pound is assigned a thiohydroquinone structure. The infrared spectrum of this compound, in the 5- to 6-micron region, corresponded to a benzene derivative with a 1,2,4 configuration.

This procedure was then applied to eight alkylphenols. The yields and properties of the resulting thiols are shown in Table I. Characterizing thiol derivatives of five of these thiols were prepared. Their melting points and analyses are presented in Table II.

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(9) Made by reaction of the disodium salt with bromoacetic acid.

(10) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

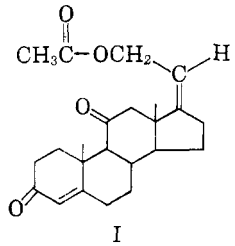
(11) E. A. Bartkus, E. B. Hotelling, and M. B. Neuworth, *J. Org. Chem.*, **22**, 1185 (1957).

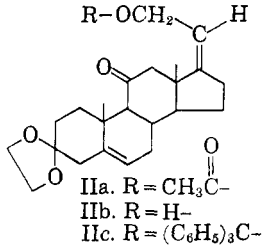
11-Alkylated Steroids. III. Two Syntheses of 11-Methylhydrocortisone[1]

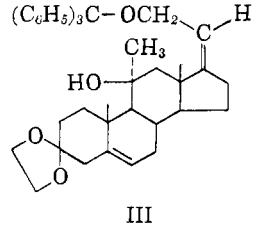
GUNTHER S. FONKEN, JOHN A. HOGG, AND A. VERN MCINTOSH, JR.

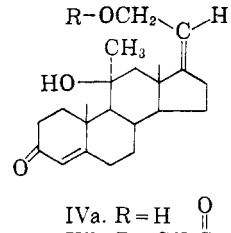
Received May 14, 1959

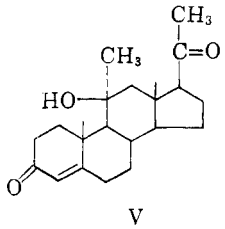
In our earlier report[1] of a synthesis of 11-methylhydrocortisone acetate (XIIa), we outlined the conversion of the known 21-hydroxypregna-4,17(20)-[*cis*]-diene-3,11-dione acetate[2] (I) to its ketal, 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal acetate (IIa), which was hydrolyzed with aqueous methanolic potassium bicarbonate to the corresponding free alcohol (IIb). Treatment of the alcohol (IIb) with triphenylmethyl chloride in dry pyridine afforded the 21-trityl ether (IIc), which, on treatment with excess ethereal methyllithium, was converted to 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (III). Efforts to substitute methyl Grignard reagent for methyllithium were unsuccessful, only unchanged IIc being recovered. Similarly, treatment of either the alcohol IIb or its acetate IIa with either methyl Grignard reagent or methyllithium gave only the alcohol IIb, with no evidence of addition to the 11-oxo group being observed. A consideration of the molecular model of IIb suggests that an initially formed 21-oxy anion, by virtue of its proximity to the 12β-hydrogen, facilitates enolization of the 11-oxo group. That the 5,6-double bond might also be implicated in some way in the mechanism of unreactivity was suggested by the failure of another 11-oxopregn-5-ene, namely pregn-5-ene-3,11,20-trione 3,20-bis(ethylene acetal)[3] (VI), to add methyllithium (see below). However, in the present case,

