with sodium hydroxide (12.5 *N*) dropwise until a clear solution resulted. The solution was stirred for 90 min. and the pH was then adjusted to 7 with concentrated hydrochloric acid. Crude IV separated as a colorless solid (2.4 g.). The analytical sample was recrystallized from methanol: m.p. 160° dec., $\lambda_{max}^{pH_2}$ 285 mμ (*E* 9.2 × 10³), $\lambda_{max}^{pH_{11}}$ 278 mμ (*E* 7.3 × 10³), $\lambda_{max}^{H_2O}$ 285 mμ (*E* 9.0 × 10³), $\lambda_{max}^{90\%\ EtOH}$ 283 mμ (*E* 7.3 × 10³).

Anal. Calcd. for $C_9H_9IN_2O_5$: C, 30.70; H, 2.58; I, 36.04; N, 7.96. Found: C, 30.81; H, 2.59; I, 35.76; N, 8.13.

O⁶,5′-6-Hydroxycyclodeoxyuridine (V).—To 1.8 g. (5 mmoles) of IV in 3% methanolic potassium hydroxide solution (100 ml.) was added 10% palladium on charcoal (3.6 g.), and the mixture was hydrogenated in a Parr apparatus for 1 hr. at 1.5 atm. pressure. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in water (200 ml.) and put on a column (2.5 × 30 cm.) of Dowex-1 (formate form). This was eluted with formic acid (0.025 *N*) and the eluate was collected in 15-ml. fractions. The product (V) (1.1 g., 95%), obtained after the removal of the formic acid *in vacuo*, was recrystallized twice from methanol to give the analytical sample: m.p. 200° dec., R_f (relative to deoxyuridine) 0.98 (70% isopropyl alcohol–ammonia) and 1.85 [ethyl acetate–water–formic acid (60:35:5)], $\lambda_{max}^{pH_2}$ 262 mμ (*E* 11.9 × 10³), $\lambda_{max}^{pH_{11}}$ 263 mμ (*E* 9.7 × 10³), $\lambda_{max}^{H_2O}$ 262 mμ (*E* 12.2 × 10³); $\lambda_{max}^{90\%\ EtOH}$ 261 mμ (*E* 11.8 × 10³).

Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.95; H, 4.34; N, 12.37.

3′-O-Acetyl-O⁶,5′-6-hydroxycyclodeoxyuridine (VI).—(This compound may be prepared from either IV or V by an essentially identical procedure; however, the product from the latter is more easily purified.) A mixture of V (678 mg., 3 mmoles), glacial acetic acid (15 ml.), acetyl chloride (20 ml.), and acetic anhydride (20 ml.) was stirred at room temperature for 17 hr. The clear solution was concentrated *in vacuo* at 40° to remove the excess acetyl chloride, the residue was dissolved cautiously in methanol (20 ml.), and the solution again concentrated *in vacuo*. This operation was repeated several times until a crystalline residue remained. It was recrystallized from ethanol to yield the pure acetyl derivative (624 mg., 77%). The analytical sample was recrystallized once more from ethanol: m.p. 246° dec., $\lambda_{max}^{pH_2}$ 262 mμ (*E* 13.2 × 10³), $\lambda_{max}^{pH_{11}}$ 262.5 mμ (*E* 9.6 × 10³), $\lambda_{max}^{H_2O}$ 262 mμ (*E* 13.2 × 10³), $\lambda_{max}^{90\%\ EtOH}$ 260 mμ (*E* 13.1 × 10³).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.47; H, 4.75; N, 10.66.

5-Iodo-3′-O-acetyl-O⁶,5′-6-hydroxycyclodeoxyuridine (VII).—A mixture of VI (536 mg., 2 mmoles), glacial acetic acid (8 ml.), iodic acid (180 mg.), iodine (300 mg.), carbon tetrachloride (2 ml.), and water (3 ml.) was stirred for 3 hr. Water (25 ml.) was added to the mixture. The aqueous layer, after one extraction with carbon tetrachloride, was concentrated *in vacuo* at 40°. The residue was dissolved in methanol (20 ml.) and the solution was again concentrated *in vacuo* at 40°; this operation was repeated several times to remove most of the acetic acid. The yellow crystalline residue (480 mg.) was recrystallized from hot water to yield the pure product (111 mg., 14%). The mother liquor, when concentrated to dryness *in vacuo*, gave IV (180 mg., 26%). The 3′-O-acetyl derivative was recrystallized once more from hot water to give the analytical sample: m.p. 142° dec., $\lambda_{max}^{pH_2}$ 282 mμ (*E* 8.9 × 10³), $\lambda_{max}^{pH_{11}}$ 275 mμ (*E* 6.9 × 10³), $\lambda_{max}^{H_2O}$ 280 mμ (*E* 9.0 × 10³), $\lambda_{max}^{90\%\ EtOH}$ 277 mμ (*E* 9.6 × 10³).

Anal. Calcd. for $C_{11}H_{11}IN_2O_6$: C, 33.52; H, 2.79; I, 32.20; N, 7.11. Found: C, 33.36; H, 3.08; I, 32.41; N, 6.87.

Iodination of O⁶,5′-6-hydroxycyclodeoxyuridine (V).—A mixture of V (349 mg., 1.5 mmoles), iodine (225 mg.), iodic acid (135 mg.), glacial acetic acid (6 ml.), carbon tetrachloride (1.5 ml.), and water (2.5 ml.) was stirred at room temperature for 5 hr. IV (85 mg., 16%) precipitated from the solution. Its infrared spectrum was identical with that of an authentic sample.

