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

Steroidal Sapogenins. XXXIX.[1] Transformations in Ring-C of the Sapogenin Series

JOHN A. ZDERIC, HUMBERTO CARPIO, DINORAH CHÁVEZ LIMÓN, AND AUGUSTO RUIZ

Received September 7, 1960

Cleavage of 11β,12β-dihydroxytigogenin with lead tetraacetate leads in good yield to the corresponding 11,12-secodialdehyde. Experiments describing attempted Dieckmann condensation of the derived dicarbomethoxy esters are presented as well as an internal Canizzaro type reaction which occurs upon treatment of the dialdehyde with alkali. Further transformations of certain intermediate compounds are described.

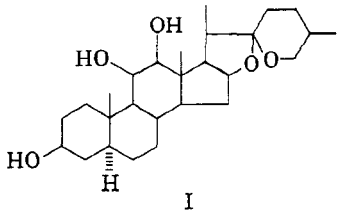
Catalytic reduction of the dialdehyde in the presence of ammoniated ethanol is shown to produce 11a-aza-c-homotigogenin. An alternate synthesis of this compound which involves the formation and lithium aluminum hydride reduction of an intermediate Schiff type base is also reported.

During attempts to prepare 11,12-secotigogenin by Huang-Minlon reduction the dialdehyde underwent a reductive ring closure thereby providing rockogenin. The conversion of rockogenin to tigogenin under these reaction conditions is also described.

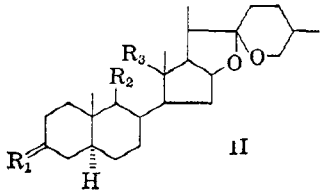
A recent report by Engel and Huculak[2] concerning certain 9,12-seco steroids prompts a disclosure of certain other ring C-seco derivatives which are currently under investigation in this laboratory.

In considering the amount of work which has been published concerning substitutions in ring-C of the steroid hormones[3] it is observed that only the 9α-fluoro derivative has possessed a sufficiently potentiating effect so as to make its introduction an important feature of most new cortical hormone syntheses.[4] It appeared therefore to be of some interest to study other synthetic routes which might lead to radically different structures from those previously reported.[5] The present paper records the results of such researches in the sapogenin series, whereas later papers will be concerned with the transformations of these derivatives to hormone analogs.

A facile entry to this new series of compounds was obtained by treatment of 11β,12β-dihydroxytigogenin (I)[6] in benzene–acetic acid solution with lead tetraacetate whence high yields of 11,12-secotigogenin-11,12-dialdehyde (IIa) resulted. In agreement with the work of Barton *et al.*[7] who



I



II

IIa. R_1 = 11β-OH, 12β-H; R_2 = R_3 = CHO

b. R_1 = O; R_2 = COOH; R_3 = CHO

c. R_1 = O; R_2 = R_3 = COOH

d. R_1 = 11β-OBz, 12β-H; R_2 = R_3 = CHO

e. R_1 = 11β-OBz, 12β-H; R_2 = R_3 = COOH

f. R_1 = 11β-OBz, 12β-H; R_2 = R_3 = $COOCH_3$

g. R_1 = 11β-OH, 12β-H; R_2 = COOH; R_3 = $COOCH_3$

h. R_1 = 11β-OH, 12β-H; R_2 = R_3 = $COOCH_3$

i. R_1 = 11β-OH, 12β-H; R_2 = COOH; R_3 = CH_2OH

j. R_1 = 11β-OH, 12β-H; R_2 = $COOCH_3$; R_3 = CH_2OH

k. R_1 = 11β-OAc, 12β-H; R_2 = R_3 = CHO

l. R_1 = 11β-OAc, 12β-H; R_2 = COOH; R_3 = CHO

m. R_1 = 11β-OAc, 12β-H; R_2 = $COOCH_3$; R_3 = CHO

(1) Paper XXXVIII, O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 439 (1959).

(2) C. R. Engel and W. W. Huculak, *Can. J. Chem.*, **37**, 2031 (1959).

(3) For a brief resume of such substitutions at C-11 and C-12 see J. A. Zderic, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 446 (1960) and references contained therein

(4) For discussion see J. Fried and A. Borman, *Vitamins and Hormones*, Vol. 16, Academic, New York, 1958, pp. 303–374.

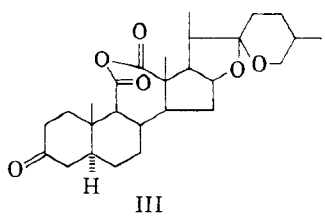
(5) In addition to the structural modifications reported in ref. 2, 3, and 4 the preparation of 9α-methylcortisone has also been announced, F. Hoffman, R. E. Beyler, and M. Tishler, *J. Am. Chem. Soc.*, **80**, 5322 (1958).

(6) C. Djerassi, H. Ma. ínez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(7) D. H. R. Barton, P. de Mayo, and J. C. Orr, *J. Chem. Soc.*, 2239 (1958).

investigated a similar cleavage on a ring-C hydroxylated derivative of the triterpene zeorin the reaction was extremely rapid, being essentially complete after thirty to sixty seconds. However, in strong contrast to their results, which indicated that the triterpene dialdehyde immediately underwent an aldol type condensation, the dialdehyde in the present case proved to be extremely stable towards such a transformation. While neither the infrared spectrum nor analytical data distinguished between the possibilities of IIa existing as the dialdehyde or the corresponding 5-membered ring aldol, the NMR spectrum[8] clearly indicated the former structure, bands being present which corresponded to an aldehyde group attached to a quaternary carbon atom (C-13) as well as one attached to a carbon atom (C-9) bearing a single hydrogen.

