The 2,4-dinitrophenylhydrazone was eluted from a column of alumina with benzene and crystallized from ethyl acetate–methanol. It formed small yellow needles, m.p. 140.6–142°.

Anal. Calcd. for $C_{33}H_{50}O_6N_4$ (598.76): C, 66.19; H, 8.42. Found: C, 66.76; H, 8.62.

Compound J (9).—A solution of 125 mg. of ketone 104 in 0.5 ml. of chloroform and 0.5 ml. of acetic anhydride was cooled in Dry Ice–acetone and about 0.8 ml. of hydrogen bromide was condensed on top of the mixture. After standing for 48 hr. at 0° the mixture was taken up in ether and the solution washed wth water and bicarbonate solution, dried and evaporated, and the residue chromatographed. A fraction eluted by 3:1 petroleum ether–benzene afforded 9 mg. of crystals, m.p. 138–144°. In another run, conducted for 24 hr., 1 g. of ketone 104 afforded 40 mg. of product after extensive chromatography. Four recrystallizations from methanol gave small prisms, m.p. 149.2–149.8°, α_D +21.4° Chf; λ^{Chf} 5.73, 5.80.

Anal. Calcd. for $C_{29}H_{47}O_4Br$ (539.58): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.94; H, 8.86; Br, 14.56.

Variations of the above procedure either gave lower yields or furnished no crystalline material.

Alcohol 104.—The glassy alcohol previously reported[4] eventually solidified, and three crystallizations from methanol (seed may be required) raised the m.p. to 105.6–106.4° α_D −19.4° Chf.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 76.96; H, 10.94.

5β-Acetoxymethyl-4-oxa-Δ²-coprostene (T. G.).—A mixture of 100 mg. of desoxyketone 104, 100 mg. of aluminum chloride and 2 ml. of acetic anhydride was boiled gently for 3 hr., cooled, decomposed with ice and water and extracted with ether. Chromatography on 3 g. of alumina afforded oily 4:1 petroleum ether–benzene fractions which solidified when rubbed with methanol. Crystallization from methanol gave needles, m.p. 74–77° (17 mg.).

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.02; H, 10.70.

Desacetyldihydro A (4), by T. G.—A solution of 1 g. of compound A (**3**) in 30 ml. of acetic anhydride when hydrogenated in the presence of 50 mg. of platinum oxide absorbed 52 ml. of hydrogen at 22° in 2 hr. The filtered solution was evaporated, ether was added and evaporated several times to remove acetic acid, and treatment of the residue with methanol afforded 300 mg. of starting material, m.p. 142–144°. Chromatography of the mother liquor afforded 530 mg. of oily product which was hydrolyzed by refluxing for 2 hr. with 6 ml. of methanol and 1.5 ml. of concd. hydrochloric acid. Ether extraction gave an oil which afforded solid when digested with petroleum ether. Two crystallizations from methanol gave 80 mg. of crystals, m.p. 149–152°; λ^{CS_2} 2.80$_w$, 5.83$_s$, 7.40$_m$, 9.25$_m$, 9.35 mμ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.87): C, 75.60; H, 10.50. Found: C, 75.54; H, 10.66.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Base-catalyzed Condensation of Progesterone with Ethyl Oxalate

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RECEIVED SEPTEMBER 10, 1959

Methoxide-catalyzed acylation of progesterone (I) by ethyl oxalate occurs at C-2 and C-21 in a relatively indiscriminate manner to give a mixture of 2-mono-, 21-mono- and 2,21-bis-ethoxalyl derivatives.

The base-catalyzed condensation of pregnane derivatives with oxalate esters affords a method for the introduction of 21-hydroxy (or acetoxy),[2a,b] 1-dehydro[2c] and 2-alkyl[3] groupings into the steroid molecule[4]; moreover, it is the basis of a procedure whereby the dihydroxyacetone side-chain may be elaborated from the simple 17β-acetyl side-chain.[2b] In view of the importance of these moieties in steroidal hormones possessing anti-inflammatory activity, it is of interest to ascertain the practicality of effecting a preferential acylation at one of the two reaction sites (C-2 and C-21) available in a 4-pregnen-3,20-dione. Moreover, it is of interest to determine what effect the presence of other groupings might have on the course of this reaction. Preferential ethoxalylation at C-21 already has been reported[2b] for 11-ketoprogesterone, 11α-hydroxyprogesterone and 11β-hydroxyprogesterone.[5] In contrast, we have found in the course of other work that 9(11)-dehydro-16α,17α-isopropylidenedioxyprogesterone reacts with ethyl oxalate, in the presence of 1.1 equivalents of sodium methoxide exclusively at C-2, although in the presence of an additional molar equivalent of methoxide, ethoxalylation takes place at C-21 as well to give a 2,21-bis-ethoxalyl derivative.[6] Moreover, Bernstein, Brown and co-workers have observed that the 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxyprogesterone undergoes preferential ethoxalylation at C-2.[7] Since 16α,17α-isopropylidenedioxyprogesterone also reacts selectively at C-2,[8] it may be concluded that the presence of the 16α,17α-isopropylidenedioxy group inhibits ethoxalylation at C-21. Furthermore, we have found that 9(11),16-bisdehydroprogesterone undergoes preferential C-21 ethoxalylation rather poorly and that the predominant reaction is a concurrent ethoxalylation at C-2 and at C-21.[9] The results of

(1) To whom inquiries concerning this paper should be addressed.

(2) (a) H. Ruschig, *Ber.*, **88**, 878 (1955); (b) 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, THIS JOURNAL, **77**, 4436 (1955); (c) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4438 (1955).