Tritylation of O⁶,5′-6-Hydroxycyclodeoxyuridine (V).—A solution of V (226 mg., 1 mmole) and trityl chloride (433 mg., 1.5 mmoles) in dry pyridine (10 ml.) was allowed to stand in a stoppered flask at room temperature for 7 days. Ice–water (25 ml.) was poured into the reaction mixture with stirring. Trityl alcohol (380 mg., 94%) was removed by filtration and the filtrate was concentrated *in vacuo* at 45°. The residue was dissolved in water (20 ml.) and the solution was adjusted to pH 11 with sodium hydroxide. It was put on a column of Dowex-1 (formate form) and eluted with formic acid (0.025 *N*). The eluate was concentrated *in vacuo* to give unreacted starting material (196 mg., 87%).

Acknowledgment.—The author is greatly indebted to Professor A. D. Welch of this department, Professor D. Lipkin of Washington University, St. Louis, Missouri, and Professor M. Saunders of Yale University for valuable discussions.

C-23 Acylation of Pseudodiosgenin Diacetate

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Prolonged treatment of diosgenin acetate with acetic anhydride in the presence of pyridine hydrochloride affords an enol acetate of 23-acetylpseudodiosgenin diacetate. Gentle hydrolysis of the ester with potassium bicarbonate during brief reaction periods gives 23-acetylpseudodiosgenin. Extended exposure under the same conditions results in migration of the olefinic linkage to the exocyclic position to supply the Δ^{22}-furostene isomer. More vigorous alkaline treatment promotes conjugate addition of the terminal hydroxyl group to the α,β-unsaturated carbonyl system, furnishing 23-acetyldiosgenin.

Discovery by Marker and Rohrmann[1] of the acetolysis of spiroketal sapogenins (1) affording open-chain dihydrofuranoid pseudo derivatives (2) immeasurably enriched steroid chemistry.[2] Evidence[3] from oxidative cleavage affirms generally excellent conversion with the original procedure employing acetic anhydride at 200°. Convenience of isolation and yields of crystalline products realized in practice vary, however, among members of the natural group. Much effort expended in study of the fundamental process has culminated in the recommendation of numerous expedients for dispensing with closed-system conditions. Thus, *n*-butyric anhydride[4] and *n*-octanoic anhydride,[5] as well as *n*-octanoic acid,[5] at reflux temperature have proved applicable. In still another refinement, addition of acid salts such as pyridine hydrochloride[6] or ammonium chloride[3] has permitted the reaction to proceed in refluxing acetic anhydride.

(1) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 3592 (1939).

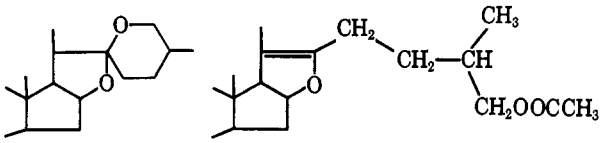
(2) L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p. 547.

(3) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.* **77**, 5665 (1955).

(4) R. E. Marker and E. Rohrmann, *ibid.*, **62**, 518 (1940); G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *ibid.*, **75**, 4888 (1954); F. C. Uhle, *ibid.*, **76**, 4245 (1954), **83**, 1469 (1961).

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

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



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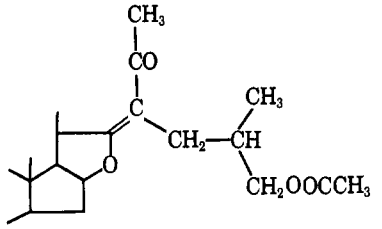


3

Although concomitant formation of at least trace amounts of Δ^{22} isomers of the normal $\Delta^{20(22)}$-furostene pseudomers has been suspected,[5,7] actual isolation of a simple exocyclic olefin has been achieved only in another manner through controlled dehydration of a 22-hemiketal.[8] More complex Δ^{22}-furostene derivatives formulated as **3** have been acquired, however, by treating sapogenin acetates with boron trifluoride etherate in acetic anhydride at ambient temperature.[9] Production of these conjugated methyl ketones had been foreshadowed earlier in the isolation of 23-acetylhecogenin after intervening ring-F fission of hecogenin acetate with perchloric acid in acetic anhydride.[5] More recently, indirect evidence has been adduced for possible acylation at the site corresponding to position 20 after attempted isomerization of a C-nor-D-homosapogenin with acetic anhydride in the presence of pyridine hydrochloride.[10]

Use of pseudodiosgenin (**5**) as a synthetic intermediate in several schemes[11] has necessitated its repeated preparation in this laboratory. Since the diol fails to crystallize reproducibly in acceptable recovery from any single solvent, it is best secured by direct aqueous precipitation after alkaline hydrolysis of scrupulously pure pseudodiosgenin diacetate (**4**). Unfortunately, the diacetate itself, though sparingly soluble, tends to deposit initially in the form of resinous granules which organize to glistening plates melting at 103–104° only after several wasteful recrystallizations.

In seeking to circumvent isolation difficulties,[12] the routinely favored pseudomerization procedure employing 1 equiv. of pyridine hydrochloride in boiling acetic anhydride during 5 hr.[6] was modified from time to time. Occasionally, a few crystals, presumed to represent unchanged diosgenin acetate, were noted to persist in the product melt well beyond the usual first range of 85–100°. Extension of the reaction period, however, led to predominance, rather than to suppression of the higher melting contaminant until, after prolonged heating, the pseudo derivative altogether gave way to a new crystalline compound of m.p. 164–166°.

