1,9-Dibromo-5,5-dimethylnonane.[6] To 9.0 g. (0.044 mole) of phosphorus tribromide at −10°, 5.0 g. (0.026 mole) of 5,5-dimethyl-1,9-nonanediol was added with stirring over a 2-hr. period. Stirring was maintained as the mixture was allowed to warm to room temperature and then heated at 80° overnight. The cooled mixture was treated with 10 ml. of water, and the lower organic layer was separated. The aqueous layer was extracted with methylene chloride. The methylene chloride extract, combined with the organic layer was washed with dilute sodium bicarbonate and dried. Distillation yielded 6.7 g. (80.1%) of the dibromide b.p. 102° (0.5 mm.) $n^{22.5}D$ 1.4952.

Anal. Calcd. for $C_{11}H_{22}Br_2$: C, 42.05; H, 7.06. Found: C, 42.38; H, 7.29.

6,6-Dimethylthiacyclodecane.[7] A solution of 3.14 g. (0.01 mole) of 1,9-dibromo-5,5-dimethylnonane in 1 l. of anhydrous ethanol was added by a Hershberg dropping funnel through a high dilution adapter[8] to 2.5 l. of refluxing anhydrous ethanol with vigorous stirring over a 34-hr. period. Simultaneously a solution of 1.56 g. (0.02 mole) of sodium sulfide in 100 ml. of anhydrous ethanol was added through a 6-in. Vigreux column over the same period of time by means of an infusion pump.[9] After the additions were complete, the solution was refluxed with stirring for an additional hour and almost all of the ethanol was distilled from the reaction mixture. The residue was steam distilled and the distillate was treated with aqueous mercuric chloride. The white complex was collected, washed with water, and steam distilled. Extraction of the distillate with ether, drying, and distillate of the residue yielded 0.64 g. (34.5%) of the sulfide, b.p. 255°/760 mm., 140–5°/20 mm., $n^{26}D$ 1.5035.

Anal. Calcd. for $C_{11}H_{22}S$: C, 70.89; H, 11.82; S, 17.24. Found: C, 70.48; H, 11.78; S, 17.68.

Thiacyclodecane. Following the procedure for 6,6-dimethylthiacyclodecane, 2.86 g. (0.01 mole) of 1,9-dibromononane (Matheson, Coleman and Bell) yielded 91 mg. (5.7%) of thiacyclodecane[10] $n^{23.5}D$ 1.5178.

Anal. Calcd. for $C_9H_{18}S$: C, 68.35; H, 11.39; S, 20.26. Found: C, 68.40; H, 11.38; S, 20.27.

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DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
STEVENS INSTITUTE OF TECHNOLOGY
HOBOKEN, N. J.

(6) A. T. Blomquist and J. Verdol, *J. Am. Chem. Soc.*, **77**, 1806 (1955).

(7) The procedure used is a modification of the method of Muller (see ref. 1).

(8) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704, (1952).

(9) Harvard Apparatus Corp., Dover, Mass., Model 600,-000.

(10) A duplicate run resulted in a 5.2% yield of thiocyclodecane.

Synthesis of 17α-Hydroxy-21-carboxypregn-4-en-3-one Lactone

H.-J. HESS

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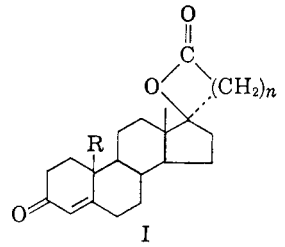
Spirolactones of the general formula I have received much attention because of their electrolyte regulating activity, antagonistic to desoxycorticosterone acetate and to aldosterone.[1a–d] More



I

R = H, CH_3; n = 2, 3

recently, it was shown that alkali salts[2] of the corresponding hydroxy acids exhibit activity of equal potency.

It was of interest to investigate the significance of the stereochemistry at C-17 and a typical spirolactone isomer (VI), with the opposite configuration at C-17, was therefore synthesized.

Addition of acetic acid to 21-methylene-17α-hydroxypregnenolone[3] (II) at 60° in the presence of sodium acetate resulted in the formation of III and subsequent acetylation with acetic anhydride in pyridine gave the diacetate IIIa. Reduction of the C-20 ketone function with sodium borohydride in methanol furnished the diacetylated tetrol IV. This material, which appeared to be homogeneous,[4] was converted directly to the methane sulfonate IVa with methanesulfonyl chloride in pyridine. Subsequent reduction of IVa with excess lithium aluminum hydride gave 3β,17α-dihydroxy-21-hydroxymethyl-pregn-5-ene (V). Protection of the double bond in V with bromine permitted simultaneous oxidation of the 3-alcohol[5] and the primary alcohol in the side chain with chromic acid in acetic acid. Elimination of bromine with zinc and isomerization with hydrochloric acid gave the α,β-unsaturated ketone. Under these conditions cyclization of the γ-hydroxy acid to the lactone VI occurred spontaneously. Isolated as a by-product, the partially oxidized spirolactone VII was identified by its infrared spectrum, analysis, and absence of absorption in the ultraviolet spectrum and by further oxidation to VI with chromic acid in ace-

(1) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957); (b) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959); (c) J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959); (d) E. A. Brown, R. R. Muir, and J. A. Cella, *J. Org. Chem.*, **25**, 96 (1960).

