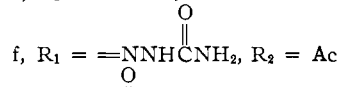
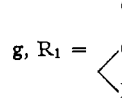
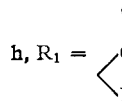


I

II



III

IIIa, R_1 = =CHCH$_3$, R_2 = H
b, R_1 = =CHCH$_3$, R_2 = Ac
c, R_1 =  , R_2 = Ac
d, R_1 = =O, R_2 = Ac
e, R_1 = =NOH, R_2 = Ac
f, R_1 =  , R_2 = Ac
g, R_1 =  , R_2 = H
h, R_1 =  , R_2 = Ac

Some years ago a group at Glaxo[4] treated tigogenin with perchloric acid in acetic anhydride and succeeded in isolating two impure substances with ultraviolet maxima similar to those reported above. On this basis and in view of what was known concerning the ultraviolet spectra of β-oxygenated-α,β-unsaturated ketones,[9] they proposed structures of type II for the substances. Structures of this type also appeared likely in the present study although marked differences in the positions of the carbonyl bands were observed from those which had been reported by the Glaxo workers.

It seemed, however, that if II was the correct structure it should be easily converted to tigogenin lactone by oxidation. Accordingly, oxidations employing pyridine–chromium trioxide[10] and 8 *N* chromium trioxide[11] were first investigated. In neither of these cases did any reaction take place to a noticeable degree and the same result obtained for the two phase chromium trioxide–acetic acid–dichloroethylene oxidation[12] which is a mild method for furostene oxidations. With chromium trioxide–acetic acid over prolonged periods or by ozonization acidic gums could be obtained, but these resisted crystallization even after careful chromatography over silica gel.

Having failed in this correlation we turned to mild catalytic reductions employing palladium–carbon in methanol or ethyl acetate. In each case only starting material was recovered. When, however, lithium aluminum hydride reduction in tetrahydrofuran was investigated a new substance IIIa was obtained which was free of any carbonyl or ultraviolet absorption and contained only three oxygen atoms. From analyses it was known that II originally contained six oxygen atoms, four of which were involved in acetate functions. It was evident, therefore, that this hydride reduction had not only effected acetate cleavage but also that the loss of one additional oxygen atom had taken place.

Information concerning the nature of the oxygens in IIIa was obtained from acetylation which provided the monoacetate IIIb. This result suggested that the two remaining oxygens were present either as tertiary hydroxyls or ethers. Evidence for the latter proposal was gained from the infrared spectrum of IIIb which was devoid of hydroxyl absorption but did exhibit several bands in the 11μ region which were suggestive of a spiroketal structure.[13] These same infrared bands were present in the 11μ region of IIIa although they were absent in II.

Additional information concerning IIIb was obtained when it was found possible to reduce this substance to a dihydro derivative now known to be 23-ethyltigogenin acetate (IIIc).

Since IIIb possessed a double bond, attempts were made to effect its oxidation with either potassium permanganate or chromic acid. When neither of these reagents proved suitable, osmylation followed by lead tetraacetate cleavage was attempted. Under these conditions traces of crystalline material were obtained which were later found to be identical to IIId. Fortunately when IIIb was subjected to ozonization at $-80°$ a smooth oxidation ensued and the resulting mixture was then subjected to steam distillation. Under these conditions an odiferous volative fragment was obtained in the distillate and by means of its dinitrophenylhydrazone it was identified as acetaldehyde.

The non-volatile still residue IIId was easily purified and its characterization was accomplished by formation of an oxime IIIe and a semicarbazone IIIf. Furthermore, it was observed that IIId upon subjection to Huang-Minlon reduction provided tigogenin (I). This finding gave immediate confirmation to the earlier suspicions that IIIa,b and c possessed spiroketal-like structures.

Callow and Massy-Beresford[14] in a paper concerned with the configuration of C-22 in sapogenins described the preparation of 23-ketotigogenin ace-

(9) See page 2809 of ref. 4.

(10) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) See for example ref. 7.