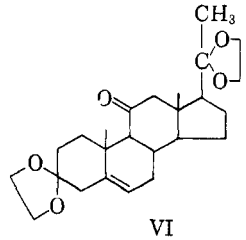

I

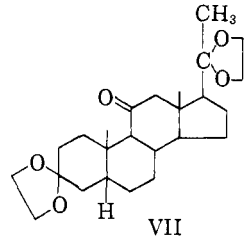

IIa. R = CH_3C–
IIb. R = H–
IIc. R = $(C_6H_5)_3C$–

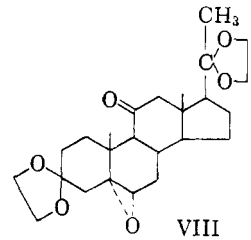

III

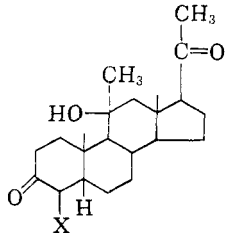

IVa. R = H
IVb. R = CH_3C–

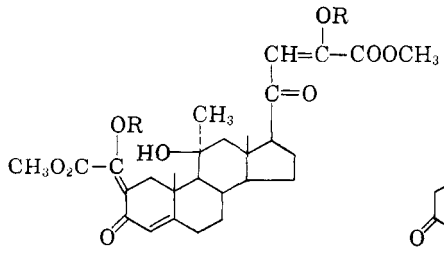

V

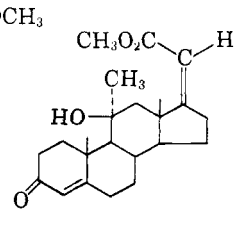

VI

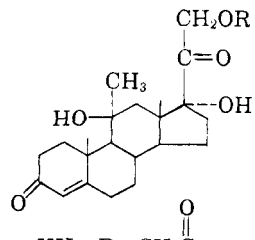

VII


VIII


IXa. X = H
IXb. X = Cl


Xa. R = Na
Xb. R = H


XI


XIIa. R = CH_3C–
XIIb. R = H

(1) Part of the material of this paper has appeared as a Preliminary Communication [G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958)]. Preceding paper in this series: see ref. (8).

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

the 5,6 double bond is also present in IIc, which does undergo addition to the 11-oxo group.

Hydrolysis of 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (III) with dilute methanolic hydrochloric acid at room temperature removed the ketal and trityl groups, giving 11β,21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IVa). Acetylation of the 21-hydroxy group occurred in acetic anhydride–pyridine, and the resulting acetate (IVb), when treated with *N*-methylmorpholine *N*-oxide peroxide in *t*-butyl alcohol–pyridine containing a catalytic amount of osmium tetroxide,[4] afforded 11β,17α,21 - trihydroxy - 11 - methylpregn - 4-ene-3,20-dione 21-acetate (11-methylhydrocortisone acetate; XIIa), together with a highly polar material that was not characterized. Hydrolysis of XIIa with aqueous potassium bicarbonate afforded the free alcohol XIIb.

It is of interest to note that although 11-methylhydrocortisone acetate gives a positive test with Tollens (ammoniacal silver oxide) reagent, the time required for the silver deposit to appear is much longer than for hydrocortisone acetate, which gives an almost instantaneous precipitate. This observation, together with some anomalies in the rotatory dispersion spectra of compounds of the 11-methyl series,[5] suggests that the interaction of the 11-methyl group with the steroid side chain is greater than would be predicted on the basis of a consideration of molecular models.

For several reasons, including the sensitive nature of several of the intermediates (particularly of the trityl ether IIc) and certain technical problems in the later steps, we felt that it would be advisable to devise an alternate synthesis of 11-methylhydrocortisone. The general synthetic scheme previously reported from these laboratories[2] seemed suitable, provided that 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V) could be prepared. Unfortunately, all attempts to prepare this compound by the direct addition of methyllithium or of methyl Grignard reagent to pregn-5-ene-3,11,-20-trione 3,20-bis(ethylene acetal)[3] (VI) were uniformly unsuccessful, only the 11-oxo steroid being recovered. Although no attempt was made to carry out an accurate measurement, a rough determination of evolved methane indicated that enolization was the exclusive reaction of VI with excess ethereal methyllithium. By contrast, a similar rough measurement with 5β-pregnane-3,11,20 - trione 3,20 - bis(ethylene acetal)[6] (VII) showed only about 20% enolization. Similarly, and somewhat surprisingly, 5α,6α-epoxypregnane-3,11,-20-trione 3,20-bis(ethylene acetal)[7] (VIII) underwent only about 3% enolization.