A chemical proof for the structure of IIa was forthcoming in the following manner. Treatment of IIa with 8*N* chromium trioxide[9] for a period of ten minutes at room temperature led in good yield to a substance IIb whose neutralization equivalent was in accord with a monocarboxylic acid. Furthermore, when IIb was subjected to an additional forty-five-minute oxidation with the same reagent a new acid was obtained and on the basis of its neutralization equivalent, analytical and spectral data it was assigned the structure of 11,12-secotigogenone-11,12-dioic acid (IIc). Alternatively this same compound could be obtained directly from the dialdehyde IIa by employing the longer reaction period. Finally, proof that the oxidation products were represented by the expressions IIb and IIc was forthcoming when IIc was easily converted by the action of acetic anhydride to III which pos-



III

sessed the typical anhydride bands at 5.58 μ and 5.72 μ as well as the 3-ketone band at 5.80 μ in the infrared.[10] That the spiroketal side chain was not involved in any of these reactions was apparent from the presence in III of the characteristic infrared spiroketal bands[11] and from the fact that desoxytigogenin[12] could be recovered unchanged after one hour's treatment with the 8*N* chromium trioxide reagent.

Having established these points concerning the basic structures, attention was turned to the possibility of employing a dimethyl ester derivative of IIc in a Dieckmann type ring closure thereby gaining a new entry to ring-C nor compounds.[13] While the preparation of the dimethyl ester of IIc could have been easily achieved, it appeared that the free ketone at C-3 might present certain complications in the Dieckmann condensation due to anion formation. For this reason the dialdehyde IIa was first converted to its 3-benzoate derivative IId and oxidized for thirty minutes with 8*N* chromium trioxide, thereby providing 11,12-secotigogenin-11,12-dioic acid 3-benzoate (IIe). Esterification of IIe with etheral diazomethane was smoothly effected and the resulting dimethyl ester IIf was then subjected to a variety of Dieckmann ring closure reactions.

Experimentally a positive nitrogen pressure apparatus[14] which had been thoroughly dried by flaming was used in all reactions. Both triphenylmethyl sodium and carefully prepared potassium *t*-butoxide were employed as condensing agents but in no case was ring closure observed. The reaction proved extremely sensitive to traces of water so that even with *t*-butyl alcohol which had been dried with calcium and distilled from potassium sufficient water remained to effect partial hydrolysis of the benzoate and/or ester groups thereby giving rise to IIh or IIg. While suitable analyses were not obtained for these reaction products, their probable structures appear sound on the basis of certain transformations adequately described in the experimental section. In any case, from the results of numerous experiments, it seems clear that the steric factors present in IIf are such as to make the desired type of ring closure virtually impossible under the reaction conditions reported here.

Further consideration of the zeorin work[7] and the ease with which aldolization took place in that series prompted a closer examination of attempts to aldolize the dialdehyde IIa.

Under acidic conditions—*e.g.* sulfuric acid or hydrochloric acid in acetic acid—the dialdehyde IIa was recovered unchanged after one half to one hour reaction time whereas with extended periods, only intractable gums resulted. Upon treatment of IIa with boron trifluoride etherate in ether at room temperature overnight only starting material could be recovered.

(8) We are grateful to Mr. J. N. Shoolery of the Varian and Associates Laboratory who recorded and interpreted this spectrum.

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

(10) W. G. Dauben and W. W. Epstein, *J. Org. Chem.*, **24**, 1595 (1959) and references therein.

(11) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

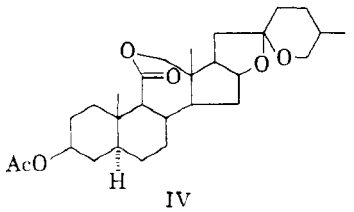
(12) R. E. Marker and D. L. Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941).

(13) N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *J. Am. Chem. Soc.*, **77**, 1632 (1955).

(14) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 43 (1951).

Under alkaline conditions the treatment of IIa took an unexpected course. Usually the reaction was conducted in methanolic potassium hydroxide at reflux temperature, whereafter dilution and extraction provided about 20% by weight of a neutral product which as yet is unidentified. The fact that it contained two bands in the infrared carbonyl region (see Experimental) indicated that it was not the desired aldol.

Upon acidification of the alkaline fraction there was obtained *ca.* 75% of a substance to which the structure of 11,12-secotigogenin-12-ol-11-oic acid (IIi) has been assigned. While the analytical data are only in fair agreement with the proposed structure, the following supporting facts are presented. Compound IIi possesses a neutralization equivalent corresponding to a monocarboxylic acid and yields a monomethyl ester IIj for which satisfactory analytical values are available. Furthermore, the hydroxy acid IIi upon oxidation is transformed to the keto dibasic acid IIc previously described. Somewhat surprisingly perhaps, when IIi was treated under mild acetylating conditions, ring closure occurred thereby providing the 7-membered ring-C lactone 3-acetate IV in very high yield. The extreme



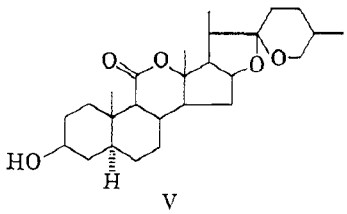
IV

susceptibility of this general system to traces of water in alkaline media is apparent from the observation that attempts to aldolize IIa in "anhydrous" methanol with "dry" sodium methoxide likewise led to the Canizzaro product IIi in approximately the same yield.