The maximal yield of 15% attained after 65 hr. in the presence of 1 or 2 equiv. of pyridine hydrochloride declined after longer heating. When mother liquors of the crystals were submitted to recycling with pyridine hydrochloride in acetic anhydride, a second substantial crop was collected, augmenting the yield to a total of 24%. As expected, preformed pseudodiosgenin diacetate survived exposure in refluxing acetic anhydride alone during many hours. The new ester crystallizes remarkably well from the red-brown product gum, two or three recrystallizations from absolute ethanol affording sharply melting, colorless needles. Despite the modest conversion, the compound is, therefore, easily prepared.

The properties and behavior of the novel acetolysis product are best reconciled with structure **7** (Chart I) arising from enol acetate formation after acylation at position 23. An acetyl determination confirmed the presence of three alkali-labile acetoxy residues. The infrared spectrum revealed two discrete carbonyl bands at 5.7 (enol acetate) and 5.8 μ (alkanol acetate) as well as bands of medium intensity at 5.9 (vinyl ether) and 6.0 μ (olefin).[13] The ultraviolet spectrum showed a maximum at 253 mμ (ϵ 4700). The low intensity of absorption probably reflects steric interactions which conspire to oppose coplanarity.[14]

The ester was recovered unchanged after treatment with maleic anhydride in refluxing xylene. In dichloromethane solution, tetracyanoethylene gave a green coloration which persisted indefinitely; no addition of the cyanocarbon could be detected after several weeks at 0 or 25°. With chromium trioxide in acetic acid, **7** gave Δ^{16}-pregnenolone acetate (**10**), the regular product of $\Delta^{20(22)}$-furostene oxidation.

Subjection of **7** to saponification in alkaline media led to isolation of crystalline entities only after assiduous experimentation. Three new hydroxy ketones representing complete ester hydrolysis eventually were obtained. With 2% potassium bicarbonate in refluxing aqueous methanol during reaction periods of no longer than 1 hr., the 23-acetyl-$\Delta^{20(22)}$-furostene **8**, m.p. 123–128°, was isolated. Further heating under these circumstances resulted in disappearance of **8** as a consequence of gradual migration of the olefinic linkage into carbonyl conjugation to afford the nicely crystalline Δ^{22}-furostene **9**, m.p. 168–170°. The double bond

(7) D. H. Gould, H. Staeudle, and E. B. Hershberg, *J. Am. Chem. Soc.*, **74**, 3685 (1952).

(8) H. Hirschmann and F. B. Hirschmann, *Tetrahedron*, **3**, 243 (1958). For an exocyclic nitrogen analog, see F. C. Uhle and F. Sallmann, *J. Am. Chem. Soc.*, **82**, 1190 (1960).

(9) J. A. Zderic, L. Cervantes, and M. T. Galvan, *ibid.*, **84**, 102 (1962). After 15–30 min., ester yields of 10–45% were obtained when the procedure was tested with tigogenin, 3-desoxytigogenin, hecogenin ketol acetate, and diosgenin. Degradative work was carried out with the product from tigogenin; chromic acid oxidation was not successful. Free diols were not isolated.

(10) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).

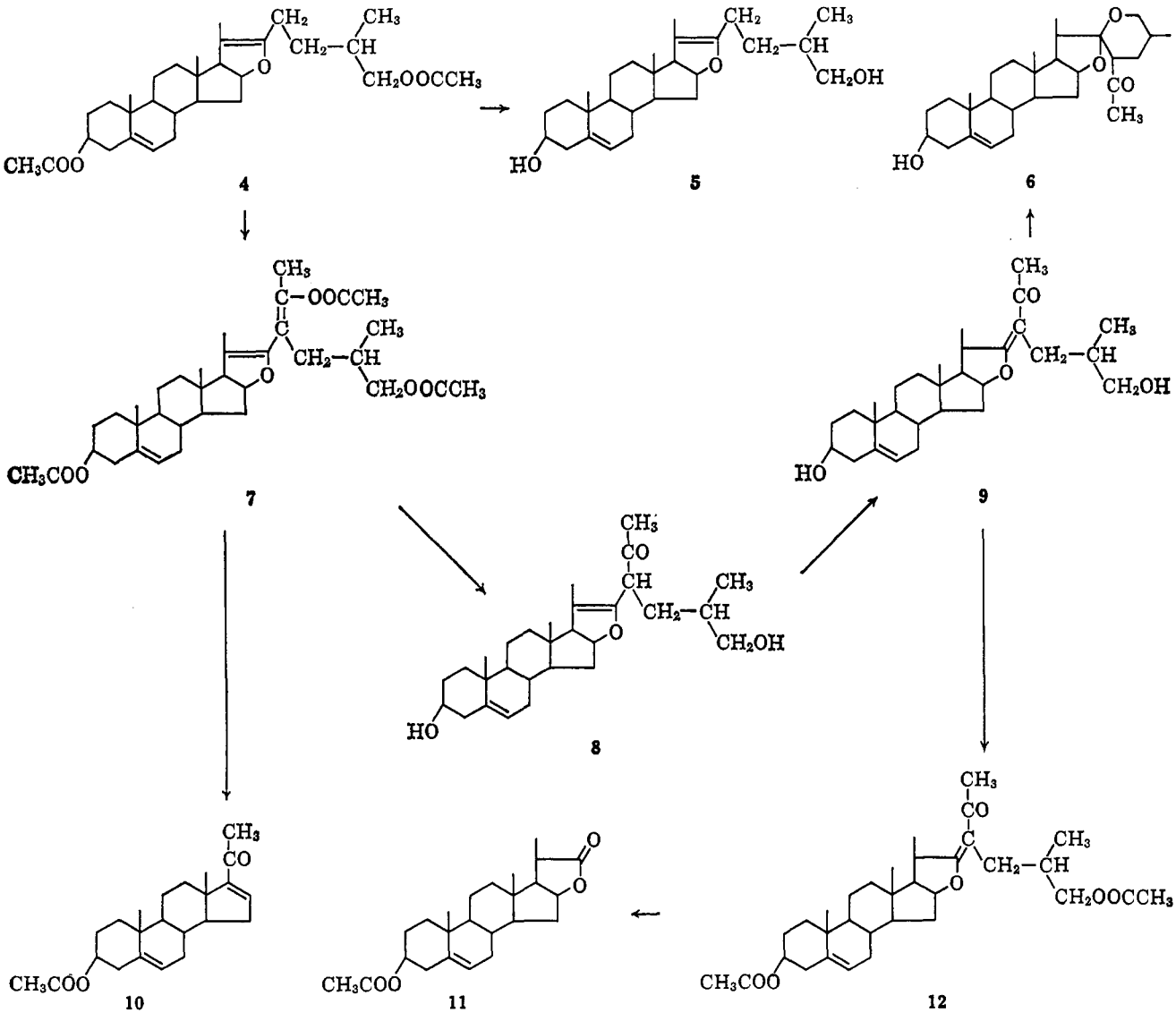
(11) F. C. Uhle, *J. Am. Chem. Soc.*, **83**, 1469 (1961); *J. Org. Chem.*, **27**, 2797 (1962); *Tetrahedron Letters*, 3099 (1964).