Fortunately, 11β - hydroxy - 11 - methyl - 5β-pregnane-dione[8] (IXa) was readily available and could be converted to 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb) by treatment with *t*-butyl hypochlorite in *t*-butyl alcohol containing hydrochloric acid.[9] Dehydrohalogenation of IXb with semicarbazide-pyruvic acid[10] or with lithium chloride-*N*,*N*-dimethylformamide[11] gave difficultly separable mixtures from which, by repeated crystallization and chromatography, the desired V could be obtained. (In the dehydrohalogenation reaction we again observed a marked difference in reaction rate, the 11-methyl steroid being more sluggish than was expected from experience with a steroid having no 11-methyl group.)

Although the reaction of V with ethyl oxalate in methanolic sodium methoxide was considerably slower than for the corresponding 11 - oxo compound,[12] it afforded the sodium salt of 11β-hydroxy-2,21 - bis(methoxyoxalyl) - 11 - methylpregn-4-ene-3,20-dione (Xa) which, when treated with acid, gave the corresponding free enol Xb. Treatment of Xb successively with methanolic sodium acetate, bromine, methanolic sodium methoxide, acetic acid, and zinc dust[12] afforded methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[*cis*]-dien-21-oate[13] (XI). Reaction of XI with pyrrolidine and *p*-toluenesulfonic acid essentially as described by Heyl and Herr[14] gave a crystalline 3-enamine that was not characterized but was reduced with lithium aluminum hydride and hydrolyzed with alkali to give 11β, 21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IVa), whose acetate IVb differed only in crystal form from that prepared by the 21-trityl ether route described earlier.[1] This acetate IVb afforded 11-methylhydrocortisone acetate XIIa identical to that obtained by the alternate route.

(3) J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 1716 (1953).

(4) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (Nov. 6, 1956).

(5) Extensive measurements on 11-methyl steroids have been carried out in these laboratories by Mr. W. A. Struck and associates. These studies will be published elsewhere.

(6) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953).

(7) From unpublished studies by G. B. Spero of these laboratories.

(8) G. S. Fonken, *J. Org. Chem.*, **23**, 1075 (1958).

(9) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri, and E. S. Gutsell, *J. Am. Chem. Soc.*, **76**, 546 (1954).

(10) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, **71**, 3262 (1949). See also V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948), and E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(11) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(12) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Am. Chem. Soc.*, **77**, 4438 (1955).

(13) This compound (and IVa derived therefrom) is assigned the *cis* configuration at the 17(20)-double bond on the basis of analogy to the structure proof in the series described in ref. (2).

(14) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

EXPERIMENTAL[15]

21-Hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal acetate (IIa). 21-Hydroxypregna-4,17(20)-[*cis*]-diene-3,11-dione acetate[2] (I, 0.50 g., 1.35 millimole) was refluxed for 6 hr. with 2 ml. of ethylene glycol and 10 mg. of *p*-toluenesulfonic acid monohydrate in 100 ml. of benzene, the return solvent being passed through a bed of calcium carbide in order to remove water as formed in the reaction. The reaction mixture was cooled, washed with aqueous 4% bicarbonate and with water, and dried over anhydrous sodium sulfate. The desiccant was filtered off and the filtrate concentrated at reduced pressure to a yellow oil which soon crystallized. Recrystallization from ethyl acetate–Skellysolve B gave 0.27 g. of IIa, m.p. 149–154°. Further recrystallization gave an analytical sample, m.p. 160–162°.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.11; H, 8.44.

21-Hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal (IIb). To a solution of 10.0 g. (24.1 millimole) of 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal 21-acetate (IIa) in 1500 ml. of absolute methanol, maintained in a nitrogen atmosphere, was added a solution of 10 g. (100 millimole) of potassium bicarbonate in 100 ml. of water. After being stirred for about 1 hr., the reaction mixture became homogeneous. It was allowed to stand at room temperature overnight, and then the volume reduced greatly by distillation at reduced pressure (bath temperature: 55–60°). Addition of 500 ml. of water with stirring precipitated the product, which was removed by filtration, washed well with water and dried *in vacuo*. The yield of good quality IIb was 8.46 g. (94.2% of the theoretical amount), m.p. 109–111.5°. Recrystallization from 50% aqueous methanol afforded long needles, m.p. 113.5–115°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16: H, 8.66. Found: C, 74.05; H, 8.95.