The preference for assigning the structure of IIi as the 11-oic-12-hydroxy acid rather than the reverse situation is derived from the consideration that the aldehyde at C-9 should be sterically more susceptible to attack by hydroxide ion[15] than that attached to the quaternary C-13. In addition there is the observation that the methyl ester IIj is hydrolyzable with 1% methanolic alkali to provide the parent acid. Had the reverse structural situation obtained, it is questionable that hydrolysis would have occurred under such mild conditions, as the literature contains numerous reports[16] pointing to the difficulties involved in hydrolyzing such quaternary esters. A final and convincing line of evidence is available in the formation of rockogenin Xa from the dialdehyde IIa, as this reaction must surely involve attack by hydrazine of the C-9 aldehyde in preference to that of C-13, *vide infra.*

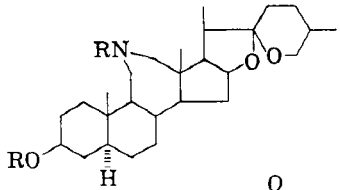
Further use of the dialdehyde IIa as a precursor for the preparation of other new ring-C type derivatives is illustrated by the following sequences.

When the dialdehyde acetate IIk was treated under the usual 8*N* chromium trioxide oxidation conditions, it was found to be oxidized much more slowly than the previously described conversion of IIa to IIb. By employing reaction periods of thirty minutes the monoacid monoaldehyde III resulted and this could then be methylated with diazomethane to yield IIm. Subjection of this substance to the Bayer Villiger reaction[17] provided after alkaline hydrolysis and acidification 12-nor-11,13-secotigogenin-13-ol-11-oic (11 → 13) lactone (V) albeit in very low yield.



V

A more practical transformation resulted when the dialdehyde IIa was treated under reductive conditions in the presence of ammoniated ethanol. By this means there was obtained in good yield IIa-aza-c-homotigogenin VIa. Proof for the secondary nature of the nitrogen atom and thus of the gross structure followed from acetylation experiments. Thus, the acetate-amide VIb clearly showed both types of carbonyl bands in the infrared and was devoid of any N—H bands in either the 3.00 μ or 6.5 μ regions.



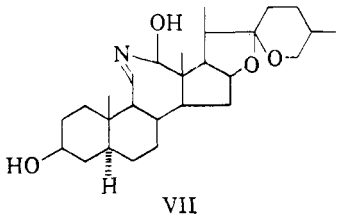
VIa. R = H
b. R = CH_3—C(=O)—

An alternate preparation of VIa was achieved by the following sequence. The dialdehyde IIa was heated at reflux temperature for *ca.* eight hours with saturated ammoniated ethanol thereby yielding the Schiff base VII. Again the assignment of structure rests on the more probable attack of the C-9 aldehyde by ammonia to provide an intermediate aldimine, which then undergoes ring closure to provide a compound tentatively identified as the dihydroxy Schiff base VII. Treatment of VII with lithium aluminum hydride led to the

(15) See C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953, pp. 704–710.

(16) For leading references see A. Wettstein, F. Hunziker, and K. Miescher, *Helv. Chim. Acta*, **26**, 1197 (1943).

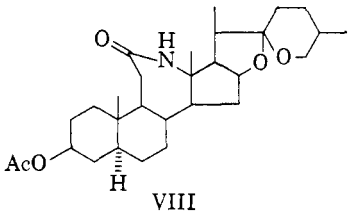
(17) C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).



VII

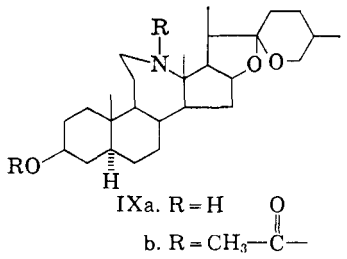
same 11a-aza compound as that obtained directly from the catalytic amination described above.

With the unambiguous synthesis of the 11a-aza compound VIa a definitive answer is now available for establishing the structure of Mazur's amide VIII,[18] which was obtained by the Beckman rearrangement of hecogenin oxime. *A priori* it was conceivable for the oxime to exist in one of two forms (*syn* or *anti*) which then upon rearrangement would provide either an 11a-amide or the 12a-amide VIII as Mazur tentatively suggested.



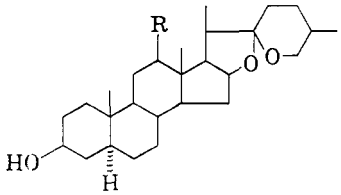
VIII

In order to permit a comparison, Mazur's amide VIII was reduced with lithium aluminum hydride. While early experiments employing this reagent either in tetrahydrofuran or anisole solvent for twenty-four-hour periods were abortive, the reduction was found to proceed in fair yield in tetrahydrofuran when the reaction time was extended to ten days at reflux temperature. The 12a-aza-c-homotigogenin IXa thus prepared gave a melting point depression on admixture with 11a-aza-c-homotigogenin VIa. A similar result obtained on comparison of the acetate amide IXb and VIb. As the two systems are different, the structure of Mazur's amide as VIII is definitely established by elimination.