(12) Pseudodiosgenin diacetate retained in solution for *in situ* oxidative scission marks the first stage of highly efficient industrial procedures for hormone synthesis from diosgenin. Problems connected with isolation of the diacetate, and of its hydrolysis product, in crystalline form apparently stem from properties associated with the crystal state, rather than from gross impurity or from intrinsic lability. Effective crystallization may be unusually influenced by the presence of even minute amounts of coprecipitates, possibly acyl derivatives of the type described in the present work.

(13) Δ^{20}-Enol acetates in the pregnane series developing through enolization from the methyl group exhibit a prominent infrared maximum at 6.0 μ of intensity greater than that of the relatively weak band observed with **7**. The Δ^{20}-enol acetates, which are prepared with isopropenyl acetate, are readily transformed to $\Delta^{17(20)}$ isomers by treatment with refluxing acetic anhydride containing *p*-toluenesulfonic acid. See R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952); H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher, *ibid.*, **74**, 2810 (1952).

(14) *Cf.* R. B. Turner and D. M. Voitle, *ibid.*, **73**, 1403 (1951).

CHART I



appeared to assume the exocyclic position surprisingly slowly since exposure periods of nearly 50 hr. were required for conversions of greater than 50%. After 10–20 hr., crystallization of **9** was limited to amounts of the order of 25%.

The infrared spectrum of **9** proved notable for three prominent maxima at 5.92, 6.05, and 6.40 μ associated with the vinyl ether, conjugated carbonyl, and conjugated olefinic elements, respectively. Ultraviolet absorption at 279 mμ (ϵ 12,200) verified the presence of the β-oxy α,β-unsaturated carbonyl chromophore.[15] Acetylation of **9** with acetic anhydride in pyridine furnished the low-melting, highly soluble diacetate **12**. Chromic acid oxidation of **12** gave acetyldiosgenin lactone (**11**).

With aqueous ethanolic potassium hydroxide, conjugate addition of the terminal hydroxyl function of **9** rapidly intervened, affording 23-acetyldiosgenin (**6**), m.p. 206–210°. Fixed alkali hydrolysis of **7** gave the hexacyclic compound directly. Small amounts could also be retrieved from mother liquors of **9** when bicarbonate hydrolysis had been unduly protracted.

Treatment of diosgenin acetate with boron trifluoride etherate in acetic anhydride during 30 min., according to the method defined with tigogenin acetate,[9] followed by potassium bicarbonate hydrolysis, furnished about 10% of **9** and returned nearly an equal amount of diosgenin. After 90 min., the starting sapogenin had been entirely consumed, but the yield of **9** had fallen to 5%. Although the diacetate **12** presumably is present as such in the boron trifluoride reaction product, direct crystallization from the complex mixture is thwarted by the unfavorable physical properties of the ester.

When allowed to react with refluxing acetic anhydride in the presence of pyridine hydrochloride, the diacetate **12** reverted to **7**. The endocyclic enol acetate thus appears to represent a particularly stable arrangement of the 23-acetylfurostene skeleton. The sluggish formation of **9** from **8**, despite the resonance stabilization inherent in the conjugated exocyclic

(15) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 1957, p. 112.

isomer, in itself testifies to the strained nature of the Δ^{22} olefinic bond.[16]

During the prolonged, preparative acetolysis, the relatively mild acylation catalyst pyridine hydrochloride possibly may tend to expedite olefinic conjugation as well, once furostene formation and placement of the 23-acetyl function have been effected. Continued exposure under equilibrating conditions nevertheless delivers the final transformation product as the $\Delta^{20(22)}$-enol acetate, superior crystallizing properties greatly abetting its isolation. Evidence at hand does not permit an estimate of the comparative rate of enol acetylation, most likely a slow process. Although the powerful boron trifluoride clearly is capable of rapidly inducing both acylation and olefinic migration, the rather untrustworthy reaction sequence initiated by the Lewis acid must be interrupted before wholly destructive further changes ensue.