21-Triphenylmethoxypregna-5,17(20)-[cis]-diene-3,11-dione, 3-ethylene acetal (IIc). A solution of 5.38 g. (14.4 millimole) of 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal (IIb) and 4.4 g. (15.8 millimoles) of triphenylmethyl chloride in 70 ml. of carefully dried pyridine was allowed to stand at room temperature for 52 hr. The solution was poured into ice and water, and the product recovered by extraction, first with 200 ml. of ether-benzene (1:1), then with three 100-ml. portions of ether. The combined extracts were washed several times with water, filtered through anhydrous potassium carbonate, and evaporated. The residual glass was crystallized from methanol to give 6.19 g. of nearly pure IIc, m.p. 195–198° with prior softening from 192° on. For analysis a small sample was recrystallized from ether-methanol (*ca.* 1:1) to give chunky crystal clusters, m.p. 201–203°.

Anal. Calcd. for $C_{42}H_{46}O_4$: C, 82.05; H, 7.54. Found: C, 81.99; H, 7.47.

11β-Hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[cis]-dien-3-one ethylene acetal (III). To a solution of 300 mg. (0.488 millimole) of 21-triphenylmethoxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal (IIc) in 5 ml. of dry benzene, maintained in a nitrogen atmosphere, was added 10 ml. of 0.33*M* ethereal methyllithium. The resultant clear colorless solution was kept at room temperature for 3 days, then was diluted with benzene, treated with 6 ml. of acetic acid–water (1:5), and washed several times with water. Filtration through anhydrous sodium acetate followed by evaporation to dryness gave the crude product, contaminated (according to the infrared spectrum) with some carbonyl compound. Chromatography over 30 g. of Florosil concentrated the product in the 5% acetone–Skellysolve B eluates. The weight of residue in these fractions totalled 294 mg. (95.5% of the theoretical amount). A similar reaction, carried out at reflux for 51 hr., gave an eluate residue of 257 mg. (83.5%). Recrystallization from ethyl acetate (or trituration with methanol) gave crystalline III, m.p. 182–184°. The analytical sample was recrystallized from methanol–ethyl acetate (1:1). There was no evidence of carbonyl absorption in the infrared spectrum: γ_{max}^{Nujol} 3480 (OH); 1672 (Δ^5); 1094, 1002 (C—O); 1596, 1492, 714, 698 (C_6H_5).

Anal. Calcd. for $C_{43}H_{50}O_4$: C, 81.87; H, 7.93. Found: C, 81.90; H, 7.95.

11β,21-Hydroxy-11-methylpregna-4,17(20)-[cis]-dien-3-one (IVa). A suspension of 200 mg. of 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-diene-3-ethylene acetal (III) in 20 ml. of methanol containing 1 ml. of *N* hydrochloric acid was stirred at room temperature for about 44 hr. (The mixture became homogeneous after about 24 hr.) After addition of 15 ml. of aqueous 1.3% sodium bicarbonate, the mixture was evaporated to dryness. The residue was triturated with 30 ml. of benzene, and the organic solution resulting was decanted and chromatographed over 30 g. of Florisil. Elution with Skellysolve B gave triphenylmethyl methyl ether, with 5% acetone in Skellysolve B triphenyl carbinol, with 10% acetone–Skellysolve B a small amount of unidentified steroidal material, and with 25% acetone–Skellysolve B 88 mg. of crude IVa, which was recrystallized thrice from ethyl acetate to m.p. 188–192°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.35; H, 9.33.

Conversion to the corresponding acetate IVb was effected by dissolving crude IVa (160 mg.) in a mixture of 5 ml. of pyridine and 3 ml. of acetic anhydride. After a day at room temperature the mixture was poured into ice water, and the precipitate was collected, dried, and chromatographed over 30 g. of Florisil. On elution with Skellysolve B containing 7% acetone, 108 mg. of crystalline fractions were obtained. Crystallization from acetone-water gave 73 mg. of the acetate, m.p. 109–112°, $[\alpha]_D$ +120°; λ_{max}^{EtOH} 244 mμ, a_M 16,075.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.66; H, 8.97.