(3) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(4) Fluorine can be introduced into the steroid molecule *via* the reaction of ethoxalyl derivatives with perchloryl fluoride [H. M. Kissman, A. M. Small and M. J. Weiss, THIS JOURNAL, **81**, 1262 (1959); *ibid.*, submitted for publication].

(5) The patent literature contains claims to the preferential C-21 ethoxalylation of progesterone [A. H. Nathan and J. A. Hogg, U. S. Patent 2,727,905 (1955); *C. A.*, **50**, 10806*g* (1956)] and of a variety of other progesterone derivatives [J. A. Hogg and co-workers; U. S. Patent 2,683,724 (1954), *C. A.*, **49**, 11034*d* (1955); U. S. Patent 2,719,855 (1955), *C. A.*, **50**, 7889*b* (1956); U. S. Patent 2,767,198 (1956); *C. A.*, **51**, 5848*e* (1957)].

(6) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959).

(7) S. Bernstein, J. J. Brown, L. Feldman and N. E. Rigler, *ibid.*, **81**, 4956 (1959).

(8) G. R. Allen, Jr., and M. J. Weiss, to be published.

(9) R. E. Schaub, G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4962 (1959).

an investigation into the ethoxalylation of progesterone[5] itself are the subject of this communication.

Reaction of progesterone (I) (10 mmoles) with ethyl oxalate (17.1 mmoles) in the presence of sodium methoxide (10 mmoles) under the conditions previously described[5] gave a 29% recovery of I and the sodium salt of an ethoxalyl derivative from which the amorphous, free ethoxalyl product was obtained upon acidification of an aqueous solution. This latter material gave combustion values intermediate between those calculated for a mono- and a bis-ethoxalylprogesterone, and preliminary bromination–acetolysis experiments indicated that it contained at least 9% of the latter. Thus, a solution of the ethoxalyl product in methanolic sodium acetate was treated with 1.08 molar equivalents of bromine followed by 1.08 equivalents of sodium methoxide to induce deacylation. The resulting mixed bromoprogesterones (ferric chloride enol test still positive)[10] could not be resolved by chromatography and were therefore treated with potassium acetate at room temperature for three days; it had already been shown that this treatment allows preferential acetolysis of a 21-bromo group in the presence of a 2-bromo substituent.[9] Resolution of the acetolysis reaction mixture by partition chromatography gave deoxycorticosterone acetate (VII) (9.8% yield), a monobromoprogesterone (20.4% yield) and a monobromodeoxycorticosterone acetate (11.7% yield). The listed yields are based on unrecovered progesterone since the exact composition of the ethoxalylated product is unknown. However, it should be noted that a minimum of 66% of the ethoxalyl product is thus accounted for. Furthermore, it is probable that the actual percentage is significantly greater, since this minimum figure is based on the assumption of a maximum number of moles in the ethoxalylated material (minimum amount of 2,21-bis-ethoxalyl derivative and no non-ethoxalyl containing steroids) and quantitative yields or recoveries for the procedures of bromination, deacylation and acetolysis. When the bromination was carried out by the addition of small increments of bromine (after the initial addition of one molar equivalent), followed by equivalent amounts of sodium methoxide, until the solution no longer gave a positive enol test (ferric chloride),[10] deoxycorticosterone acetate (VII) was obtained in 5% yield, the monobromoprogesterone derivative in 18% yield and the monobromodeoxycorticosterone acetate derivative in 9% yield. As above, these yields are based on unrecovered progesterone and account for at least 58% of the ethoxalylated product.

It was postulated that the monobromoprogesterone was the 2α-bromo derivative VIII, since a comparison of its infrared spectrum with that of progesterone revealed a shift of the 3-carbonyl absorption band (see Table I) which was characteristic for that of a 2α-bromo-Δ^4-3-ketone.[6,11] Isolation of 1-dehydroprogesterone (XII)[12] in 32% yield by treatment of the monobromide with refluxing collidine confirmed this hypothesis. It may be noted that the introduction of a bromo substituent at C-2 *via* an ethoxalylation procedure makes it probable on mechanistic grounds that this substituent is α-oriented.[6]

The monobromodeoxycorticosterone acetate was tentatively assigned the 2α-bromo structure X[13] on the basis of infrared spectral evidence (see Table I), and confirmation of this assignment was obtained by comparison of this material with a sample of X prepared in the course of other ethoxalylation experiments (see below).

Since 2α-bromoprogesterone (VIII), deoxycorticosterone acetate (VII) and 2α-bromodeoxycorticosterone acetate (X) were formed from progesterone (I) by the sequence—ethoxalylation, bromination, deacylation and acetolysis—*it can only be concluded that progesterone reacts with ethyl oxalate at C-2 and C-21 in a relatively indiscriminate manner to give a mixture of 2-mono-, 21-mono- and 2,21-bis-ethoxalyl derivatives.*

Because of the low yields obtained by the above sequence and the inability to isolate a reasonable quantity of 2α-bromodeoxycorticosterone acetate (X) by partition chromatography, it was necessary to prepare X *via* another procedure. This was accomplished in the following manner. Reaction of progesterone with 2.2 molar equivalents of sodium methoxide and 3.4 molar equivalents of ethyl oxalate[2] afforded, after acidification of the sodium salt, an ethoxalyl derivative which was assumed to be crude 2,21-bis-ethoxalylprogesterone (II).[13a] Treatment of this product with two molar equivalents of bromine, followed by methoxide-induced deacylation, gave a crude gum which was resolved by adsorption chromatography into a dibromoprogesterone (26% yield) and a tribromoprogesterone (8% yield). The former product was assigned the 2α,21-dibromo structure VI for the following reasons. Since it had already been shown that progesterone condensed with ethyl oxalate at C-2 and C-21, it was reasonable to assume that a dibromide prepared *via* the ethoxalylation procedure would have bromine substituents at these positions. Moreover, a comparison of the infrared spectrum of the dibromide with that of progesterone (I) (see Table I) was consistent with such an assignment, and mechanistic considerations[6] made it probable that the 2-halogen is α-oriented. Preferential acetolysis[9] of the dibromide gave 2α-bromodeoxycorticosterone acetate (X) in 79% yield. This product was identical with that obtained previously in the "monoethoxalylation" experiments. Confirmation of its structure, as well as that of the precursor dibromide VI, was obtained by treatment of X with refluxing collidine to give the known 1-