(13) For a description of these bands see M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

tate (IIId) by direct chromic acid oxidation of tigogenin acetate. The results of our analytical data coupled with the reasonable correspondence to the reported[14] physical constants not only for IIId but also for IIIf indicated that IIId truly represented the product obtained by ozonization. Confirmation of this view followed from a direct comparison of IIId with authentic 23-ketotigogenin acetate.

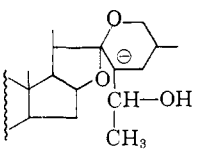
With this point established, the structures of IIIa, IIIb and IIIc were settled and there remained only the problem of the structure of II. As previously noted by analysis, this substance gave evidence of being a diacetate which contained six oxygens. Since four of the oxygens were involved as acetate functions and no free hydroxyls were present, it followed that the remaining two oxygens must occur either as ketones or ethers, or both. While repeated attempts to obtain crystalline ketonic derivatives of II were unsuccessful, evidence for the presence of such a grouping located alpha to a methyl group was obtained by means of a positive iodoform test.

One of the two acetate functions, must be present at C-3. As no other free hydroxyls are present in I, it follows that the second acetate function in II must have arisen by fission and acetylation of one of the rings involved in the spiroketal system. Since in most reactions involving the opening of a single ring in the spiroketal system it is ring-F which undergoes fission,[15] thereby providing either furostene or furostane derivatives, this same type of ring fission has been assumed to occur in the present case. Under these conditions, the second acetate function should be present at C-26. If now this assumption is correlated with the following facts—(a) an ultraviolet spectrum of the β-oxygenated-α,β-unsaturated ketone type; (b) an extra two carbon fragment on C-23; (c) the presence of a methyl ketone—the results may be combined in the expression II.[16]

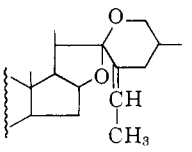
Some support for structure II has been obtained from the following reaction sequence. Attempts to treat II under the conditions of a mild Huang-Minlon reduction led in low yield to a new product which still contained a ketonic grouping, as indicated by the presence of a carbonyl band at 5.89 μ (chloroform). It was later found however that this same ketonic product IIIg could be obtained in good yield when II was treated with potassium *t*-butoxide in *t*-butyl alcohol. This reaction is interpreted as involving hydrolysis of the C-27 acetate whence Michael addition of the C-27 hydroxyl to the α,β-unsaturated ketone provides 23-acetyltigogenin (IIIg). Evidence for the correctness of this structure rests on its reduction by the Huang-Minlon procedure to provide after acetylation authentic 23-ethyltigogenin acetate (IIIc).

The unusual infrared spectrum of 23-acetyltigogenin bears some comment. When IIIg is either sublimed or recrystallized from any variety of solvent pairs such as acetone–hexane, ether–hexane or even from pure acetone, its infrared spectrum exhibits peaks at 5.85 and 5.93 μ when observed in potassium bromide pellet. That this is a phenomenon associated with the crystalline state is apparent when the spectrum is rerun in chloroform solution. In this case only a single carbonyl peak appears at 5.89 μ, a fact that is consistent with the assigned structure.

The following mechanism or a closely related one may be responsible for the loss of the extra oxygen during transformation of II to the ethylidene derivative IIIa. Hydride cleavage of the acetate functions along with concomitant Michael addition to the double bond and reduction of the methyl ketone provides an intermediate of the type d which then undergoes hydroxyl elimination to provide e.



d



e

A final point concerns the stereochemistry of II at C-20. This center may be assigned to the normal configuration since it should remain unchanged during cyclization to IIIa which possesses the same configuration at C-20 as does tigogenin.[17] As regards the stereochemistry of the Δ^{22}-double bond, it remains unknown and no inferences should be drawn from the drawing II.

Acknowledgment.—The authors are indebted to Dr. R. K. Callow for carrying out the direct comparison of IIId and 23-ketotigogenin acetate.