IXa. R = H
b. R = $CH_3-\overset{O}{\overset{\|}{C}}-$

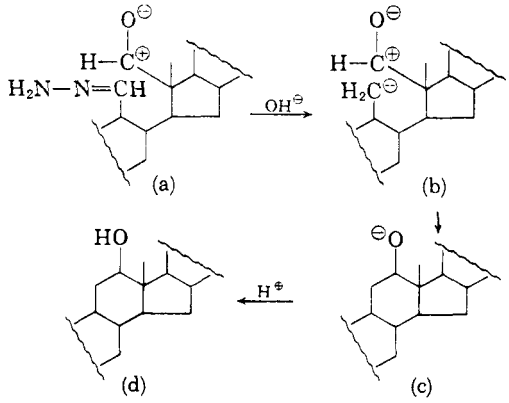
With the original purpose of preparing a compound wherein the two aldehyde groups of IIa would be reduced to methyl groups, IIa was subjected to Huang-Minlon reduction. After heating several hours with hydrazine hydrate and potassium hydroxide in ethylene glycol there were obtained, following the usual concentration procedure, two compounds Xa and Xb which had respectively lost one and two of the oxygen atoms originally present in the dialdehyde IIa. Further experimentation showed that the yield of Xa could be improved by avoiding the concentration step ordinarily employed in the Huang-Minlon reduction. Moreover, it was observed that when Xa was subjected to prolonged Huang-Minlon reduction the second product Xb could be prepared. The nature of these products became evident when they were subjected to spiroketal side chain degradation. Thus Xa was established as rockogenin by its degradation to 12β-hydroxy-Δ^{16}-5α-pregnen-3β-ol-20-one diacetate and Xb as tigogenin since it led to Δ^{16}-5α-pregnen-3β-ol-20-one acetate. Mixture melting points between Xa and Xb with authentic rockogenin and tigogenin, respectively, as well as infrared spectral comparisons upheld the identity of the compounds.



Xa. R = OH
b. R = H

It is of interest that the reductive cyclization of the dialdehyde will also take place, although in low yield, under the mild conditions of heating with potassium hydroxide and hydrazine hydrate in ethanol solvent. In light of this the following mechanistic route which accords with ionic intermediates[19] is suggested.

The fact that the reaction product Xa is oxygenated at C-12 leads to the conclusion that the reductive step occurs exclusively with the aldehyde group at C-9. This in turn suggests that hydrazone formation occurs to provide the intermediate (a) whose reduction[19] is *accelerated by a proximity*



(18) R. H. Mazur, *J. Am. Chem. Soc.*, 81, 1454 (1959).

(19) E. R. Alexander, *Principles of Ionic Organic Reactions*, Wiley, New York, 1950, pp. 274–276.

effect of the C-12 carbonyl group. The resulting intermediate carbanion (b) then attacks the C-12 carbonyl thereby giving rise to the oxy anion (c) which is finally protonated to provide rockogenin (d).

The conversion of rockogenin (Xa) to tigogenin (Xb) may be explained by the intermediate conversion of Xa to 12-ketotigogenin which then undergoes a normal Wolff-Kishner reduction. Processes describing the oxidation of secondary alcohols to intermediate ketones under the influence of strong alkali have been recorded in the literature.[20]

EXPERIMENTAL[21]

11,12-Secotigogenin-11,12-dialdehyde (IIa). To a mixture of 1.4 l. of acetic acid, 2.1 l. of anhydrous thiophene free benzene, and 81.0 g. of 11β,12β-dihydroxytigogenin (I)[6] was added 121 g. of dry lead tetraacetate. After 5 min. at room temperature the mixture was diluted with 2 l. of water containing 1 kg. of sodium acetate and 40 g. of potassium iodide. The resulting color in the mixture was then discharged by the addition of a saturated aqueous solution (100 ml.) of sodium thiosulfate[22] and the solution was extracted twice with 2-l. portions of ethyl acetate. The combined organic extracts were then washed to neutrality by employing first water, then saturated aqueous sodium bicarbonate and finally water. After drying over sodium sulfate and evaporating to dryness the residue was dissolved in 600 ml. of methanol and diluted with *ca.* 125 ml. of water. Upon chilling the solution deposited crystals which were collected to provide 75.2 g. in two crops, m.p. 140–146°. Three recrystallizations from the same solvent pair provided the analytical sample, m.p. 146–147°, $[\alpha]_D$ −72°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. O, 17.91. Found: C, 72.14; H, 9.23; O, 18.33.

11,12-Secotigogenone-12-aldehyde-11-oic acid (IIb). Acetone (50 ml.) containing 0.35 g. of the dialdehyde IIa was treated with 1.1 ml. of 8*N* chromium trioxide[9] for 10 min. at room temperature. The excess reagent was destroyed with methanol and the mixture was then diluted with 100 ml. of water. After three extractions with 60-ml. portions of methylene chloride the combined extracts were washed with water, dried over sodium sulfate, and evaporated to leave 0.35 g. of gum which was crystallized from acetone-ether-hexane to provide 0.16 g. of material, m.p. 237–240°. Two further crystallizations from acetone-ether gave pure IIIb, m.p. 243–245°, $[\alpha]_D$ −81°.