Experimental Section[17]

3β,27-Diacetoxy-23-(α'-acetoxyethylidene)-25α-5,20(22)-furostadiene (7).—A mixture of 4.56 g. (0.01 mole) of diosgenin acetate, 2.32 g. (0.02 mole) of pyridine hydrochloride, and 25 ml. of acetic anhydride was heated under reflux during 68 hr. The cooled solution was added to 500 ml. of water to give a resinous deposit which was segregated by decantation and gravity filtration. A solution of the resin in ether was washed with aqueous potassium bicarbonate and with water, dried over anhydrous magnesium sulfate, and concentrated under diminished pressure. The residual dark red gum was dissolved in 4 ml. of hot absolute ethanol. After 20 hr. at 0°, the mass was transferred to a suction funnel. When vacuum had been applied for some time to drain away much of the dark, viscous liquor, the remaining deposit was washed repeatedly with small portions of cold ethanol. Recrystallization from a mixture of dichloromethane and absolute ethanol afforded 875 mg. (15%) of nearly colorless needles, m.p. 159–164°. The analytical sample (long, white needles from dichloromethane–absolute ethanol) melted at 164–166°: [α] −77°; λ_{max} 253 mμ (ε 4700); infrared 5.70, 8.20 (enol acetate), 5.80, 8.05 (alkanol acetate), 5.92 (m) (vinyl ether), and 6.0 μ (m) (olefin).

Anal. Calcd. for $C_{35}H_{50}O_7$ (582.75): C, 72.13; H, 8.65; CH_3CO, 22.16. Found: C, 72.14; H, 8.64; CH_3CO, 21.92.

In a similar experiment in which 1.16 g. (1 equiv.) of pyridine hydrochloride had been employed during 48 hr., the yield of **7** was 12%. The mother liquors were heated in 25 ml. of acetic anhydride with 1.16 g. of pyridine hydrochloride during 69 hr. to afford an additional 12% of **7**. This total yield of 24% could not be duplicated in any single cycle attempted. When 3 equiv. of pyridine hydrochloride, added in three portions at regular intervals during a total heating time of 67 hr., was employed, the yield of **7** was 12%. Three equivalents added in a single portion at the start of a 90-hr. heating period gave 10% of **7**. After 25 hr. with 2 equiv., the yield of **7** was 5%. With 1 or 2 equiv. during reaction periods of about 65 hr., yields of 15% were consistently obtained. Longer heating appeared deleterious. In one experiment, when the mother liquors from 15% of **7** were treated with refluxing isopropenyl acetate containing *p*-toluenesulfonic acid, an additional 3% of **7** was isolated.

The ester was recovered unchanged after chromatography on aluminum oxide (Woelm nonalkaline). It failed to react with *p*-nitrophenylhydrazine in refluxing ethanol containing acetic acid. Treatment with 5 equiv. of maleic anhydride in refluxing xylene during 4 hr. led only to recovery of **7**. In dichloromethane solution, 1 equiv. of tetracyanoethylene gave a dull green coloration which persisted undiminished for a number of weeks.

3β-Acetoxy-5,16-pregnadien-20-one (Δ[16]-Pregnenolone Acetate) (10).—To a magnetically stirred solution of 292 mg. (0.0005 mole) of **7** in 10 ml. of acetic acid was added dropwise during 15 min. a solution of 200 mg. (0.002 mole) of chromium trioxide in 10 ml. of 80% aqueous acetic acid. After the solution had been stirred for an additional 1 hr., it was diluted with water and extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in 25 ml. of acetic acid was heated under reflux during 2 hr. The mixture was concentrated *in vacuo* to give a residue which was diluted with water and extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Recrystallization of the residue (200 mg.) from methanol gave 72 mg. (40%), m.p. 155–171°. Two additional recrystallizations from methanol afforded the analytical sample: m.p. 175–178°[18]; [α] −43°; λ_{max} 239 mμ (ε 10,200); infrared 5.80, 8.05 (acetoxy), 6.05 (conjugated ketone), and 6.35 μ (conjugated olefin).

Anal. Calcd. for $C_{23}H_{32}O_3$ (356.49): C, 77.49; H, 9.05. Found: C, 77.46; H, 8.97.

3β,27-Dihydroxy-23-acetyl-25α-5,20(22)-furostadiene (23-Acetylpseudodiosgenin) (8).—To a boiling solution of 292 mg. (0.0005 mole) of **7** in 70 ml. of methanol was added a hot solution of 2 g. (0.002 mole) of potassium bicarbonate in 30 ml. of water. The solution was heated under reflux during 1 hr., cooled, and concentrated under reduced pressure to give an aqueous residue which was extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vauco*. Recrystallization of the residue from ethyl acetate afforded 103 mg. (45%), m.p. 108–128°. Additional recrystallizations from ethyl acetate gave the analytical sample as material with a texture resembling that of asbestos: m.p. 122–128°; [α] +40°; λ_{max} 290 mμ (ε 750); infrared 5.85 (ketone) and 5.92 μ (m) (vinyl ether).

Anal. Calcd. for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 76.51; H, 9.79.