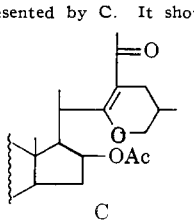
Experimental[18]

Treatment of Tigogenin with Boron Trifluoride Etherate in Acetic Anhydride; 23-Acetyl-5α-furost-22-ene-3β,26-diol 3,26-Diacetate (II).—Acetic anhydride (200 ml.) containing 20 g. of tigogenin was treated at room temperature with 20 ml. of freshly distilled boron trifluoride etherate. After 15 min. the resulting solution was poured into 3 l. of water containing 500 g. of ice. Stirring was continued until all of the acetic anhydride had been hydrolyzed and the reaction product was semi-solid in nature. The water was then decanted and the residue dissolved in 1.5 l. of ethyl

(14) R. K. Callow and P. N. Massey-Beresford, *J. Chem. Soc.*, 4482 (1957).

(15) (a) See ref. 3; (b) C. Djerassi, O. Halpern, G. R. Pettit and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959); (c) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 846 (1939); (d) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.* **25**, 84 (1960), and references therein.

(16) An alternative structure equally capable of explaining the observed results is represented by C. It should be noted, however



C

that this structure would involve the unlikely possibility of ring E having undergone fission in preference to ring F.

(17) J. W. Corcoran and H. Hirschmann, *J. Am. Chem. Soc.*, **78**, 2325 (1956).

(18) All melting points are uncorrected and all rotations have been determined in chloroform. The authors are indebted to Dr. J. Matthews and his staff for the determination of all rotations and the recording of spectra.

acetate. After washing first with water and 5% aqueous sodium bicarbonate and then again with water, the organic phase was dried over sodium sulfate and evaporated almost to dryness. The residue was then allowed to stand in acetone–hexane from which mixture crystals, 10.5 g., m.p. 75–81°, slowly separated. Recrystallization from this same solvent pair then gave 7.5 g. of II, m.p. 80–84°, which was eventually raised by further crystallizations to m.p. 87–88°, $[\alpha]_D$ −14.22°, λ_{max}^{EtOH} 274–276 mμ, log ε 4.02; λ_{max}^{KBr} 5.78, 6.01, 6.36 and 8.08 μ.

Anal. Calcd. for $C_{33}H_{50}O_6$: C, 73.02; H, 9.19; O, 17.69; acetyl, 15.84. Found: C, 73.03; H, 9.13; O, 17.22; acetyl, 14.61.

By the procedure outlined above, 3-desoxytigogenin[19] gave **23-acetyl-5α-furost-22-en-26-ol acetate**[20] recrystallized from dilute methanol; m.p. 92–94°, $[\alpha]_D$ +16°, λ_{max}^{EtOH} 276 mμ, log ε 4.03; λ_{max}^{KBr} 5.78, 5.99 and 6.35 μ.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98; O, 13.20. Found: C, 77.11; H, 10.01; O, 13.16.

Hecogenin ketol diacetate[21] gave **23-acetyl-5α-furost-22-en-3β,12β,26-triol-11-one 3,12,26-triacetate**, recrystallized from acetone–ether; m.p. 223–225°, $[\alpha]_D$ +5°, λ_{max}^{EtOH} 274–276 mμ, log ε 4.05; λ_{max}^{KBr} 5.83, 6.04 and 6.41 μ.

Anal. Calcd. for $C_{35}H_{50}O_8$: C, 68.38; H, 8.20; O, 23.42. Found: C, 68.68; H, 8.56; O, 23.08.

Diosgenin gave **23-acetyl-Δ⁵-furost-22-en-3β,26-diol 3,26-diacetate** recrystallized from ether; m.p. 93–96°, $[\alpha]_D$ −16°, λ_{max}^{EtOH} 274–476 mμ, log ε 4.02; λ_{max}^{KBr} 5.78, 6.00 and 6.36 μ.

Anal. Calcd. for $C_{33}H_{48}O_6 + C_4H_{10}O$: C, 72.27; H, 9.51; O, 18.22; acetyl, 15.92. Found: C, 72.66; H, 9.37; O, 18.18; acetyl, 14.20.