Anal. Calcd. for $C_{27}H_{40}O_6 + {}^1/_4\ H_2O$: C, 69.72; H, 8.77; O, 21.50. Found: C, 69.80; H, 8.49; O, 21.80.

11,12-Secotigogenone-11,12-dioic acid (IIc). (A) *From the dialdehyde* (IIa). Under the conditions reported in the previous experiment 0.5 g. of IIa was treated with 3.5 ml. of 8*N* chromium trioxide[9] for 50 min. at room temperature. By the usual procedure there was obtained following crystallization from acetone 0.20 g. of crystals, m.p. 287–290° whose melting point was not altered by further recrystallization, $[\alpha]_D$ −45°.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07; O, 23.60. Found: C, 68.06; H, 8.49; O, 23.75.

(B) *From the acid aldehyde* IIb. One hundred milligrams of IIb was treated with 0.5 ml. of 8*N* chromium trioxide[9] for 45 min. at room temperature. After workup there was obtained upon crystallization from acetone 20 mg. of IIc, m.p. 287–290°, identical in all respects with the material isolated above in A.

(C) *From the hydroxymethyl acid* IIi. Two hundred milligrams of IIi was treated under the conditions reported in A, thereby yielding after crystallization from actone 50 mg. of crystals, m.p. 285–287°. This substance gave no depression in melting point on admixture with authentic IIc.

11,12-Secotigogenone-11,12-dioic acid anhydride (III). Acetic anhydride (0.5 ml.) and 50 mg. of dioic acid IIc were treated for 1 hr. at 100°. The excess reagent was removed under reduced pressure and the residual gum was allowed to sublime at 270°, 0.01 mm. The crystalline sublimate 20 mg., was then resublimed to prepare the analytical sample, m.p. 232–235°, $[\alpha]_D$ −33°, λ_{max}^{KBr} 5.58, 5.72, 5.80 μ and 10.16, 10.82, 11.10, and 11.56 μ.[11]

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35; O, 20.94. Found: C, 70.53; H, 8.42; O, 21.58.

11,12-Secotigogenin-11,12-dialdehyde 3-benzoate (IId). Pyridine (40 ml.) containing 6 ml. of benzoyl chloride and 4.0 g. of the dialdehyde (IIa) was kept at 0° for 15 min., then at room temperature for an additional 15 min. Dilution with water (100 ml.) and extraction with ethyl acetate (3 × 60) provided after the usual washings of the organic extracts, drying and evaporation a residue which readily crystallized from acetone-hexane, 2.5 g., m.p. 150–156°. Three further crystallizations from acetone then provided the analytical sample, m.p. 172–174°, $[\alpha]_D$ −48°.

Anal. Calcd. for $C_{34}H_{46}O_6$: C, 74.15; H, 8.42; O, 17.43. Found: C, 73.82; H, 8.37; O, 17.56.

11,12-Secotigogenin-11,12-dioic acid 3-benzoate (IIe). A mixture of 1.43 g. of IId, 50 ml. of acetone, and 3 ml. of 8*N* chromium trioxide[9] was maintained at room temperature for 30 min., then processed as has been previously described. By crystallization from acetone there was obtained 0.75 g. of material, m.p. *ca.* 280° which was purified by recrystallization from a mixture of methylene chloride, ether, and acetone, m.p. 293–297°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{34}H_{46}O_8$: C, 70.08; H, 7.96; O, 21.97. Found: C, 69.49; H, 7.88; O, 23.03.[23]

Dimethyl-11,12-secotigogenin-11,12-dioate 3-benzoate (IIf) Two grams of IIe in 50 ml. of methylene dichloride was treated with a large excess of ethereal diazomethane. The addition of a porcelain chip aided in the evolution of nitrogen and, after 10 min. at room temperature, 3 ml. of acetic acid was added to destroy the excess reagent. The solution was then washed with 5% hydrochloric acid followed by 5% aqueous sodium bicarbonate and water. After drying over sodium sulfate and evaporation, there remained 2.0 g. of gum which was chromatographed over 100 g. of neutral alumina. From the benzene-hexane (3:2) eluates there was obtained 1.4 g. of material which crystallized from hexane-pentane to yield 1.22 g., m.p. 169–171°. Four recrystallizations from the same solvent pair gave IIf m.p. 170–172°, $[\alpha]_D$ −34°.

Anal. Calcd. for $C_{35}H_{48}O_8$: C, 70.44; H, 8.11; O, 21.45. Found: C, 70.88; H, 7.94; O, 21.05.

Attempted Dieckmann condensation of IIf. The *t*-butyl alcohol used in this experiment was heated under reflux with calcium for 20 hr. and then distilled from excess solid potassium. The apparatus employed has been described.[14]

To 100 ml. of *t*-butyl alcohol was added 1.0 g. of potassium and the mixture was gently heated to effect solution. The dimethyl ester IIf (1.5 g.) was then added and the solution

(20) W. Von E. Doerring and J. C. Aschner, *J. Am. Chem. Soc.*, **71**, 88, (1949).