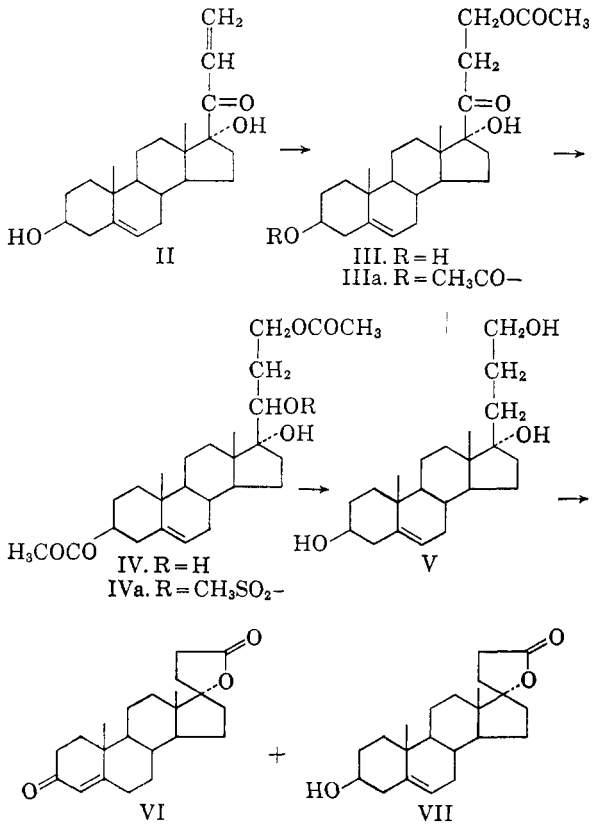
(2) C. M. Kagawa and E. A. Brown, *Proc. Soc. Exptl. Biol. Med.*, **105**, 648 (1960).

(3) H.-J. Hess, S. K. Figdor, G. M. K. Hughes, Rex Pinson, Jr., and W. T. Moreland, Abstracts 138th Meeting, ACS, 1960, p. 39P.

(4) The possibility, however, that it consisted of a mixture of epimeric alcohols can not be excluded. In view of the fact that this asymmetric center was to be eliminated at a later stage, no attempts for separation or purification were undertaken.

(5) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936); L. F. Fieser, *Org. Syntheses*, **35**, 43 (1955).

tone,[6] followed by isomerization with hydrochloric acid.



Preliminary pharmacological results[7] show that 17α-hydroxy-21-carboxy pregn-4-en-3-one lactone (VI) does not have the electrolyte regulating effects reported for its isomer,[8] indicating the stereochemical importance of C-17 for physiological activity.

EXPERIMENTAL[9]

3β,17α-Dihydroxy-21-acetoxymethylpregn-5-en-20-one (III). To a solution of 60 g. of potassium acetate in 300 cc. of glacial acetic acid was added 10.35 g. of 21-methylene-17α-hydroxypregnenolone[3] (II) and the suspension was stirred at 60°.[10] A clear solution was obtained after 4 hr. which was cooled to room temperature after 15 hr. and poured into 1.5 l. of water. The precipitated solids were filtered, washed with water, and dried, yielding 11.2 g. of material, m.p. 122–128° (dec.). Paper chromatography (benzene/formamide) indicated that it was mainly the desired product admixed with some starting material and two minor impurities. Recrystallization from acetone gave 4.8 g. (38%) of the addition product (III) of m.p. 168.5–171°. A higher over-all yield can be obtained when the crude material is used in the next step without further purification.

The analytical sample was recrystallized from methanol-water, m.p. 172–175°, $[\alpha]^{24}D$ −17°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.52; H, 8.89.

3β-17α-Dihydroxy-21-acetoxymethylpregn-5-en-20-one 3β-acetate (IIIa). A solution of 3.5 g. of III in 70 cc. of pyridine and 35 g. of acetic anhydride was stored at room temperature for 18 hours. The mixture was then poured into ice water, stirred for 15 min., and the solids filtered and dried, furnishing 3.0 g. (77%) of IIIa, m.p. 139–142°. This product was homogeneous by paper chromatography (benzene–formamide).

A sample was recrystallized for analysis from methanol-water, m.p. 142.5–144°, $[\alpha]^{24}D$ −24°.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.84; H, 8.55.