When heating was conducted for only 30 or 40 min., the initial yield of crystalline product was lower but recrystallization appeared more readily accomplished. Recovery from ethyl acetate was rather poor and final yields were variable. The infrared spectrum of the analytical sample did not differ from that of the first crystalline precipitate.

3β,27-Dihydroxy-23-acetyl-25α-5,22(23)-furostadiene (9). A.—A mixture of 292 mg. (0.0005 mole) of **7**, 1 g. (0.01 mole) of potassium bicarbonate, 15 ml. of water, and 35 ml. of methanol was heated under reflux during 48 hr. The methanol was removed under reduced pressure to give an aqueous residue which was extracted with ether. The ethereal phase was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from acetone to afford 130 mg. (57%), m.p. 153–160°. Additional recrystallizations from acetone gave the analytical sample as long needles, m.p. 168–170°; [α] +23°; λ_{max} 279 mμ (ε 12,200); infrared 5.92 (m) (vinyl ether), 6.05 (conjugated ketone), and 6.40 μ (conjugated olefin) (intensity of the olefinic band surpasses that of the carbonyl band).

Anal. Calcd. for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 75.97; H, 9.80.

When heating was conducted during shorter periods, yields were lower and somewhat erratic as shown by the following figures: 4 hr., 15%; 8 hr., 19%; 8 hr., 28%; 20 hr., 24%; 48 hr., 50%; 74 hr., 55%; 75 hr., 34%. The number of recrystallizations required to furnish material of comparable melt-

(16) The English school contributed importantly to early descriptions of "three-carbon systems." For example, studies of equilibria between α,β-unsaturated and β,γ-unsaturated carbonyl compounds demonstrated that cyclopentylideneacetone and ethyl cyclopentylideneacetate are energetically preferred to the corresponding cyclopentenyl derivatives; in related six-membered ring compounds, the endocyclic, unconjugated forms appeared more stable: R. P. Linstead, *J. Chem. Soc.*, 2579 (1927); G. A. R. Kon and R. P. Linstead, *ibid.*, 1269 (1929); A. H. Dickins, W. E. Hugh, and G. A. R. Kon, *ibid.*, 572 (1929); G. A. R. Kon, R. P. Linstead, and G. W. G. Maclennen, *ibid.*, 2454 (1932). For general discussions of the energy relationships of endocyclic–exocyclic olefin pairs, see H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); J. Weinstock, R. G. Pearson, and F. G. Bordwell, *ibid.*, **78**, 3468 (1956); R. B. Turner and R. H. Garner, *ibid.*, **80**, 1424 (1958).

(17) Melting points were observed on a calibrated micro hot stage and hence are corrected. Infrared spectra in potassium bromide disks were recorded with a Perkin-Elmer spectrophotometer, Model 137. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Rotations were measured in chloroform (1%) at *ca.* 25°, and ultraviolet spectra in ethanol were recorded with a Beckman DK-2 instrument, by Huffman Laboratories, Inc., Wheatridge, Colo.

(18) Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, **25**, 783 (1960).

ing range also varied. In the 75-hr. experiment which gave only 35%, work-up of the mother liquors gave 23 mg. (10%) of material whose infrared spectrum was identical with that of 23-acetyldiosgenin (6).

B.—To a suspension of 456 mg. (0.001 mole) of diosgenin acetate in 5 ml. of acetic anhydride was added 0.4 ml. (*ca.* 0.003 mole) of boron trifluoride etherate. The starting material rapidly dissolved. After 90 min. at ambient temperature, the mixture was added to 100 ml. of water. The deposit was segregated by decantation and gravity filtration and was dissolved in ether. The ethereal solution was washed with aqueous potassium bicarbonate and with water, and was concentrated *in vacuo*. A solution of the residue with 1 g. (0.01 mole) of potassium bicarbonate and 15 ml. of water in 35 ml. of methanol was heated under reflux during 67 hr. The methanol was removed under reduced pressure to give an aqueous residue which was extracted with ether. The ethereal phase was washed with water, dried over anhydrous magnesium sulfate, and concentrated under diminished pressure. Recrystallization of the residue from acetone afforded 23 mg. of needles, m.p. 158–165°; the infrared spectrum was identical with that of the product from potassium bicarbonate hydrolysis of **7** (procedure A).

In a similar run allowed to proceed for only 30 min., the final crystallization from acetone gave, first, 23 mg. of needles, m.p. 183–203° (diosgenin). Two recrystallizations of the mother liquors from acetone afforded 36 mg. (8%) of **9**, m.p. 156–161°. In another experiment (1 hr.) in which the hydrolysis step was omitted, 9% of unchanged diosgenin acetate was isolated.

3β,27-Diacetoxy-23-acetyl-25a-5,22(23)-furostadiene (12).—To a solution of 91 mg. (0.0002 mole) of **9** in 3 ml. of anhydrous pyridine was added 1 ml. of acetic anhydride. After 20 hr. at 25°, the solution was diluted with 20 ml. of 25% aqueous potassium chloride to give a deposit which was segregated by gravity filtration and dissolved in ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from petroleum ether (b.p. 30–60°) to give 40 mg. (37%), m.p. 70–73°. The analytical sample, from petroleum ether, melted at 73–74°: $[\alpha]$ 0°; λ_{max} 278 mμ (ϵ 14,800); infrared 5.85, 8.05 (acetoxy), 6.0 (conjugated ketone), and 6.35 μ (conjugated olefin).

Anal. Calcd. for $C_{33}H_{48}O_6$ (540.71): C, 73.30; H, 8.95. Found: C, 73.16; H, 8.97.