(21) All melting points are uncorrected and the rotations have been determined in chloroform unless otherwise noted. While the infrared spectra of all compounds have been recorded and are in agreement with the proposed structures, only those of special interest are reported. We wish to thank Dr. J. Matthews and his staff for the determination of all rotations and spectra. It should be noted that several compounds described herein could only be obtained as hydrates or solvates.

(22) R. Criegee, *Ber.*, **64**, 264 (1931).

(23) A satisfactory analysis could not be obtained for this compound.

maintained at reflux temperature for 20 hr. The major portion of the solvent was evaporated and the residue was acidified with 6 ml. of glacial acetic acid. Following dilution with water and extraction with ethyl acetate, the extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on 40 g. of neutral alumina when elution with the usual solvent systems through ethyl acetate provided only traces of material. Continued elution with ethyl acetate–acetic acid (9:1) however provided 0.60 g. of gum which was crystallized from ether to provide 0.45 g. of crystals, m.p. 133–136°. A second crystallization from the same solvent gave a compound whose melting point was unaltered on further crystallization, m.p. 148–150°, $[\alpha]_D$ −67°, λ_{max}^{KBr} 3.10 (broad), 5.82 (s), and 5.90 (s) μ.[23] On the basis of the subsequent transformations this substance is tentatively assigned the structure of *methyl 11,12-secotigogenin-12-oate 11-oic acid* (IIg).

Treatment of IIg (300 mg.) with excess diazomethane, *vide supra*, led to a noncrystalline residue which after chromatography provided directly from the column *ca.* 0.10 g. of a compound with m.p. 90–93°. Attempts to recrystallize this material were unsuccessful.

In another Dieckmann condensation which employed 1.50 g. of IIf and 0.15 g. of potassium there was isolated, by separation of neutral and acidic fractions, 1.30 g. of neutral material which was chromatographed on 30 g. of neutral alumina. Elution with benzene gave 0.78 g. of crystals, m.p. 90–93°, which were undepressed on admixture with the material obtained by esterification of IIg. As in the previous case this substance resisted recrystallization. To it, however, is assigned the structure of *dimethyl 11,12-secotigogenin-11,12-dioate* (IIh) as on benzoylation, *vide supra*, of 300 mg. followed by chromatography there was obtained 165 mg. of the dimethyl benzoate IIf, m.p. 169–172°. A mixed melting point with authentic IIf was not depressed.

11,12-Secotigogenin-12-ol-11-oic acid (IIi). (A) *From the dialdehyde* IIa. Ethanol (150 ml.) containing 10.6 g. of sodium hydroxide and 10.0 g. of IIa was heated at reflux temperature for 1 hr. The solution was then diluted with water (300 ml.) and extracted four times with 70 ml. of ethyl acetate. The combined extracts were then washed with water, dried over sodium sulfate, and evaporated to leave 2.0 g. of neutral gum. This substance was crystallized several times from acetone-hexane to give m.p. 167–168°, $[\alpha]_D$ −40°, λ_{max}^{KBr} 2.98 (s), 5.79 (ms), and 5.90 (s), $\lambda_{max}^{C_2H_5OH}$ none. *Anal.* Found: C, 71.20; H, 9.91.

The original alkaline solution was acidified and extracted five times with 80-ml. portions of ethyl acetate. Following washing with water, drying, and evaporation there was obtained 7.0 g. of gum which was crystallized from ethyl acetate to provide 6.16 g. of acidic material, m.p. 274–276°, $[\alpha]_D$ −83°. The melting point was unchanged on further crystallization.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 69.79; H, 9.55. Found: C, 69.29; H, 9.59.

(B) *From the methyl ester* IIj. Twenty five milliliters of 1.2% methanolic potassium hydroxide containing 300 mg. of IIj was heated on a steam bath under reflux for 5.5 hr. The solution was then concentrated and diluted with water (25 ml.). Following acidification and extraction with ethyl acetate, the extracts were washed to neutrality, dried over sodium sulfate and evaporated. Crystallization of the residue provided 0.16 g. of material, m.p. 273–275°, which was identical in all respects with the acid isolated above in A.

Methyl-11,12-secotigogenin-12-ol-11-oate (IIj). An etheral solution (50 ml.) of diazomethane (large excess) was added to 1.66 g. of IIi in 40 ml. of methanol containing a small porcelain chip. After 1 hr. at room temperature the excess reagent was destroyed by the addition of 2 ml. of acetic acid. The mixture was then worked up by the previously described procedure to provide after one crystallization from ethyl acetate 1.26 g., m.p. 133–134°, $[\alpha]_D$ −46°. The melting point remained unchanged on further recrystallization.

Anal. Calcd. for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69; O, 20.05. Found: C, 70.10; H, 9.54; O, 19.91.

11,12-Secotigogenin-12-ol-11-oic 3-acetate-(11 → 12)-lactone (IV). Pyridine (0.6 ml.) containing 0.1 ml. of acetic anhydride and 100 mg. of IIi was maintained at room temperature overnight. Dilution with water (2 ml.) followed by filtration provided 80 mg. of crystals, m.p. 292–295°. A single recrystallization from acetone gave the analytical sample m.p. 293–295°, $[\alpha]_D$ −92°, λ_{max}^{KBr} 5.85 (s) and 8.10 (s) μ.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08; O, 19.64 Found: C, 71.29; H, 9.14; O, 19.54.