23-Ethylidenetigogenin (IIIa).—To 1 l. of anhydrous tetrahydrofuran was added 20 g. of II and 6 g. of lithium aluminum hydride. After being held at reflux temperature for 15 hr., the excess reagent was destroyed by the cautious addition of ethyl acetate and eventually saturated aqueous sodium sulfate. Following the addition of 15 g. of solid sodium sulfate the mixture was filtered and evaporated to provide 14 g. of a crude product, m.p. 205–218°, which upon crystallization from methanol–acetone gave 11 g. of crystals, m.p. 233–235°. Sublimation at 225° (0.04 mm.) yielded the analytical sample, m.p. 233–235°, $[\alpha]_D$ −59.3°; λ_{max}^{KBr} 2.86, 10.20, 10.54, 10.94, 11.16, 11.34 and 11.47 μ.

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.38; H, 10.11.

23-Ethylidenetigogenin Acetate (IIIb).—Treatment of IIIa (11 g.) with pyridine (35 ml.) and acetic anhydride (20 ml.) at room temperature for 15 hr. gave after dilution with water and recrystallization from methanol–acetone 9 g. of crystals, m.p. 198–200°, $[\alpha]_D$ +42°; λ_{max}^{KBr} 5.80, 10.21, 10.48, 11.03 and 11.50 μ.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.96; O, 13.20; acetyl, 8.88. Found: C, 76.80; H, 9.90; O, 13.68; acetyl, 9.51.

23-Ethyltigogenin Acetate (IIIc). **A. By Hydrogenation of IIIb.**—To 25 ml. of ethyl acetate containing 10 mg. of prereduced platinum oxide was added 500 mg. of IIIb. After stirring in a hydrogen atmosphere for 15 hr., the mixture was filtered and evaporated to dryness. The residue (490 mg.) was then chromatographed over 20 g. of neutral alumina. Hexane elution provided 420 mg. of crystals which were purified by recrystallization from acetone–methylene chloride; m.p. 180–183°. Sublimation of this material at 170° (0.04 mm.) gave the analytical sample, m.p. 180–183°, $[\alpha]_D$ −59°; λ_{max}^{KBr} 5.74, 10.17, 10.56, 10.82, 11.12 and 10.60 μ.

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36; O, 13.15. Found: C, 76.80; H, 10.10; O, 13.24.

B. By Huang-Minlon Reduction[22] **of IIIg.**—A mixture containing 300 mg. of IIIg, 5 ml. of ethylene glycol, 1 ml. of hydrazine hydrate and 0.5 g. of potassium hydroxide was heated at reflux temperature for 2 hours. The condenser was then removed and the mixture was concentrated until a temperature of 186° was reached. The condenser was then replaced and heating was continued for 5 hr. Following dilution with water (25 ml.) and extraction with ethyl acetate (100 ml.), the extract was washed with water, dried with sodium sulfate and evaporated to dryness. Without purification the residue was treated with pyridine (1 ml.) and acetic anhydride (1 ml.) for 15 hours at room temperature. After the usual workup 200 mg. of semi-solid was obtained. Following chromatography over 6 g. of neutral alumina and elution with hexane, there was obtained 95 mg. of crystals, m.p. 175–180°. A single recrystallization from acetone–methylene chloride then provided crystals with m.p. 180–183° which were identical in all respects with the material isolated above in A.

Ozonization of **23-Ethylidenetigogenin Acetate** (IIIb).—Pure methylene chloride (200 ml.) containing 3 g. of IIIb was cooled to −80° in a Dry Ice–acetone mixture. A slow current of ozone was then bubbled through the solution for 20 min. after which time a strong blue-violet color was apparent. Upon warming to room temperature the solution was mixed with 100 ml. of water and the methylene chloride was removed by gentle heating. The resulting mixture was then subjected to steam distillation, the distillate being collected in 150 ml. of water containing 1.3 g. of 2,4-dinitrophenylhydrazine and 6 ml. of concd. sulfuric acid. This solution was then extracted with benzene (100 ml.) and after filtration of the extracts they were passed through a column containing 20 g. of alumina. Elution with benzene and evaporation then gave a crystalline residue which was triply recrystallized from methylene chloride–methanol to provide 340 mg. of crystals, m.p. 162–164°.

Anal. Calcd. for $C_8H_8O_4N_4$: C, 42.86; H, 3.60; O, 28.55; N, 24.99. Found: C, 42.67; H, 3.77; O, 28.91; N, 25.19.