(10) A 21-bromo-21-ethoxyalyl derivative still contains an enolic hydrogen and presumably should give a positive enol test. Addition of bromine to the point of a *negative* enol test could result in the formation of substantial amounts of 21,21-dibromo-21-ethoxalyl derivative. We wish to thank a referee of this paper for pertinent comments on this point.

(11) (a) M. Fieser, M. A. Romero and L. F. Fieser THIS JOURNAL, **77**, 3305 (1955); (b) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(12) F. Sondheimer, M. Velasco and G. Rosenkranz, THIS JOURNAL, **77**, 5073 (1955).

(13) Compound X has been reported in the patent literature, but its characterization is lacking [A. H. Nathan and J. A. Hogg, U. S. Patent 2,730,537 (1956); *C. A.*, **50**, 13103g (1956)].

(13a) J. A. Hogg, P. H. Beal, A. H. Nathan and F. H. Lincoln, U. S. Patent 2,862,010 (1958).

dehydrodeoxycorticosterone acetate (XI)[14] in 40% yield.

Although unequivocal proof was not obtained, it was indicated that the tribromoprogesterone was the 2α,21,21-tribromide V. When this compound was treated with methanolic sodium methoxide at room temperature for four hours, an amorphous product resulted. The ultraviolet spectrum (λ_{max} 231 mμ, $E^{1\%}_{1\,cm.}$ 525) of this material was consistent with the postulation that it contained an α,β-unsaturated ester (IX) which would be expected from the Favorskiĭ rearrangement[2b,2] of a structure such as V. It is noteworthy that in addition to the shift of the 3-carbonyl absorption band expected for a 2α-bromo-Δ⁴-3-ketone,[11] the tribromide V shows a greater shift of the 20-carbonyl absorption band than does the corresponding 2α,21-dibromide (VI) (see Table I). This small, but reproducible, difference probably results from the introduction of the second bromine atom at C-21.

TABLE I

CARBONYL BAND POSITIONS OF PROGESTERONE, DEOXYCORTICOSTERONE ACETATE AND CERTAIN OF THEIR BROMO DERIVATIVES[a]

	3-Carbonyl, cm.⁻¹	Δν on bromination[b]	20-Carbonyl, cm.⁻¹	Δν on bromination[c]
Progesterone (I)	1673		1709	
2α-Bromoprogesterone (VIII)	1695	22		
2α,21-Dibromoprogesterone (VI)	1690	17	1720	11
2α,21,21-Tribromoprogesterone (V)	1690	17	1730	21
Deoxycorticosterone acetate (VII)	1672			
2α-Bromodeoxycorticosterone acetate (X)	1680[d]	8		

[a] All spectra are for pressed potassium bromide disks. [b] Cummins and Page[11b] have recorded a shift of 16 cm.⁻¹ on passing from 4-cholestene-3-one to its 2α-bromo derivative; the carbonyl absorption band of the latter was found to be at 1690 cm.⁻¹. [c] The recorded shift for the introduction of a single bromine atom at C-21 in 20-ketones is 16–22 cm.⁻¹ (ref. 15). [d] The intensity of this band was less than that of the 20-carbonyl band; this is the reverse of the situation existing in the corresponding non-brominated steroid VII and supports the assigned structure (see ref. 15).

Acknowledgment.—We are indebted to Mr. Charles Pidacks and Miss Donna Archibald for carrying out certain of the partition chromatography procedures reported herein. The microanalyses were carried out by Mr. L. Brancone and staff, and spectroscopic and polarimetric data were supplied by Mr. W. Fulmor and staff.

Experimental[16]

Condensation of Progesterone with Ethyl Oxalate.[5]—A solution of 10 ml. of 1 *N* methanolic sodium methoxide in 100 ml. of benzene was distilled until the head temperature reached 80°, 55 ml. of distillate being collected. The residual mixture was diluted with 40 ml. of benzene and 1 ml. of ethanol and treated with 3.16 g. (10 mmoles) of progesterone. After all solid had dissolved, the solution was treated with 2.50 g. (17.1 mmoles, 2.7 ml.) of ethyl oxalate and magnetically stirred for two hours. Within one minute after the ethyl oxalate addition, solid began precipitating. The mixture then was diluted with 250 ml. of ether, and stirring was continued for 45 minutes. The mixture was filtered, and the residual solid was washed well with ether and dried to give 2.23 g. of yellow, amorphous solid.

Anal. Calcd. for $C_{25}H_{33}O_5Na$ (monoethoxalyl monosodio salt): C, 68.79; H, 7.62. Calcd. for $C_{29}H_{36}O_8Na_2$ (bisethoxalyl disodio salt): C, 52.89; H, 5.51. Found: C, 60.36; H, 6.67; H_2O, 3.40 (Karl Fischer), 2.75 (loss on drying).