3β,17α,20-Trihydroxy-21-acetoxymethylpregn-5-ene 3β-acetate (IV). To a solution of 16 g. of IIIa in 800 cc. of methanol was added 1.36 g. of sodium borohydride in 160 cc. of methanol. After 3 hr. at room temperature, the excess sodium borohydride was destroyed with acetic acid, most of the methanol evaporated *in vacuo*, and the remaining concentrate poured into 2 l. of ice water. The precipitate was filtered off and dried, yielding 15.5 g. (97%) of IV, m.p. 142–144°, which was used in the next step without further purification.

3β,17α,20-Trihydroxy-21-acetoxymethyl-20-methanesulfonylpregn-5-ene 3β-acetate (IVa). Methanesulfonyl chloride (17 cc.) was added dropwise at 0° to a solution of 15.5 g. of IV in 340 cc. of pyridine, stirred in an ice bath for 1 hr., and then stored at +4° for 15 hr. Ice water (100 cc.) was added and the resulting mixture poured into 1 l. of ice water, extracted with chloroform, the extract washed with 2*N* hydrochloric acid and water, and dried with sodium sulfate. Evaporation of the solvent *in vacuo* furnished 18 g. (99%) of a foamy residue. The infrared spectrum showed strong sulfonate absorption at 1175 cm.$^{-1}$ and 1342 cm.$^{-1}$

3β,17α-Dihydroxy-21-hydroxymethylpregn-5-ene (V). A suspension of 10.3 g. of lithium aluminum hydride in 160 cc. of tetrahydrofuran was cooled to 0° and 18 g. of IVa in 225 cc. of tetrahydrofuran added dropwise over a period of 60 min. The mixture was stirred for 3 hr. at room temperature and subsequently 1 hr. at reflux temperature. After cooling, 30 cc. of ethyl acetate and 100 cc. of ice water were added carefully, and it was then poured into 1 l. of ice water. The precipitate was extracted several times with chloroform, the extract washed with water, dried, and the solvent evaporated, yielding a residue of 9.7 g. (81%). This was filtered through a column of Florisil (300 × 30 mm.) in chloroform–methanol (9:1) and three fractions of 500 cc. each were collected. Fraction I (1.24 g.) contained a small amount of V and mainly less polar materials,[11] as shown by paper chromatography (benzene–cyclohexane (1:1)-formamide). Fraction II (3.74 g.) and Fraction III (4.51 g.), combined yield 8.25 g. (69%), consisted largely of product. Fraction III was recrystallized from acetone yielding 3.49 g. of V of m.p. 187.5–189.5°.

The analytical sample was recrystallized once more from acetone, m.p. 186.5–189°, $[\alpha]^{23}D$ −72°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.59; H, 10.41.

17α-Hydroxy-21-carboxypregn-4-en-3-one lactone. A slurry of 1.036 g. of V in 10 cc. of methylene chloride was cooled to 8° and then, at the same temperature, 0.477 g. of bromine in

(6) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

(7) These experiments were kindly carried out by Dr. J. G. Llaurado and his associates of our Pharmacology Department.

(8) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(9) Melting points were taken in open capillaries and are uncorrected. Rotations are in dioxane, infrared spectra were measured in potassium bromide pellets, and ultraviolet spectra in methanol solution.

(10) The author is indebted to Dr. J. M. Grisar for the preliminary investigation of this reaction.

(11) Possible partial hydrolysis of the 3- and 22-acetoxyl function during the sodium borohydride reduction of IIIa in methanol may account for these less polar materials. [See, for example: D. Taub, R. R. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959)].

5 cc. of methylene chloride was added over a period of 45 min. The mixture was stirred for 10 min., 6 cc. of glacial acetic acid and 0.58 cc. of water added, and then warmed to 20°. Chromic acid (0.66 g.) dissolved in 0.4 cc. of water and 0.75 cc. of glacial acetic acid was added subsequently over a period of 10 min., and the resulting mixture stirred for 15 hr. The dark solution was then poured into 50 cc. of water and 10 cc. of methylene chloride, the organic phase separated, and the water layer extracted three more times with 10 cc. of methylene chloride each. To the combined extracts was added 3.5 cc. of methanol and 0.46 g. of zinc dust and the mixture refluxed for 45 min. An additional 0.5 cc. of glacial acetic acid and 0.40 g. of zinc dust was added and reflux continued for another 30 min.

The zinc dust was filtered, washed with methylene chloride, and the filtrate stirred at room temperature for 2 hr. after addition of 2 cc. of concd. hydrochloric acid. The solution was then poured into water, the methylene chloride layer separated, and the water phase extracted with more methylene chloride. Evaporation of the solvent yielded 1.05 g. of a residue, which was chromatographed on a column of Florisil (280 × 20 mm.). Ether eluted pure VII (0.120 g.), fraction I, followed by a mixture of VI and VII, fraction II and pure VI (0.384 g.), m.p. 171–175°, fraction III. Subsequent elution with ether–ethyl acetate resulted in a mixture of VI and VII.