Upon direct comparison of this compound with authentic acetaldehyde dinitrophenylhydrazone, the two were found to be identical in all respects.

The still residue from the steam distillation was filtered to yield 2.8 g. of crystals, m.p. 178–180°. After four recrystallizations from methanol–acetone the crystals possessed m.p. 236–237°. Sublimation then gave analytically pure **23-ketotigogenin acetate** (IIId), m.p. 239–242°, $[\alpha]_D$ −51°, λ_{max}^{KBr} 5.78 μ, λ_{max}^{EtOH} 296–304 mμ, log ε 1.37; lit.[14] m.p. 233–235°, $[\alpha]_D$ −53°, λ_{max}^{KCl} 5.78 μ, λ_{max}^{EtOH} 298–300 mμ, log ε 1.5.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38; O, 16.93. Found: C, 73.41; H, 9.27; O, 17.32.

Oxime of 23-Ketotigogenin Acetate (IIIe).—Following the usual procedure employing pyridine,[23] 300 mg. of IIId provided 240 mg. of crystals, m.p. 256–260°. Three recrystallizations from methanol–acetone gave the analytical sample, m.p. 265–267°, $[\alpha]_D$ −55°, λ_{max}^{KBr} 2.95 and 5.74 μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$: C, 71.42; H, 9.30; O, 16.40; N, 2.87. Found: C, 71.28; H, 9.48; O, 16.60; N, 2.96.

Semicarbazone of 23-Ketotigogenin Acetate (IIIf).—By employing the previously described method,[14] 300 mg. of IIId gave 270 mg. of IIIf, recrystallized three times from methanol–ethyl acetate; m.p. 215–217°, $[\alpha]_D$ −21°, λ_{max}^{EtOH} 228–230 mμ, log ε 3.83; lit.[14] m.p. 212–215°, $[\alpha]_D$ −15°.

Huang-Minlon Reduction of IIId to Tigogenin (I).—Three hundred mg. of IIId was treated as described in the reduction of IIIg to IIIc. By these means and following chromatography there was obtained 200 mg. of crystals which after several recrystallizations from methanol exhibited m.p. 209–211°, $[\alpha]_D$ −66°; lit.[24] m.p. 207–210°, $[\alpha]_D$ − 76°. Direct comparison with authentic tigogenin showed the compounds to be identical in all respects.

(19) R. E. Marker and D. L. Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941).

(20) For nomenclature see IUPAC rules, *ibid.*, **82**, 5575 (1960).

(21) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(22) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(23) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York N. Y., 1948, p. 202.

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23-Acetyltigogenin (IIIg).—After dissolving 0.5 g. of potassium in 40 ml. of *t*-butyl alcohol, 1.0 g. of II was added and the resulting mixture was heated at reflux temperature for 15 hours. Following dilution with water (50 ml.), the solution was extracted with ethyl acetate and the extracts were washed with water, dried over sodium sulfate and evaporated to dryness. The residue (0.75 g.) was chromatographed over 30 g. of neutral alumina. Elution with benzene provided 0.51 g., m.p. 215–220°. Several crystallizations from acetone–hexane followed by sublimation at 215° (0.04 mm.) gave the analytical sample, m.p. 221–223°, $[\alpha]D$ −94°, λ_{max}^{KBr} 5.85 and 5.92 μ, $\lambda_{max}^{CHCl_3}$ 5.89 μ (infrareds recorded on material from the same sample).

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.49; H, 9.94.

23-Acetyltigogenin Acetate (IIIh).—Compound IIIg (0.55 g.) was acetylated by the previously described conditions. The crude product was recrystallized from methanol–acetone to give 0.52 g. of crystals, m.p. 129–130°. Several recrystallizations from the same solvent pair provided the pure acetate, m.p. 149–150°, $[\alpha]D$ −96°, λ_{max}^{KBr} 5.76 and 5.87 μ.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66; O, 15.98. Found: C, 74.76; H, 9.84; O, 15.76.