A 2.18-g. aliquot of this crude sodium salt was dissolved in water to give a clear yellow solution which was made acid to litmus paper by the addition of a 5% hydrochloric acid solution. The amorphous precipitate was collected,

(14)(a) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, THIS JOURNAL, **77**, 661 (1955); (b) E. Vischer, Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **38**, 835 (1955).

(15) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1954).

(16) Melting points were determined in an open capillary tube and are uncorrected values. The ultraviolet spectra were determined on a Cary recording spectrophotometer, and the infrared spectra (pressed potassium bromide discs) were determined with a Perkin-Elmer spectrophotometer (model 21). All evaporations were carried out under reduced pressure. Except where otherwise noted, the petroleum ether used was that fraction boiling at 60–70°.

washed with water until the washings were neutral to litmus paper, and dried to give 1.984 g. of amorphous yellow solid, λ_{max}^{MeOH} 242 and 294 mμ ($E_{1\,cm.}^{1\%}$ 348, 197); λ_{max}^{NaOH} 252, 302 and 342 mμ (shoulder) ($E_{1\,cm.}^{1\%}$ 348, 335, 190)[17]; λ_{max} 5.75, 5.85, 5.97, 6.12, 7.90, 8.98 μ.

Anal. Calcd. for $C_{25}H_{34}O_5$ (monoethoxalyl): C, 72.43; H, 8.27. Calcd. for $C_{25}H_{34}O_5 \cdot H_2O$ (monoethoxalyl monohydrate): C, 69.42; H, 8.39; H_2O, 4.17. Calcd. for $C_{29}H_{38}O_8$ (bisethoxalyl): C, 67.88; H, 7.44. Found: C, 69.16; H, 8.19; H_2O, 1.60 (Karl Fischer).

The mother liquor from the separation of the crude sodium salt was taken to dryness and the residue was dissolved in a small amount of benzene. This solution was adsorbed onto a column prepared from 30 g. of silica gel and benzene (column size: 1.8 × 18 cm.). The column was washed with 125 ml. each of benzene and a 5% ether-in-benzene solution; these washings were discarded. The column was then washed with a 10% ether-in-benzene solution, 125-ml. fractions being collected. The solids contained in fractions 3–12 were combined and recrystallized from acetone–hexane to give 0.921 g. (29% recovery) of progesterone (I), m.p. 128–130°. Identity was established by mixture melting point and infrared spectral comparisons.

Preparation of the Mixture of Bromoprogesterones.—A solution of 1.200 g. of the mixed ethoxalyl derivatives and 0.472 g. (6.24 mmoles) of sodium acetate in 20 ml. of methanol was chilled to about 5° with magnetic stirring. On the basis of a preliminary experiment, this ethoxalylated mixture contained at least 9% (0.108 g., 0.21 mmole) of 2,21-bisethoxalylprogesterone (II) and as much as 91% (1.092 g., 2.62 mmoles) of mixed monoethoxalylprogesterones. The cold, stirred solution was accordingly treated with 5.64 ml. of a 0.54 *M* solution of bromine in carbon tetrachloride by dropwise addition over a period of 13 minutes. The solution was stirred an additional 5 minutes and then was treated with 3.04 ml. of 1 *M* methanolic sodium methoxide. After stirring the solution an additional 5 minutes, it was distributed between methylene chloride and water. The organic phase was washed with water, dried over magnesium sulfate and taken to dryness to give 1.104 g. of an amber oil. An aliquot of this material gave a wine color when treated with an alcoholic ferric chloride solution.

Acetolysis of the Mixed Bromoprogesterones.—A mixture of 5.1 g. of potassium bicarbonate and 3.7 ml. of glacial acetic acid was thoroughly ground with a mortar and pestle. The resulting powder was added to a solution of 1.10 g. of the mixed bromoprogesterones in 50 ml. of acetone; the mixture was magnetically stirred at room temperature for three days. The product, 1.02 g. of amber gum, was isolated in the usual manner (see below). An aliquot of this material gave a wine color with alcoholic ferric chloride solution.

Resolution of the Products from Acetolysis of the Bromoprogesterones.—A 106.8-mg. sample of the product(s) derived by acetolysis of the mixed bromoprogesterones was dissolved in 2 ml. of the upper and 2 ml. of the lower phase of the solvent system methanol–*n*-heptane (1:1), and the two-phase solution was mixed thoroughly with 4 g. of powdered cellulose (Whatman standard grade used as received). This mixture was packed on top of a column which had been prepared from 150 g. of powdered cellulose and 75 ml. of the lower phase of the solvent system just described. The column (2.8 × 41 cm.) was eluted with the upper phase, 5-ml. fractions being collected. The individual fractions were tested for the presence of ultraviolet absorbing materials by spotting an aliquot on paper and examining the spots under ultraviolet light with a wave length of 254 mμ. Only those fractions having ultraviolet absorbing material were investigated further.

On allowing fractions 14–36 to evaporate partially at room temperature an amorphous solid separated. These fractions were combined and taken to dryness to give 23.4 mg. of residue. An amorphous powder, m.p. 84–88°, was obtained by dissolving this material in ether and reprecipitating it with hexane; it was not investigated further.

After partial evaporation of the solvents at room temperature, fractions 37–55 deposited needles. These fractions were combined and taken to dryness to give 36.3 mg. (20.4% adjusted yield, based on unrecovered progesterone) of **2α-bromoprogesterone** (VIII). This material was recrystallized from acetone–hexane to give 30.6 mg. of white needles, m.p. 153–155° dec., $[\alpha]^{25}D$ +193° (*c* 1.42, chloroform); λ_{max}^{MeOH} 244 mμ (ε 15,000); λ_{max} 5.84, 5.91, 6.15 μ. For analysis see below.

