lowed by recrystallization from acetone afforded the 16-isoetianic acid XV, m.p. 264–268°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.23; H, 8.79. Found: C, 68.89; H, 8.67.

D-Homoannulation of IIa.—A solution of 500 mg. of IIa in 20 cc. of toluene was refluxed with 500 mg. of aluminum *t*-butoxide for 3 hours. At the end of this period the toluene was evaporated *in vacuo* and the residue decomposed with 10% aqueous hydrochloric acid. The organic material was extracted with ethyl acetate and ethyl acetate extract, washed with potassium bicarbonate solution and brine. Evaporation of the dry ethyl acetate solution and crystallization of the residue from ether afforded 260 mg. of the 17a-D-homo ketone derivative IIIa, m.p. 210.5–213°; mixed m.p. with an authentic sample of IIIa was not depressed.

RAHWAY, N. J.

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

The Ethoxalylation of 16α,17α-Isopropylidenedioxyprogesterone

BY GEORGE R. ALLEN, JR., AND MARTIN J. WEISS[1]

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Reaction of 16α,17α-isopropylidenedioxyprogesterone (II) with ethyl oxalate under mono-acylation conditions is described. Treatment of the product with one or two molar equivalents of bromine gave 2α-bromo- (III) or 2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI), respectively, in 60–65% yields. Condensation of II at C-21 could not be effected. The 16α,17α-isopropylidenedioxy group inhibits ethoxalylation at C-21. A method for the hydrolytic deacetonation of 16α,17α-isopropylidenedioxysteroids is described.

Recently we reported[2a] that 16α,17α- isopropylidendioxy - 4,9(11) - pregnadiene - 3,20 - dione (I) condenses with ethyl oxalate in the presence of one molar equivalent of sodium methoxide exclusively at C-2.[2b] This preferential acylation at C-2 is not the result of an inability of C-21 to undergo acylation, for a 2,21-bis-ethoxalyl derivative is formed on reaction of I with excess ethyl oxalate in the presence of two molar equivalents of sodium methoxide.[2a] Since progesterone appears to undergo ethoxalylation at C-2 and at C-21 in a relatively indiscriminate manner,[3,4] the very real selectivity (at least 90%) for C-2 observed with I is presumably the result of steric hindrance exerted by the 16α,17α-isopropylidenedioxy function on the acetyl side-chain[8] or, as is less likely, an activating effect of the $\Delta^{9(11)}$-moiety on the Δ^4-3-ketone system. In order to evaluate the influence of these groups on the course of the ethoxalylation reaction, we undertook an investigation of this acylation with 16α,17α-isopropylidenedioxyprogesterone (II).

Reaction of the known 16α,17α-isopropylidenedioxyprogesterone (II)[9] with 1.1 molar equivalents of sodium methoxide and 1.7 molar equivalents of ethyl oxalate[5] for 24 hours gave a sodioethoxalyl derivative and an 8% recovery of II. The free ethoxalyl derivative, for which satisfactory analytical values could not be obtained, resulted on acidification of an aqueous solution of the sodium salt. When the condensation time was decreased to three hours, the ethoxalyl derivative was formed in lower yield, and II was recovered to the extent of 35–47%.

A solution of this ethoxalyl derivative in methanolic potassium acetate was treated with one molar equivalent of bromine. Subsequent deacylation *in situ* of the presumed bromoethoxalyl intermediate by addition of methanolic sodium methoxide gave, in 64% yield, a crystalline monobromo - 16α,17α - isopropylidenedioxyprogesterone. It may be noted that this monobromide was formed in equally good yield when the addition of the sodium methoxide was eliminated. The monobromo derivative of II was formulated as 2α - bromo - 16α,17α - isopropylidenedioxyprogesterone (III), since infrared spectral evidence indicated the presence of a 2α-bromo-Δ^4-3-keto moiety (see below and Table I).[10,11] Confirmation of the 2-bromo structure was obtained on treatment with refluxing collidine to give, in 70% yield, 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene-3,20-dione (VII). The structure of this latter product was established by infrared spectral evidence,[12] polarographic assays and the ultraviolet absorption maxima of its dinitrophenylhydrazone.[13]

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

(2) (a) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959). (b) Apparent preferential ethoxalylation at C-2 has also been observed with 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxyprogesterone [S. Bernstein, J. J. Brown, L. Feldman and N. E. Rigler, *ibid.*, **81**, 4956 (1959)].