11β,17α,21-Trihydroxy-11-methylpregn-4-ene-3,20-dione 21-acetate (XIIa). To a stirred solution of 1.86 g. (5.0 millimoles) of 11α,21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one 21-acetate (IVb) in 65 ml. of *t*-butyl alcohol were added, sequentially, 12.5 millimoles of *N*-methylmorpholine oxide peroxide (as 9.4 ml. of *t*-butyl alcohol solution) 2.5 ml. of pyridine, and 30 mg. of osmium tetroxide in 13.8 ml. of *t*-butyl alcohol. After 3 hr., the mixture was diluted with 50 ml. of water and concentrated *in vacuo* to about 50 ml. volume, whereupon an oil precipitated. This oil was reprecipitated from aqueous methanol, giving 0.563 g. of crude XIIa which was combined with similar crops from several other experiments to make 1.77 g., was recrystallized from ethyl acetate–Skellysolve B (1:2) to give 1.416 g. of XIIa, m.p. 191–197°. Treatment of this material with Magnesol in *N,N*-dimethylformamide (DMF), followed by recrystallization from aqueous DMF, gave 1.315 g. of pure XIIa, m.p. 202–204°.

A sample not subjected to the Magnesol–DMF purification, but instead recrystallized repeatedly from ethyl acetate, had m.p. 191–195°; λ_{max}^{EtOH} 243 mμ, a_M 16,350; λ_{max}^{Nujol} 3400, 3345 (OH); 1744, 1724 (C=O); 1631 (Conj. C=O); 1606 (Δ^4); 1232 (C—O acetate). This sample was used for combustion analysis.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.85; H, 8.22.

[Extraction of the aqueous filtrates from the precipitation of XIIa with methylene chloride afforded an additional 0.958 g. of material that was chromatographed over 100 g. of Florisil. Elution with 17.5% acetone–Skellysolve B afforded an additional 162 mg. of XIIa, while elution with

(15) Infrared spectra were measured using a Perkin-Elmer Model 21 Spectrophotometer. Maxima are expressed in cm.$^{-1}$ Rotations were determined in chloroform ($c \sim 1\%$). Melting points, determined on a Fisher-Johns block, are uncorrected.

22.5% acetone–Skellysolve B gave 418 mg. of a more polar steroidal material that was not characterized.]

11β,17α,21-Trihydroxy-11-methylpregn-4-ene-3,20-dione (XIIb). A solution of 103 mg. of the acetate XIIa in 7.5 ml. of methanol was stirred at reduced pressure for several minutes to remove dissolved air, and then was blanketed with nitrogen. Following addition of 0.5 ml. of aqueous 20% (w./w.) potassium bicarbonate (nitrogen was bubbled through the water before dissolving the bicarbonate) the mixture was stirred in a sealed vessel under nitrogen at room temperature for 2 days. The mixture was acidified with 2 ml. of *N* hydrochloric acid and evaporated to dryness at reduced pressure, maintaining a bath temperature less than 35°. Trituration of the resultant crystal mass with water, followed by filtration, afforded 79 mg. of XIIb, m.p. 196–198.5°. A mixture m.p. with XIIa was depressed to 180–195°.

The analytical sample crystallized from aqueous acetone as a hemihydrate, m.p. 199–203°.

Anal. Calcd. for $C_{22}H_{32}O_5 \cdot {}^1/_2H_2O$: C, 68.54; H, 8.63. Found: C, 68.06; H, 8.57.