Fractions 91–120 were combined and taken to dryness to give 23.5 mg. (11.7% adjusted yield, based on unrecovered progesterone) of **2α-bromodeoxycorticosterone acetate** (X). This material was recrystallized from acetone–hexane to give 17.1 mg. of white crystals, m.p. 173–175° dec., $[\alpha]^{25}D$ +176° (*c* 0.67, chloroform); λ_{max}^{MeOH} 243 mμ (ε 13,800); λ_{max} 5.70, 5.80, 5.91, 6.15, 8.10, 9.43 μ. For analysis see below.

Fractions 350–385 were combined and taken to dryness to give 17.0 mg. (9.8% adjusted yield, based on unrecovered progesterone) of **deoxycorticosterone acetate** (VII). This material was recrystallized from acetone–hexane to give 10.8 mg. of white crystals, m.p. 154–156° alone or when mixed with authentic deoxycorticosterone acetate; identity was further established by the sameness of the infrared spectra of the two samples.

Yield.—Total yield of VII + VIII + X = 41.9%, based on unrecovered progesterone. This accounts for a minimum of 66% of the mixed ethoxalyl derivatives—on the assumption that this material contained the maximum possible number of moles of ethoxalylated steroids (minimum amount of bis-ethoxalylprogesterone (II)—corresponding to isolated yield of X; no non-ethoxalylated steroid) and disregarding the fact that actually the amount of bromine used was about 0.05 mmole less than the stoichiometry, as ultimately worked out, required.

Preparation of the Mixture of Bromoprogesterones by Addition of Bromine to the Ethoxalyl Derivative to Point of Negative Ferric Chloride Enol Test.—The mixed ethoxalyl derivative used for this experiment was prepared in the manner described above in the absence of the 1 ml. of ethanol and for a reaction time of 23 hours rather than 2 hours. By this procedure, 3.14 g. of progesterone (I) afforded 1.928 g. of mixed ethoxalyl derivative; 0.623 g. (20%) of I was recovered. The analysis for two separate preparations follows.

Anal. Calcd. for $C_{25}H_{34}O_5$ (mono-ethoxalyl): C, 72.43; H, 8.27. Calcd. for $C_{29}H_{38}O_8$ (bis-ethoxalyl): C, 67.68; H, 7.44. Found: C, 69.47; H, 7.99. Found: C, 70.22; H, 7.93.

Bromination.—A solution of 1.927 g. of the mixed ethoxalyl derivatives described immediately above and 0.910 g. of potassium acetate in 25 ml. of methanol was chilled to about 5° with magnetic stirring. This solution was treated, by dropwise addition over a period of 12 minutes, with 4.5 ml. of 1.03 *M* bromine in carbon tetrachloride solution; the solution became turbid about halfway through the addition. The mixture was stirred for 5 minutes after the addition was completed and then was treated with 4.65 ml. of 1 *N* methanolic sodium methoxide solution. After stirring the mixture for two additional minutes, an aliquot of approximately 0.2 ml. was withdrawn and treated with alcoholic ferric chloride solution; a wine color developed instantaneously. Measured volumes of the bromine in carbon tetrachloride solution then were added to the reaction mixture. After the addition of each increment was completed, a molar equivalent of the methanolic sodium methoxide solution was added; and the reaction mixture was tested for the presence of an enol by treatment of a small aliquot with alcoholic ferric chloride solution. After the addition of 8.17 ml. (8.4 mmoles) of the bromine reagent and an equivalent amount of methanolic sodium methoxide, the reaction mixture no longer gave a positive enol test.

The reaction mixture was distributed between 50 ml. of methylene chloride and 65 ml. of a saturated sodium chloride solution. The aqueous layer was washed with an additional 50 ml. of methylene chloride. The combined organic solutions were dried over magnesium sulfate and taken to dryness to give 2.336 g. of partially crystalline residue.

In three other experiments conducted in the above manner, 0.83, 1.40, and 1.78 g. of mixed ethoxalyl derivatives gave 0.78, 1.60 and 2.38 g., respectively, of the mixed bromoprogesterones.

Acetolysis of the Mixed Bromoprogesterones.—A mixture of 11.1 g. of potassium bicarbonate and 6.5 ml. of glacial acetic acid was thoroughly ground with a mortar and pestle. The resulting powder was added to a solution of 2.336 g. of mixed bromoprogesterones (preparation of this material by

(17) For the base spectra, a methanolic solution was diluted 1:1 with 0.1 *N* sodium hydroxide solution.

addition of bromine to negative ferric chloride test is detailed above) in 50 ml. of acetone; the mixture was magnetically stirred at room temperature for three days. Water (50 ml.) was added to the mixture; all of the solids dissolved. An additional 50 ml. of water was added, and the resulting mixture was extracted with methylene chloride (3 × 50 ml.). The combined organic extracts were washed with a saturated sodium chloride solution (3 × 100 ml.), dried over magnesium sulfate and evaporated to give 1.815 g. of a glass.

In a preliminary experiment acetolysis of 1.603 g. of the mixed bromoprogesterones gave 1.367 g. of a gum.