11,12-Secotigogenin-11,12-dialdehyde 3-acetate (IIk). By employing pyridine (15 ml.) and acetic anhydride (8 ml.) under the usual conditions at room temperature overnight 5.0 g. of the dialdehyde IIa provided 3.8 g. of crystals m.p. 148–150°. Several recrystallizations from acetone-hexane led to material with a constant melting point, m.p. 152–154°, $[\alpha]_D$ −56°.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08; O, 19.65. Found: C, 70.88; H, 9.23; O, 20.00.

11,12-Secotigogenin-12-aldehyde-11-oic acid 3-acetate (III). Twenty milliliters of acetone containing 1.10 g. of IIk was treated with 0.78 ml. of 8*N* chromium trioxide[9] for 35 min. at room temperature. If shorter reaction periods were employed, considerable amounts of starting material could be recovered. Following dilution with water (50 ml.) the solution was extracted with ethyl acetate. After washing with water, drying, and evaporation these extracts provided 0.75 g. of acid, m.p. 169–171° raised on recrystallization from acetone-hexane to m.p. 170–172°, $[\alpha]_D$ −61°.

Anal. Calcd. for $C_{29}H_{44}O_7$ + 2-C_3H_6O: C, 67.71; H, 9.09; O, 23.20. Found: C, 67.37; H, 8.66; O, 23.56.

Methyl-11,12-secotigogenin-12-aldehyde-11-oate 3-acetate (IIm). Ether (30 ml.) containing 0.55 g. of III was treated with an excess of ethereal diazomethane exactly as previously described. In this manner there was obtained 0.4 g. of crystals, m.p. 85–92° which were obtained pure after four recrystallization from ether-hexane, m.p. 135–136°, $[\alpha]_D$ − 71°.

Anal. Calcd. for $C_{30}H_{46}O_7$: C, 69.47; H, 8.94; O, 21.59. Found: C, 69.69; H, 8.88; O, 21.72.

12-Nor-11,13-secotigogenin-13-ol-11-oic (11 → 13)- lactone (V). To an ethereal solution (16.5 ml.) of 0.5*N* perbenzoic acid was added 1.1 g. of IIm dissolved in 1.1 ml. of acetic acid. After being maintained in the dark at room temperature for 50 hr., the mixture was diluted with 100 ml. of ether and washed several times with 5% aqueous sodium bicarbonate. Following further washing with water, drying, and evaporation there remained 1.2 g. of material which could not be crystallized. Treatment of this substance was then carried out by boiling for 4 hr. in a nitrogen atmosphere with 17 ml. of 5% methanolic potassium hydroxide. Most of the methanol was evaporated and the residue was diluted with water. Ethyl aceteate extraction (four times with 20-ml. portions) provided after washing, drying, and evaporation 0.49 g. of gum which could not be crystallized.

Acidification of the original alkaline solution was followed by ethyl acetate extraction and the extracts were washed with water, dried, and evaporated to leave 800 mg. of noncrystalline material. By crystallization from ether-hexane *ca.* 50 mg. of crystals were obtained, m.p. 258–260°, which upon one single further crystallization possessed a constant melting point, m.p. 271–273°, $[\alpha]_D$ −24°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.13; H, 9.23.

11a-Aza-c-homotigogenin (VIa) (A). *By reductive amination.* To 130 ml. of ethanol containing 10 ml. of saturated ammoniated ethanol was added 2 g. of IIa and 875 mg. of 5% palladium/carbon catalyst. The resulting mixture was then shaken in a hydrogen atmosphere at 40 lbs. pressure for 17 hr. whereafter it was filtered and evaporated to dryness. Crystallization of the residue from acetone provided

1.40 g., m.p. 140–145°, which was further purified by sublimation at 140° 0.01 mm, m.p. 160–165°, $[\alpha]_D$ −45°, λ_{max}^{KBr} 3.00 (broad) μ.

Anal. Calcd. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51; O, 11.12; N, 3.25. Found: C, 74.74; H, 10.33; O, 11.59; N, 3.50.

(B) *Via the Schiff base* VII. A solution of saturated ammoniated absolute ethanol (1.7 l.) containing 68 g. of IIa was heated on a steam bath overnight. The solution was then evaporated to leave a solid residue which upon crystallization from acetone gave 60 g. of crystalline VII, m.p. 133–136°, essentially unchanged upon further crystallization, m.p. 134–135°, $[\alpha]_D$ − 135°, $\lambda_{max}^{C_2H_5OH}$ 260 mμ, log ϵ 1.92, λ_{max}^{KBr} 2.85 (pip), 3.07 (s), 6.00 (ms, sharp) μ.

Anal. Calcd. for $C_{27}H_{43}O_4N$: N, 3.14. Found: N, 2.67.

Forty grams of VII was heated at reflux temperature for 20 hr. in 3 l. of anhydrous tetrahydrofuran containing 15 g. of lithium aluminum hydride. Following the cautious addition of 200 ml. of ethyl acetate and 150 ml. of saturated aqueous sodium sulfate the mixture was filtered and evaporated to dryness. The residue upon crystallization from acetone gave 30 g. of VIa m.p. 159–161° which proved identical to the material isolated above in A.

11a-Aza-c-homotigogenin 3β-acetate-N-acetate (VIb). By the procedure employed for the preparation of IXb, *vide infra*, VIa was acetylated to provide VIb, recrystallized from ethanol-water, m.p. 173–175°, $[\alpha]_D$ −14°, λ_{max}^{KBr} 5.79 (s), 6.18 (vs) and 8.07 (vs) μ.