Rough enolization determinations. Into a closed system consisting of a glass reaction vessel attached to a gas-measuring burette filled with saturated sodium chloride solution was placed 0.42 g. (1 millimole) of carefully dried 5β-pregnane-3,11,20-trione 3,20-bis(ethylene acetal)[6] (VII) and 5 ml. of dry benzene. The bottle was placed in a water bath at 15–20°, the contents stirred magnetically, and 5 ml. (excess) of 0.4*M* ethereal methyllithium was introduced slowly through a rubber stopple, using a hypodermic syringe. The observed volume of evolved gas, corrected for the volume of liquid introduced and for the change measured in a blank (no steroid) experiment, was 5.2 ml. (21% of the theoretical amount for 1 mole of methane per mole of steroid).

In a similar manner, using 0.43 g. (1.03 millimole) of pregn-5-ene-3,11,20-trione 3,20-bis(ethylene acetal)[3] (VI), there was obtained 26.4 ml. (corrected volume) of methane, corresponding to 110% of the theoretical amount for 1 mole of methane per mole of steroid. When 432 mg. (1 millimole) 5α,6α-epoxypregnane-3,11,20-trione 3,20-bis(ethylene acetal)[7] (VIII) was substituted for VI, the corrected gas volume was 0.7 ml., corresponding to about 3% of the theoretical.

4-Chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb). A solution of 20.0 g. (0.058 mole) of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXa) was dissolved in 700 ml. of *t*-butyl alcohol by heating and stirring. The solution was cooled to 23° and protected from light, then 6.9 ml. (1.1 equiv.) of *t*-butyl hypochlorite and 6.0 ml. of concentrated hydrochloric acid in 30 ml. of water were added. The mixture was stirred 18 hr. at room temperature, then was cooled to 14° for several hours. The white precipitate of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb) was removed by filtration and washed with water; wt. 12.12 g., m.p. 197–200°.

A sample was chromatographed over 120 g. of Merck acid–washed alumina, the product being eluted with 1% acetone–methylene chloride. Crystallization from aqueous acetone and then from methylene chloride–Skellysolve B afforded an analytical sample of IXb, m.p. 226–230°, $[\alpha]_D$ +111°.

Anal. Calcd. for $C_{22}H_{33}ClO_3$: C, 69.36; H, 8.73; Cl, 9.30. Found: C, 69.04; H, 8.76; Cl, 9.07.

11β-Hydroxy-11-methylpregn-4-ene-3,20-dione (V). A. *Lithium chloride procedure.*[11] A solution of 1.8 g. (5 millimoles) of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb), m.p. 185–195°, and 1.0 g. of dry lithium chloride in 50 ml. of DMF under nitrogen was heated to 130° for 20 min. The reaction mixture was then allowed to cool and poured into 500 ml. of water. The precipitate was separated by filtration and the filtrate was extracted with methylene chloride. The residue from the extract was combined with the precipitate (total 1.64 g.) chromatographed over 150 g. of Merck acid–washed alumina. Fractions 7–12, eluted with methylene chloride and 0.5–1% acetone, contained halogen and weighed 711 mg. Fractions 13–18, 501 mg., were eluted with 2–4% acetone in methylene chloride and consisted of the 4-pregnene (V) melting above 160°. After two crystallizations from acetone-water a sample melting at 174–175°, 177–178° (double m.p.), $[\alpha]_D$ +181° was obtained; λ_{max}^{EtOH} 245 mμ, a_M 13,400.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.75; H, 9.49.

B. *Semicarbazide procedure.*[10] A solution of 1.90 g. of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb), m.p. 206–213°, in 40 ml. of redistilled DMF was stirred under nitrogen and a solution of 2.0 g. of semicarbazide hydrochloride and 1.50 g. of anhydrous sodium acetate was added. The temperature rose rapidly from 26° to 37°. A mixture of 5 ml. of redistilled pyruvic acid and 5 ml. of water was added and the temperature was raised to 60° for 2.5 hr. The reaction mixture was poured over 200 g. of crushed ice and diluted with water to 800 ml. The mixture was placed in the refrigerator overnight, then was filtered to give 1.07 g. of precipitate. An additional 0.676 g. was recovered by methylene chloride extraction. The entire yield was chromatographed over Florisil and eluted with methylene chloride–acetone. The higher melting fractions were combined and crystallized from acetone-water to give 0.949 g. of 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V), m.p. 169–172°.