Resolution of the Products from Acetolysis of the Bromoprogesterones. Method A.—The product derived from the acetolysis of 1.603 g. of mixed bromoprogesterones (obtained in the above preliminary experiment) was dissolved in the minimum quantity of benzene and adsorbed onto a column prepared from 150 g. of silica gel[18] (column size: 4.0 × 22.5 cm.). The column was washed with 750 ml. of benzene and 1000 ml. of a 2% ether-in-benzene solution; these washings were discarded. The column then was eluted with a 5% ether-in-benzene solution; 250-ml. fractions were collected. Fractions 1–20 all gave gummy residues on removal of the solvent; only the material in fractions 7–11 could be crystallized. This material was combined and recrystallized four times from acetone–petroleum ether to give 0.170 g. (4% yield, based on the 3.14 g. of progesterone used at the outset) of **2α-bromoprogesterone (VIII)** as white needles, m.p. 148–149° dec., $[\alpha]^{25}D$ +197° (*c* 1.18, chloroform); λ_{max}^{MeOH} 244 mμ (ε 14,800); λ_{max} 5.84, 5.91, 6.15 μ.

Anal. Calcd. for $C_{21}H_{29}BrO_2$: C, 64.08; H, 7.43; Br, 20.30. Found: C, 63.63; H, 7.57; Br, 20.29.

Method B.—A 61.8-mg. sample of the product derived by acetolysis of the mixed bromoprogesterones (from the experiment detailed above wherein bromination was carried to the point of a negative ferric chloride test to give 1.815 g. of a glass) was dissolved in 2 ml. of the upper and 2 ml. of the lower phase of the system methanol–petroleum ether (b.p. 90–100°) (1:1), and the two-phase solution was mixed thoroughly with 4 g. of Celite.[19] This mixture was packed on top of a column which had been prepared from 60 g. of Celite and 30 ml. of the lower phase of the solvent system just described. The column was eluted with the upper phase, and the effluent was allowed to pass through a recording spectrophotometer which had been set at 240 mμ. Although the first 166 ml. of effluent probably contained five substances, as indicated by five separate peaks, the overlap of these peaks prevented the isolation of these materials. The next 63 ml. of effluent contained much ultraviolet-absorbing material (fraction I). Although the following 84 ml. of effluent contained a slight amount of ultraviolet-absorbing material, it was discarded. The next 85 ml. of effluent contained a single substance (fraction II). Further elution gave no more ultraviolet-absorbing material. The column then was washed with methanol to give fraction III.

Fraction I was taken to dryness to give 19.4 mg. (18% adjusted yield, based on unrecovered progesterone) of **2α-bromoprogesterone (VIII)**. This material was recrystallized from acetone–petroleum ether to give 15.7 mg. of white needles, m.p. 152–154° dec. A mixture with a sample of the material isolated in method A melted at 151–154° dec. Moreover, the infrared spectra of the two samples were identical.

Fraction II was taken to dryness to give 11.2 mg. (9% adjusted yield, based on unrecovered progesterone) of **2α-bromodeoxycorticosterone acetate (X)**. This material was recrystallized from acetone–petroleum ether to give 7.6 mg. of white crystals, m.p. 170–173° dec. A mixture of this material with a sample prepared from 2α,21-dibromoprogesterone (VI) (see below) melted at 172–175° dec. Furthermore, the infrared spectra of the two samples were identical.

Fraction III was taken to dryness, and the amorphous material contained therein partially crystallized when triturated with acetone. The mother liquor was decanted, and the crystals were recrystallized from acetone–petroleum ether to give 5.1 mg. (5% adjusted yield, based on unrecovered progesterone) of **deoxycorticosterone acetate (VII)** as white crystals, m.p. 155–156° alone or when mixed with authentic deoxycorticosterone acetate; identity was further established by the sameness of the infrared spectra of the two samples.

Attempts to duplicate this separation by the chromatography of larger samples of the crude mixture on larger Celite columns were singularly unsuccessful, presumably as a result of overloaded columns.

Yield.—The total yield of VII + VIII + X was 32%, based on unrecovered progesterone. This accounts for a minimum of 58% of the mixed ethoxalyl derivatives—on the same assumptions described in the acetolysis experiment above.

1,4-Pregnadiene-3,20-dione (1-Dehydroprogesterone) (XII).—A solution of 48 mg. (0.12 mmole) of 2α-bromoprogesterone (VIII) and 1 ml. of 2,4,6-collidine was allowed to reflux for 45 minutes. The solution became dark and some solid separated; the cooled mixture was diluted with 20 ml. of ether and filtered to give 13 mg. of collidine hydrobromide. The ethereal solution was extracted with 10% sulfuric acid solution (2 × 15 ml.), and the combined acid washes were extracted with 20 ml. of ether. The combined ethereal solutions were dried over a mixture of magnesium sulfate and Norite and taken to dryness; no residue was found. Fortunately, the product was desorbed from the magnesium sulfate and Norite cake by washing of the latter with methylene chloride (5 × 20 ml.). These washings were taken to dryness to give a residue which on recrystallization from acetone–petroleum ether furnished 12 mg. (32% yield) of white crystals, m.p. 149–151° (on a Kofler hot-stage), $[\alpha]^{25}D$ +111° (*c* 0.22, ethanol); λ_{max}^{MeOH} 244 mμ (ε 15,600); λ_{max} (ν) 5.89 (1697), 6.02 (1660), 6.15 (1627) and 6.25 μ (1601 cm.$^{-1}$). Reported[12] values are m.p. 152–153°, $[\alpha]^{20}D$ +120° (chloroform); λ_{max}^{EtOH} 244 mμ (ε 17,700); $\nu_{max}^{CHCl_3}$ 1700, 1660, 1620 and 1600 cm.$^{-1}$.