Fraction I was recrystallized from methanol yielding 0.08 g. material of m.p. 248–250.5°, $[\alpha]^{23}D$ −95°, infrared absorption at 1764 cm.$^{-1}$ (5-membered lactone).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.77; H, 9.36.

Fraction III, m.p. 171–175° (0.384 g.) was recrystallized from acetone-water: yield, 0.154 g., m.p. 186–187°, $[\alpha]^{23}D$ +49°, infrared absorption at 1672 cm.$^{-1}$ (α,β-unsaturated ketone), 1773 cm.$^{-1}$ (5-membered lactone), λ_{max} 240 mμ (ϵ 16,100).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.05; H, 8.80.

Oxidation of VII. To 0.2 g. of VII in 40 cc. of acetone at 10° was added 0.2 cc. of chromic acid reagent[5] and the mixture stirred for 4 min. It was then poured into ice water, the precipitated material filtered, dissolved in 6 cc. of methylene chloride, and, after addition of 1 cc. of methanol and 0.3 cc. of conc. hydrochloric acid, stirred at room temperature for 2 hr. Water was then added, the methylene chloride layer separated, and the water phase extracted with methylene chloride. The extract was dried with sodium sulfate and the solvent evaporated yielding 0.180 g. residue. This was filtered in benzene through a column of 15 g. of Florisil, furnishing 0.143 g. of material, which, after recrystallization from methanol, gave 0.070 g. product identical with VI by infrared and ultraviolet spectra, mixed m.p., and rotation.

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MEDICAL RESEARCH LABORATORIES
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Derivatives of Phosphonic Acids

D. C. SCHROEDER, P. O. CORCORAN, C. L. HOLDEN, AND M. A. MULLIGAN

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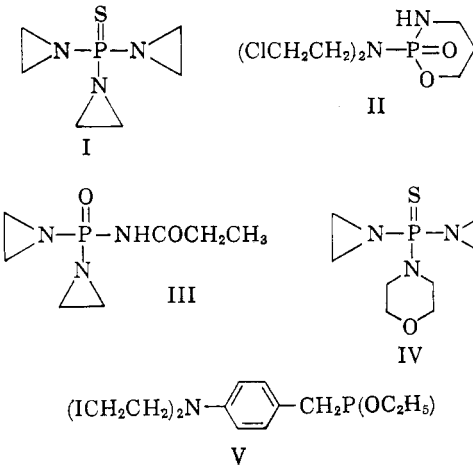
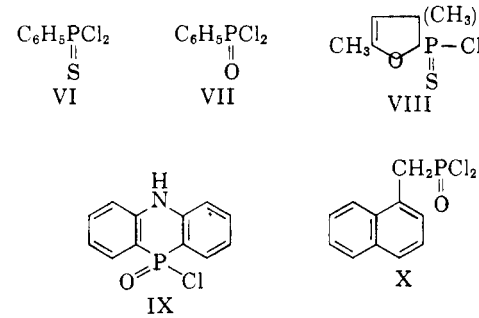
A number of organophosphorus compounds—*e.g.*, I, II, III, IV, and V—have shown varying degrees



of effectiveness in the treatment of cancer.[1] As most of these compounds are derivatives of phosphoric acid, it seemed of interest to prepare certain derivatives of phosphonic acids and have them screened for antitumor activity. We concentrated mostly on phosphonamides, but also included a few esters and salts. In some cases the phosphorus atom was incorporated into a heterocyclic ring as in II. The phosphonamides were prepared by treating phenylphosphonothionic dichloride (VI), phenylphosphonic dichloride (VII), 2-chloro-2-thiono-3,3,5-trimethyl-1,2-oxaphosphol-4-ine (VIII), dibenzophosphazinyl chloride (IX), and 1-naphthylmethylphosphonic dichloride (X) with primary or secondary amines.[2] In some cases the reaction was



quite exothermic and reached completion with no further heating. In other instances a reflux period was required. These reactions were encouraged either by using an excess of the amine or by adding a tertiary amine such as trimethylamine or pyridine to remove the hydrogen chloride which was formed. When equivalent quantities of a *tert*-aminoalkylamine and phosphonyl chloride were used, the hydrochloride of the *tert*-aminoalkylamide of the phosphonic acid resulted. Cyclic compounds were prepared by treating phosphonyl dichlorides with certain amino alcohols.

In general these reactions were carried out in an

(1) "Cancer," *Chemical and Engineering News*, American Chemical Society, Vol. **37**, October 12, 1959, p. 60.

(2) G. M. Kosolapoff, *Organophosphorus Compounds*, Wiley, New York, 1950, p. 279.