11β-Hydroxy-2,21-bis(methoxyoxalyl)-11-methylpregn-4-ene-3,20-dione (Xb). A solution of 10.7 g. of 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V) and 25 ml. of ethyl oxalate in 125 ml. of *t*-butyl alcohol was stirred at room temperature under nitrogen as 25 ml. of 25% (wt./wt.) sodium methoxide in methanol was added. A yellow precipitate formed rapidly. The reaction mixture was stirred 17 hr., then 200 ml. of dry ether was added and stirring was continued for 1 hr. The yellow precipitate was separated by filtration and washed with 300 ml. of dry ether, then dried *in vacuo* to give 22.0 g. of sodium salt (Xa). This was dissolved in 125 ml. of 0.01*N* aqueous sodium hydroxide and made acid with 100 ml. of 1*N* aqueous hydrochloric acid to give the free enol Xb as an amorphous precipitate, wt. 14.7 g. Two recrystallizations from aqueous acetic acid gave 4.93 g. of Xb, m.p. 172–175°, $[\alpha]_D$ +172°, λ_{max}^{EtOH} 289 mμ, a_M 14,400.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.10; H, 7.03. Found: C, 64.37; H, 6.98.

Methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[cis]-dien-21-oate (XI). A suspension of 5.45 g. (0.01 mole) of 11β-hydroxy-2,21-bis(methoxyoxalyl)-11-methyl-pregn-4-ene-3,20-dione in 60 ml. of methanol was stirred under nitrogen at room temperature. A solution of 3.0 g. (0.0365 mole) of anhydrous sodium acetate in 40 ml. of methanol was added immediately. The solution was cooled in an ice bath and held at 0–5° while 24 ml. of a solution of 2.0 ml. of bromine in 33 ml. of methanol (precooled in a dry ice–acetone bath) was added over a 15 min. period, when the mixture became nearly colorless. This corresponded to 2.8 equivalents of bromine. The mixture was stirred 5 min., then 15 ml. of 25% (wt./wt.) sodium methoxide in methanol (6.4 equivalents) was added. The reaction mixture was stirred 2 hr. at room temperature, then 15 ml. of glacial acetic acid was added, followed by 6 g. of zinc dust added in portions during 1 hr. The mixture was stirred 30 min. longer and the excess zinc was separated by filtration.

The filtrate was poured into 1500 ml. of ice water and placed in the refrigerator overnight, giving 3.514 g. of precipitate. The aqueous filtrate was extracted with methylene chloride to give 0.471 g. of gum. This was combined with the precipitate (total, 3.98 g.) and chromatographed over 200 g. of Florisil. Elution with Skellysolve B and 5–7% acetone–Skellysolve B gave crystalline fractions which were recrystallized from methanol-water to give 1.76 g. of methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[*cis*]-dien-21-

oate (XI), m.p. 187–195°. Crystallization from methylene chloride–Skellysolve B mixture gave an analytical sample, m.p. 194–197°, $[\alpha]_D$ +147°; λ_{max}^{EtOH} 238 mμ, a_M 23,100.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.19; H, 8.74.

11β,21-Dihydroxy-11-methylpregna-4,17(20)-[cis]-dien-3-one (IVa). A mixture of 3.19 g. of methyl 11β-hydroxy-11-oxopregna-4,17(20)-[*cis*]-dien-21-oate, 40 mg. of *p*-toluenesulfonic acid monohydrate, and 3 ml. of redistilled pyrrolidine in 75 ml. of benzene was heated under reflux, with a water take-off, for 1.5 hr. Then 65 ml. of benzene was removed by distillation and the remaining solvent was removed by distillation *in vacuo* below 45°. The crystalline residue of the 3-pyrrolidyl amine was dissolved in 40 ml. of benzene and added to a stirred suspension of 2.0 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred 1.5 hr., then 20 ml. of ethyl acetate was added slowly, followed by 20 ml. of water. The remaining ether was removed by distillation *in vacuo*, then 120 ml. of methanol was added and the mixture was stirred 20 min. at 45°. After addition of 30 ml. of 5% aqueous sodium hydroxide, stirring was continued 15 min. at 50°, then 8 ml. of glacial acetic acid was added and the methanol was removed *in vacuo*. A solution of 10 ml. of concentrated sulfuric acid in 200 ml. of water was added and the mixture was placed in the refrigerator overnight, giving 2.893 g. of IVa, m.p. 195–202°. Crystallization from methanol-water gave 2.258 g., m.p. 200–208°. A sample was crystallized from aqueous pyridine, aqueous acetic acid, and ethyl acetate, and melted at 205–211°.