Although spectral properties are similar, the melting point and rotation noted above do not agree with those (m.p. 93–96°, $[\alpha]$ −16°) reported by Zderic, Cervantes, and Galvan[9] for a product isolated from ether, in unspecified yield, after treatment of diosgenin acetate with boron trifluoride etherate in acetic anhydride at 25°, giving combustion values acceptable only if an etherate of crystallization is assumed. In the milligram quantities handled here, the ester could be induced to crystallize from no single solvent other than petroleum ether. Even with petroleum ether, recovery is poor. Once crystals have been secured, recrystallization may be accomplished fairly satisfactorily from aqueous ethanol.

The ester was converted to **7** as follows. A solution of the residue (from vacuum evaporation of the ethereal extract after acetylation of 91 mg. of **9**, as described above) in 10 ml. of acetic anhydride was treated with 48 mg. (0.0004 mole) of pyridine hydrochloride and heated under reflux during 20 hr. The cooled mixture was added to water to give a deposit which was segregated by gravity filtration and dissolved in ether. The ethereal solution was washed with aqueous potassium bicarbonate and with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Recrystallization of the residue from absolute ethanol gave 14 mg. (12%), m.p. 143–158°. A second recrystallization from absolute ethanol afforded 10 mg. of long needles, m.p. 158–163°, whose infrared spectrum was identical with that of **7**.

3β-Acetoxy-16β-hydroxy-5-pregnen-20-carboxylic Acid γ-Lactone (Acetyldiosgenin Lactone) (11).—To a magnetically stirred solution of 216 mg. (0.0004 mole) of **12** in 10 ml. of acetic acid was added dropwise during 30 min. a solution of 200 mg. (0.002 mole) of chromium trioxide in 10 ml. of 80% aqueous acetic acid. After the mixture had been allowed to stir for an additional 3.5 hr. at ambient temperature, the solution was concentrated under reduced pressure. The residue was diluted with water and was extracted with ether. The ethereal phase was washed with water and was concentrated *in vacuo* to give a residue which was dissolved in 10 ml. of aqueous ethanol containing 200 mg. of potassium hydroxide. The solution was kept at 25° for 20 hr. and was then heated under reflux during 15 min. Concentration under reduced pressure gave a residue which was diluted with water and extracted with ether. The ether solution was discarded. The aqueous phase was acidified with dilute hydrochloric acid to give a precipitate which was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a residue (90 mg.) which was dissolved in 3 ml. of anhydrous pyridine and treated with 1 ml. of acetic anhydride. After 20 hr. at 25°, the solution was diluted with 25% aqueous potassium chloride to give a deposit which was collected by filtration, washed with water, and dissolved in ether. The ethereal solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a residue (60 mg.) which was crystallized from methanol to afford 15 mg. (10%) of needles: m.p. 205–214°[19]; $[\alpha]$ −106°; infrared 5.72 (lactone), 5.80, and 8.05 μ (acetoxy).

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.51): C, 74.57; H, 8.87. Found: C, 74.39; H, 8.79.

23-Acetyldiosgenin (6). A.—A mixture of 117 mg. (0.0002 mole) of **7**, 224 mg. (0.004 mole) of potassium hydroxide, 2 ml. of water, and 8 ml. of ethanol was heated under reflux during 2 hr. The ethanol was removed under reduced pressure to give an aqueous residue which was extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. A mixture of the residue with 200 mg. (0.0011 mole) of Girard's reagent P [1-(carboxymethyl)pyridinium chloride hydrazide] and 0.5 ml. of acetic acid in 4.5 ml. of ethanol was heated under reflux during 1 hr. The ethanol was distilled under reduced pressure to give a residue which was diluted with water and extracted with ether. The ethereal extract was discarded. The aqueous phase was acidified with 2 drops of 6 *N* aqueous hydrochloric acid and was warmed during 30 min. to complete hydrolysis of the hydrazone. After 20 hr. at 0°, the precipitate was collected by filtration, washed with water, dried, and recrystallized from acetone to afford 33 mg. (36%) of needles, m.p. 201–207°. Additional recrystallizations from acetone gave the analytical sample as long needles: m.p. 206–210°; $[\alpha]$ −125°; infrared 5.85 and 5.90 μ (m) (ketone),[20] rich fingerprint region with 25 bands between 7 and 14 μ of which the most prominent are 9.9, 10.1, 10.3, 10.5, 10.6, 11.0, 11.3, 12.0 and 12.4 μ.

Anal. Calcd. for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 76.03; H, 9.66.

B.—A solution of 46 mg. (0.0001 mole) of **9**, 100 mg. of potassium hydroxide, and 1 ml. of water in 4 ml. of ethanol was kept at ambient temperature during 20 hr. The ethanol was distilled under reduced pressure to give a residue which was diluted with water. The precipitate was collected by filtration, washed with water, dried, and recrystallized from acetone to afford 10 mg. (22%), m.p. 198–203°; the infrared spectrum was identical with that given by the compound prepared according to procedure A.

Although yields of **6** never exceeded 40%, search for optimal conditions was not undertaken. Material of good quality was obtained by treating accumulated mother liquors of **9** with aqueous ethanolic potassium hydroxide at reflux temperature. Chromatography on aluminum oxide (Woelm nonalkaline) proved effective in purification; elution was accomplished with ether–dichloromethane (4:1). The 23-acetyl substituent appears to exert a marked solubilizing influence on compounds in this series; recovery on recrystallization from acetone or methanol is less complete than is usually the case with spiroketal sapogenins.