2,21-Bis-ethoxalylprogesterone (II).—A solution of 22 ml. of 1 *N* methanolic sodium methoxide in 100 ml. of dry benzene was distilled until 74 ml. of distillate was collected. The cooled residual mixture was treated with 5.00 g. (0.034 mole, 4.6 ml.) of ethyl oxalate and was stirred magnetically; all of the solid dissolved. This solution was treated with 3.14 g. (0.010 mole) of progesterone (I), 5 ml. of benzene being used to aid in transfer. A yellow solution resulted; within one minute an amorphous solid separated. This mixture was magnetically stirred at room temperature for 24 hours, whereafter 100 ml. of ether was added and stirring was continued for one hour. The mixture was filtered, and the 5.904 g. of crude sodio derivative was thoroughly agitated with 125 ml. of water. The turbid, orange solution was filtered through a bed of Celite to give a clear filtrate which was acidified with 5% hydrochloric acid solution. The solid was collected by filtration, washed well with water and dried under reduced pressure over phosphoric anhydride to give 4.80 g. (93% yield) of ivory-colored solid which had λ_{max}^{MeOH} 248 and 298 mμ ($E_{1cm.}^{1\%}$ 254, 235); λ_{max}^{NaOH} 252, 302 and 342 mμ ($E_{1cm.}^{1\%}$ 285, 365, 270)[17]; λ_{max} 5.75, 6.14, 7.90(broad), 8.99 μ.

Anal. Calcd. for $C_{29}H_{38}O_8$: C, 67.68; H, 7.44. Found: C, 65.87; H, 7.40.

Bromination of the Crude 2,21-Bis-ethoxalylprogesterone (II).—A solution of 1.028 g. (2.0 mmoles) of the above crude 2,21-bis-ethoxalylprogesterone (II) and 0.392 g. (4.0 mmoles) of potassium acetate in 15 ml. of methanol was chilled in an ice-bath with magnetic stirring. Over a period of 10 minutes there was added dropwise 4.3 ml. of 0.93 *M* bromine in carbon tetrachloride solution; some solid separated during the addition. The resulting mixture was stirred for 5 minutes, and 4.0 ml. of 1 *N* methanolic sodium methoxide was added dropwise over a period of 1 minute. The mixture was filtered, and the water-soluble residue was discarded. The filtrate was concentrated to remove the carbon tetrachloride, and the concentrate was diluted with 50 ml. of water. The resulting mixture was extracted with methylene chloride (2 × 50 ml.), and the combined organic extracts were dried over magnesium sulfate and taken to dryness to give 1.004 g. of a gummy residue. This material was dissolved in the minimum amount of benzene necessary for solution and adsorbed onto a column prepared from 25 g. of silica gel[18] (column size: 1.8 × 15.5 cm.). The column was eluted with a 1% ether-in-benzene solution;

(18) A product of Davison Chemical Co., Baltimore, Md.

(19) The material used in these partition columns was Celite[20] 545 which had been washed with 6 *N* hydrochloric acid and then distilled water until neutral and finally with methanol. The substance was dried to give a fluffy powder.

(20) Celite is a Johns-Manville registered trademark for diatomaceous silica products.

50-ml. fractions were collected. The material contained in fractions 5 and 6 was combined and crystallized from 3 ml. of ether to give 80 mg. (8% yield) of what is presumed to be **2α,21,21-tribromoprogesterone (V)** as white crystals, m.p. 147–149° dec. This material was recrystallized from acetone–petroleum ether to give 62 mg. of crystals, m.p. 145–146° dec., $[\alpha]^{24}D$ +162° (*c* 0.78, methanol); λ_{max}^{MeOH} 242 mμ (ε 14,700); λ_{max} 5.79, 5.92, 6.15 μ.

Anal. Calcd. for $C_{21}H_{27}Br_3O_2$: C, 45.76; H, 4.94; Br, 43.50. Found: C, 45.51; H, 5.20; Br, 43.09.

The material contained in fractions 8–14 was combined and crystallized from acetone–petroleum ether to give 0.200 g. (26% yield) of **2α,21-dibromoprogesterone (VI)** as white crystals, m.p. 160–161° dec. This material was recrystallized from acetone–petroleum ether to give 172 mg. of white crystals, m.p. 163–165° dec., $[\alpha]^{24}D$ +201° (*c* 0.71, chloroform); λ_{max}^{MeOH} 242 mμ (ε 18,100); λ_{max} 5.81, 5.92, 6.16 μ.

Anal. Calcd. for $C_{21}H_{28}Br_2O_2$: C, 53.41; H, 5.98; Br, 33.84. Found: C, 53.26; H, 6.15; Br, 33.81.

2α-Bromodeoxycorticosterone Acetate (X).—A mixture of 2.1 g. of potassium bicarbonate and 1.2 ml. of glacial acetic acid was thoroughly ground with a mortar and pestle. The resulting powder was added to a solution of 0.343 g. (0.73 mmole) of 2α,21-dibromoprogesterone (VI) in 25 ml. of acetone, and this mixture was magnetically stirred at room temperature for three days. The mixture was slowly diluted with water until the total volume was about 125 ml.; during the dilution all solid dissolved, and more solid then separated. This mixture was filtered, and the filtrate was extracted with 100 ml. of methylene chloride. The organic solution was washed with water (2 × 100 ml.), dried over magnesium sulfate and taken to dryness. The residue was combined with solid from above and recrystallized from acetone–petroleum ether to give 0.251 g. (79% yield) of white crystals, m.p. 176–178° dec. An additional recrystallization from acetone–petroleum ether gave white crystals, m.p. 173–175° dec., $[\alpha]^{25}D$ +174° (*c* 1.07, chloroform); λ_{max}^{MeOH} 243 mμ (ε 13,600); λ_{max} 5.71, 5.79, 5.92, 6.15, 8.11, 9.40 μ.

Anal. Calcd. for $C_{23}H_{31}BrO_4$: C, 61.20; H, 6.92; Br, 17.74. Found: C, 61.08; H, 7.14; Br, 17.71.