The acetate (IVb), prepared as described above, had m.p. 112–115°, $[\alpha]_D$ + 119°. The infrared spectra (Nujol mull) of samples of IVb prepared by the two routes were different, but chloroform solution spectra were identical, indicating that the samples were polymorphic. The same is true of the two samples of IVa having such different melting points.

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The Chemistry of the Aliphatic Esters of Phosphorodithioic Acids. IV. *O,O,S*-Trialkyl Phosphorodithioates by the Reaction of *O,O*-Dialkyl Hydrogen Phosphorodithioates with Their Salts[1]

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The preparation of trialkyl phosphates by the disproportionation of a mixture of a dialkyl hydrogen phosphate and its sodium salt at 300° has been reported.[2]

In the presence of acid, the zinc salts of *O,O*-dialkyl phosphorodithioates have been reported to decompose into mixtures of olefins, hydrogen sulfide and meta-thiophosphate polymers at 130–180°.[3]

The present investigation has shown that the *O,O*-dialkyl hydrogen phosphorodithioates react with their amine salts to yield *O,O,S*-trialkyl phosphorodithioates. The reaction proceeds smoothly at temperatures above 70° in benzene and dioxane, and appears to be general for the alkyl esters. In agreement with the equation shown below, only one alkyl group was transferred from the alkylating moiety in the reactions studied, and H_2S was evolved simultaneously. The yields were in the range of 40–97% based on this equation.

$$(RO)_2PSSH + (RO)_2PSS^-B^+ \longrightarrow (RO)_2PSSR + H_2S + (ROPOS)B$$

The reaction rate was followed readily by titration of the unreacted acid in the reaction mixture. Table I shows the reaction rates, expressed as the time required for 50% reaction, for the reaction of *O,O*-diethyl hydrogen phosphorodithioate with its salts in refluxing benzene solution. The results indicated that the reaction rate increased with the increasing base strength of the unhindered amines; but the rates decreased with increasing substitution around the nitrogen atom of the amine.

TABLE I

REACTION RATES OF *O,O*-DIETHYL HYDROGEN PHOSPHORODITHIOATE WITH ITS AMINE SALTS

Salt	Hours required for 50% reaction
Triethylamine	1.8
Piperidine	2.4
Pyridine	3.8
α-Picoline	7.2
Aniline	7.8
2,6-Lutidine	11.6

The diaryl hydrogen phosphorodithioates do not undergo this reaction as shown by the fact that *O,O*-diphenyl hydrogen phosphorodithioate with its triethylamine salt gave no decrease in acidity after 5 hr. reflux in benzene.

Table II shows the reaction rates of several *O,O*-dialkyl hydrogen phosphorodithioates with their triethylamine salts in benzene solution, expressed as the time required for 50% reaction. In the group tested, the acids prepared from primary alcohols reacted faster than those prepared from secondary alcohols. Within each series the reaction rates decreased with increasing molecular weight.

(1) For preceding article in this series, see W. E. Bacon and W. M. LeSuer, *J. Am. Chem. Soc.*, **76**, 670 (1954).

(2) G. M. Kosolapoff, "Organo-phosphorus Compounds," John Wiley & Sons, New York, 1950, p. 231.

(3) G. W. Kennerly, G. L. M. Christopher, and C. M. Judson, Abstracts of Papers, 122nd Annual Meeting, American Chemical Society, Atlantic City, N. J., Sept. 14–19, 1952, p. 31M.