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Intramolecular S–O and S–N Acetyl Transfer Reactions

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Specific base catalyzed intramolecular acetyl transfer from sulfur to oxygen proceeds about 30 times faster in S-acetylmercaptoethanol than in the corresponding propyl compound. Intramolecular acetyl transfer from sulfur to nitrogen in S-acetylmercaptoethylamine exhibits inverse dependence on hydrogen ion concentration at low *p*H and is general base catalyzed at high *p*H. A detailed mechanism for S–N transfer including dehydration to yield methylthiazoline is presented and absolute values for all rate constants are either evaluated or estimated.

Acetyl transfer from sulfur to oxygen occurs readily in the series[1] $CH_3COS(CH_2)_nOH$ when n is 2 or 3 and not at all when n is 4. For n = 3, the equilibrium constant[2] for S–O transfer if 56 at 39°. Acetyl transfer from sulfur to nitrogen takes place in the series[3] $CH_3COS(CH_2)_nNH_3^+$ when n is 2 or 3, but little or no transfer is detected when n is 4, 6 or 10. The equilibrium constant for S–N transfer is *p*H dependent.[4,5] The above results implicate intermediate ring formation in both S–O and S–N transfer reactions. In this paper further investigations of the transfer reactions are reported, including *p*H, temperature and catalytic studies. Finally, a detailed mechanism of S–N transfer is presented which can account for all the observations on S–N acetyl transfer reactions and on methylthiazoline and methylthiazine hydrolysis studies.[4,5]

Experimental

S-acetylmercaptoethanol[6] had b.p. 116–119° (26 mm.) and an absorption maximum with ϵ_{232} = 4400 in aqueous solutions. S-acetylmercaptopropanol had b.p. 79° (1.2 mm.) and exhibited an absorption maximum with ϵ_{232} = 4260 in aqueous solutions. This molar extinction coefficient agrees well with a value determined in ethanol[1] but differs from ϵ_{235} = 5200 reported in 0.01 *N* HCl.[2]

S-Acetyl-β-mercaptoethylamine HCl[7] was prepared as previously[4] and had m.p. 145° and a maximum with ϵ_{229} = 4260. S-Acetylcysteine ethyl ester hydrochloride required more vigorous conditions for its preparation. Fifteen ml. of acetyl chloride was added to 5 g. of L-cysteine ethyl ester hydrochloride and the heterogeneous mixture was refluxed at 50° for about 1.5 hr. Upon boiling off the excess acetyl chloride, the remaining white crystalline solid was washed several times with dry ether and recrystallized from absolute ethanol. The final product had m.p. 116–117° and an absorption maximum with ϵ_{229} = 3800.

Initial rates of change were measured on a Cary 11 spectrophotometer with a thermostatable absorption cell compartment or on a Radiometer TTT1 *p*H-stat equipped with temperature control. Formate, acetate or phosphate buffers were used at about 10^{-2} *M* concentration and ionic strength was controlled at 0.2 *M* with KCl. Temperature was maintained to 0.1° and is 25.0° unless otherwise specified. Initial rates followed spectrophotometrically were evaluated by log $(A_t - A_\infty)$ *vs.* time plots. The A_∞ values were determined from known equilibrium constants,[2,5] but the calculated rate constant is not usually sensitive to the value chosen.

Results

S–O Transfer.—For both S-acetylmercaptoethanol (AME) and S-acetylmercaptopropanol (AMP) the initial rate of disappearance of thioester absorption is first order in ester in the 1–3 × 10^{-4} *M* concentration range. At 25° in solutions 0.02 *N* to 3 *N* HCl the observed rate constants are proportional to the first power of (H^+) with AME disappearing only slightly more rapidly than AMP. Comparison of the rates with those of hydrolysis of thioesters in aqueous solutions[8] indicates that hydrolysis may contribute as much as 20% to the over-all initial rate. Addition of 0.2 *M* glycine at *p*H 2.5 did not accelerate the over-all rate of disappearance of AME. The specific acid catalyzed transfer was not investigated further.

The initial rates of disappearance in basic solutions are inversely proportional to the first power of (H^+) in the range 6.0 < *p*H < 8.0 at 25°. The results at 3 temperatures are presented in Table I. The apparent first order rate constant is multiplied by (H^+) to obtain a *p*H independent constant. The observed activation energy ΔE and the ap-

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