An attempted Wolff–Kishner reduction of 23-acetyldiosgenin according to the modified procedure of Cram, Sahyun, and Knox[21] (preparation of the hydrazone with hydrazine, followed by slow addition to a solution of potassium *t*-butoxide in dimethyl sulfoxide at ordinary temperature) failed to give a crystalline product.

23-Acetyldiosgenin 3β-Acetate.—A mixture of 56 mg. (0.00012 mole) of 23-acetyldiosgenin (**6**), 1 ml. of acetic anhydride and 3 ml. of anhydrous pyridine was kept at ambient temperature

(19) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **25**, 789 (1960).

(20) 23-Acetyltigogenin likewise gives rise to a second, anomalous carbonyl band when the infrared spectrum is measured in potassium bromide.[9]

(21) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.* **84**, 1734 (1962).

during 20 hr. The solution was diluted with 25% aqueous potassium chloride to give a precipitate which was collected by filtration and dissolved in ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Two recrystallizations of the residue from methanol afforded 21 mg. (35%) of needles, m.p. 161–165°. Additional recrystallizations from a mixture of dichloromethane and methanol gave the analytical sample: m.p. 162–167°; $[\alpha]$ −120°; infrared 5.80, 8.05 (3β-acetoxy), and 5.88 μ (23-acetyl).

Anal. Calcd. for $C_{31}H_{46}O_5$ (498.68): C, 74.66; H, 9.30. Found: C, 74.89; H, 9.44.

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Scrambling Equilibria on Carbon. I. Chloro- and Dimethylamino-Terminated Polyoxymethylenes

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The chloromethyl groups of bis(chloromethyl) ether are readily scrambled (on the bridging oxygens) with the methylene groups of either trioxane or paraformaldehyde at 120°. Likewise, the dimethylamino groups of N,N,N′,N′-tetramethyldiaminomethane can be scrambled (on the methylene groups) with the bridging oxygens of paraformaldehyde at the same temperature. In both cases, equilibration is achieved within 1 to 3 days at 120° without a catalyst. There is a small amount of cyclic trioxane in equilibrium with the chain molecules. In all cases, a distribution of various sized chains is obtained, depending on the ratio of the reagents used. Proton n.m.r. was employed as the analytical procedure and the reaction products are quantitatively accounted for on the basis of the modern theory of equilibrium chemistry.

Because of the great success of reaction–mechanism theory in providing a rationale for most of organic chemistry on a kinetic basis, the role of equilibrium control in directly determining the kinds and amounts of products from chemical reactions in which there is extensive scrambling has, in our opinion, been neglected. Although such equilibrium-controlled reactions are of primary interest in inorganic chemistry (where investigations of this type are opening broad new fields of study), there are some areas[1] of organic chemistry to which this concept may be profitably applied and examples are presented here.

This paper describes a new organic reaction resulting in one new family of compounds, the α,ω-bis(dimethylamino)polyoxymethylenes, as well as another family, the α,ω-dichloropolyoxymethylenes, of which only the three smallest chains have been reported.[2] The work presented here is part of a broad theoretical[3,4] and experimental[5–7] program of investigation in the kind of equilibrium chemistry in which there is an exchange of parts between molecules. Since modern methods of analysis for molecular species have been employed in conjunction with a mathematical treatment to demonstrate the existence of the new compounds reported herein, we have felt that it was not necessary to isolate the relatively labile and difficultly separable individual compounds. As a result, the new compounds described in this study are characterized by their n.m.r. chemical shift instead of the usual parameters, such as boiling point and refractive index (which, by the way, may be estimated from semiempirical equations).

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Experimental Section

Reagents.—Bis(chloromethyl) ether was purchased from Eastman Organic Chemicals and N,N,N′,N′-tetramethyldiaminomethane was obtained from Aldrich Chemicals. Both of these reagents were fractionally distilled and only the center cuts exhibiting the correct boiling points were employed. The trioxane and paraformaldehyde were used directly as obtained from Fisher Scientific Co. All reagents were examined for hydrogen-containing impurities by proton n.m.r. and were found to contain no observable contaminants (<0.5% of total H).

Reaction Mixtures and Equilibration.—Chosen proportions of the reagents were studied in 5-mm.-o.d. thin-walled precision Pyrex-glass n.m.r. tubes which were sealed with a torch. In all cases, more than half of the tube was filled with liquid so that at 120° the relative amount of material in the vapor phase would be small. The over-all composition (*i.e.*, the ratio of the reagents) is presented in terms of a composition ratio, R, which equals the ratio of the formula weight of total terminating groups (either chlorine or dimethylamino) to that of the total methylenes.

The kinetic runs were carried out by apportioning a previously prepared batch of starting ingredients into a number of different n.m.r. tubes which were then sealed and placed in the oven. Data corresponding to selected heating times were obtained by removing a tube and cooling it quickly (within 1 min.) to room temperature. The reported equilibrium data for the chloro-terminated polymethylene oxides correspond to 8 days at 120°. The same distribution of products was obtained after 3 days at the same temperature. The equilibrium data reported for the α,ω-bis(dimethylamino)polyoxymethylenes correspond to 48 hr. at 120°, there being no change from the data obtained after 24 hr. at the same temperature.

Analytical Method.—Analysis for the various molecular species was carried out by proton n.m.r. using a Varian A-60 spectrometer running at 60.000 Mc. For α,ω-dichloropolyoxymethylenes, a sweep width of 50 cycles was employed with a sweep rate