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58; O, 15.51; N, 2.72. Found: C, 71.73; H, 9.42; O, 16.04; N, 3.00.

12a-Aza-c-homotigogenin (IXa). One gram of 12-keto-12a-aza-c-homotigogenin 3β-acetate[18] (VIII) was added to 500 ml. of tetrahydrofuran containing 2.0 g. of lithium aluminum hydride. The mixture was then heated at reflux temperature for 10 days (calcium chloride tube) whereafter the excess hydride was destroyed by the addition of ethyl acetate (100 ml.) and 20 ml. of saturated aqueous sodium sulfate. Following filtration and evaporation there remained 1.0 g. of clear gum which was chromatographed over 20 g. of neutral alumina. Elution with benzene-ether (1:1) provided 0.2 g. of semisolid which was crystallized from acetone to give 135 mg., m.p. 150–152°. Several crystallizations from the same solvent gave pure IXa, m.p. 169–171°, $[\alpha]_D$ −56°, λ_{max}^{KBr} 3.00 (m), 3.07 (m) and 3.16 (m) μ.

Anal. Calcd. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51; O, 11.12; N, 3.25. Found: C, 75.22; H, 10.57; O, 11.07; N, 3.72.

12a-Aza-c-homotigogenin 3β-acetate-N-acetate (IXb). Ten milliliters of pyridine containing 0.40 g. of IXa and 2 ml. of acetic anhydride was heated at reflux temperature for 2 hr. The solution was poured into water, extracted with ethyl acetate and the extracts were then washed with dilute acid followed by water. After drying and evaporation there remained 0.35 g. of gum which upon repeated recrystallization from hexane led to the analytical sample, m.p. 214–215°, $[\alpha]_D$ −108°, λ_{max}^{KBr} 5.80 (s), 6.12 (vs) and 8.05 (vs) μ.

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58; O, 15.51; N, 2.72. Found: C, 72.34; H, 9.56; O, 14.96; N, 3.14.

Rockogenin (Xa). Three grams of IIa, 130 ml. of ethylene glycol, 10 ml. of 70% hydrazine hydrate, 3.2 g. of sodium hydroxide, and 3.2 ml. of water were heated for 1.5 hr. at reflux temperature. Following dilution with water (500 ml.) and extraction with methylene chloride (four times with 100-ml. portions) the combined extracts were washed with water, dried over sodium sulfate, and evaporated. The residual 3.27 g. of gum was then crystallized from ether-hexane to provide 1.55 g. of crystals, m.p. 185–190°. Three successive recrystallizations from ether-acetone led to the analytical sample, m.p. 215–217°, $[\alpha]_D$ −62°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25; O, 14.79. Found: C, 74.96, 74.66; H, 10.26, 10.21; O, 14.99, 14.71.

Admixture with authentic rockogenin, lit.[24] m.p. 218–220°, $[\alpha]_D$ −63.8° (acetone) did not depress the melting point. Further characterization was afforded by the preparation of the 3,12-diacetate, m.p. 208–210°, $[\alpha]_D$ − 63°, lit.,[24] m.p. 206–209°, $[\alpha]_D$ −65.4° (acetone) and degradation[25] to 12β-hydroxy-Δ^{16}-pregnen-3-β-ol-20-one diacetate, m.p. 136–137°, $[\alpha]_D$ +28°, lit.,[26] m.p. 134–135°, $[\alpha]_D$ +18°.

Tigogenin (Xb). To 25 ml. of ethylene glycol containing 1.66 ml. of hydrazine hydrate, 0.5 g. of sodium hydroxide, and 0.5 ml. of water was added 0.5 g. of rockogenin (Xa). The resultant mixture was evaporated over 4 hr. almost to dryness (*ca.* 5 ml.) and then heated under reflux for 5 hr. In those cases where the mixture was not sufficiently concentrated only rockogenin could be recovered from the reaction. Following the usual work-up there was obtained 0.17 g. of material which after several recrystallizations from acetone provided 0.10 g. of tigogenin, m.p. 210–211°, $[\alpha]_D$ −67°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; O, 11.52. Found: C, 77.77; H, 10.38; O, 12.01.

This material was identical in all respects to authentic tigogenin, lit.,[27] m.p. 207–210°, $[\alpha]_D$ − 76° and was further characterized as its acetate, m.p. 208–210°, $[\alpha]_D$ −61°, lit.[28] m.p. 202°, $[\alpha]_D$ −74.4° as well as by degradation[25] to Δ^{16}-pregnen-3β-ol-20-one acetate, m.p. 164–166°, $[\alpha]_D$ +47.3°, lit.[29] m.p. 166–167°, $[\alpha]_D$ +42.2°.

APARTADO POSTAL 2679
MEXICO, D. F.

(24) R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

(25) Accomplished by the general method of ref. 3, which employs a 55 min. reaction time for the acetolysis step.

(26) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955).

(27) P. Lang and C. R. Noller, *J. Am. Chem. Soc.*, **57**, 525 (1935).

(28) R. Tschesche and A. Hagedorn, *Ber.*, **68B**, 1412 (1935).

(29) Pl. A. Plattner, L. Ruzicka, H. Heusser, and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).