21-Acetoxy-1,4-pregnadiene-3,20-dione (1-Dehydrodeoxycorticosterone Acetate) (XI).—A solution of 0.190 g. (0.42 mmole) of 2α-bromodeoxycorticosterone acetate (X) and 3 ml. of 2,4,6-collidine was allowed to reflux for 45 minutes. Solid began separating from the solution when reflux temperature was reached, and the cooled mixture was distributed between 50 ml. of methylene chloride and 50 ml. of 10% sulfuric acid solution. The organic phase was washed further with 50 ml. of 10% sulfuric acid solution and then 50 ml. of water. After drying the solution over a mixture of magnesium sulfate and Norite, the solvent was removed to give a crystalline residue. This material was recrystallized from acetone–petroleum ether to give 0.065 g. (40% yield) of needles and rods, m.p. 200–201°, $[\alpha]^{25}D$ +131° (*c* 1.7, chloroform); λ_{max}^{MeOH} 243 mμ (ε 14,800); λ_{max} 5.72, 5.80, 6.00, 6.14, 6.23, 8.03, 9.38 μ. Reported[14] values are m.p. 202.6–204.0°, $[\alpha]D$ + 125.6° (ethanol), +134 ± 3° (chloroform)[14]; λ_{max}^{EtOH} 243 mμ (ε 15,400); $\lambda_{max}^{CS_2}$ 5.71, 5.79 μ; and $\lambda_{max}^{CHCl_3}$ 6.00, 6.17, 6.24 μ.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.48; H, 8.26.

Reaction of 2α,21,21-Tribromoprogesterone (V) with Sodium Methoxide.—A slurry of 0.285 g. (0.52 mmole) of V in 5 ml. of methanol was treated with 3.1 ml. of 1 *N* methanolic sodium methoxide; all of the solid dissolved and the yellow solution was allowed to stand at room temperature for four hours. The solution was diluted to a volume of 25 ml. with water and extracted with methylene chloride (2 × 25 ml.). The combined extracts were dried over magnesium sulfate and taken to dryness to give 0.147 g. of a glass. This material had λ_{max}^{MeOH} 231 mμ ($E_{1\,cm.}^{1\%}$ 525); λ_{max} 5.83, 5.95, 6.18, 8.60 μ.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Compounds Related to Podophyllotoxin. X. Synthesis of Picropodophyllin[1]

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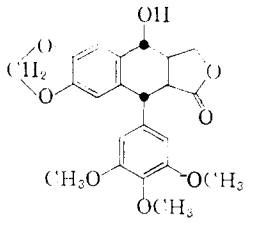
RECEIVED AUGUST 11, 1959

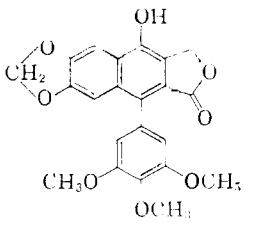
A total synthesis of picropodopyllin is described. 3,4-Methylenedioxy-3',4',5'-trimethoxybenzophenone, from the Friedel–Crafts reaction of methylenedioxybenzene and trimethoxybenzoyl chloride, was condensed with ethyl succinate in the presence of potassium *t*-butoxide. Hydrolysis of the product gave two geometrically isomeric itaconic acids, one of which was carried through the subsequent steps. This acid was hydrogenated, and the resulting benzhydrylsuccinic acid cyclized to 1-trimethoxyphenyl-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic acid. The corresponding ester was formylated, reduced with sodium borohydride, and hydrolyzed to DL-epiisopodophyllic acid. Dehydration furnished DL-β-apopicropodophyllin, which was hydrolyzed to DL-α-apopodophyllic acid. Resolution at this stage with quinine gave α-apopodophyllic acid. Lactonization to α-apopicropodophyllin followed by acid-catalyzed hydration furnished picropodophyllin. Reactions of the isomeric itaconic acid are recorded. Arguments concerning the mode of cyclization of the pertinent benzhydrylsuccinic acids are presented.

Introduction

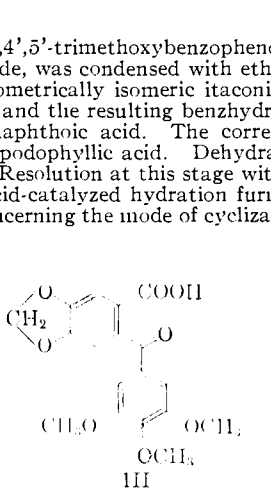
The lignan lactone picropodophyllin (I) has been obtained from several species of *Podophyllum*.[2]



picropodophyllin I



dehydropodophyllotoxin II



III

The more practical and convenient source, however, is through mild, base-catalyzed epimerization[3–6] of

(1) This work was supported by Grants from American Cancer Society (CBC-6), and from National Cancer Institute, U. S. Public Health Service (CY2891).

(2) V. Podwyssotzki, *Ber.*, **15**, 377 (1882); M. V. Nadkarni, J. L. Hartwell, P. B. Maury and J. Leiter, THIS JOURNAL, **75**, 1308 (1953); S. C. Chakravarti and D. P. Chakraborty, *J. Am. Pharm. Assoc.*, **43**, 614 (1954) [*C. A.*, **49**, 569 (1955)]; A. Stoll, J. Renz and A. von Wartburg, *Helv. Chim. Acta*, **37**, 1747 (1954); A. von Wartburg, E. Angliker and J. Renz, *ibid.*, **40**, 1331 (1957); J. Bartek, H. Potěšilová, V. Mašínová and F. Šantavý, *Coll. Czechoslov. Chem. Comm.*, **21**, 392 (1956).