(3) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **82**, 1709 (1960).

(4) Apparent selectivity for C-21 has been reported for 11α-hydroxy-, 11β-hydroxy- and 11-keto-progesterone[6] and in the patent literature for 4,16-pregnadiene-3,20-dione.[6] However, in our laboratory attempts to effect preferential ethoxalylation of 11α-hydroxy-Δ^{16}-progesterone and of $\Delta^{9(11),16}$-progesterone were essentially unsuccessful.[7] With the latter compound, under monoethoxalylation conditions, the bulk of the product was the 2,21-bis-ethoxalyl derivative.[7]

(5) 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).

(6) A. H. Nathan and J. A. Hogg, U. S. Patent 2,719,855 (1955); *C. A.*, **50**, 7889b (1956).

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

(8) For a discussion of the steric effect of a 16α,17α-isopropylidenedioxy group on the acetyl side-chain see footnotes 26 and 38 in ref. 2a.

(9) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 3373 (1955).

(10) (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).

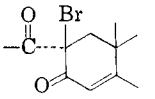
(11) In addition to the spectral evidence for the α-orientation of the bromo substituent in III, it may be noted that the introduction of a 2-bromo substituent *via* an ethoxyalylation procedure makes it probable that this group is so oriented.[2a] Similar considerations have led to the postulation of an α-orientation for certain 2-methyl steroids also prepared *via* a 2-ethoxalyl derivative [J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955)].

(12) *Inter alia* see (a) J. Fried, R. W. Thoma and A. Klingsberg, *ibid.*, **75**, 5764 (1953); (b) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, *ibid.*, **77**, 4781 (1955); (c) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

Quite unexpectedly, it was found that when the same ethoxalyl preparation was treated for 20 minutes with two, instead of one, molar equivalents of bromine, III was formed in 17% yield and a *dibromoketone* resulted in 52% yield. Extension of the reaction time to four hours gave the dibromoketone as the sole product (65% yield). The structure of this dibromide was deduced in the following manner. Inasmuch as monobromination of the ethoxalyl derivative had given a 2α-bromide, it was reasonably assumed that one of the bromines in the dibromoketone was also located at C-2. Secondly, the ultraviolet absorption maximum of the dibromoketone (256 mμ) represented a bathochromic shift of 13 mμ from the maximum shown by the monobromoketone III. This profound effect on the chromophoric system by the second bromine implied its presence in ring A or at C-6[14a]; since treatment of the dibromoketone with refluxing collidine gave in 76% yield a new monobromoketone A (λ_{max} 252 mμ), it was a reasonable conclusion that the second bromine was not located at C-6.[14b] In view of the available evidence it was then considered that the dibromoketone was either the 2,2-dibromide or the 2α,4-dibromide VI. On the assumption that the latter was the more probable structure, selective debromination at C-2 was investigated.[15] Reaction of the dibromide with sodium iodide gave a crude product which was presumed to contain a substantial amount of the 4-bromo-2-iodoketone V. Treatment of the latter with refluxing collidine, a procedure known to effect reductive deiodination of 2-iodo-Δ⁴-3-ketones,[16a] furnished a monobromide in 28% yield. Since this product was not the previously prepared 2α-bromo-16α,17α-isopropylidenedioxyprogesterone (III) and in view of its ultraviolet absorption spectrum (λ_{max} 260 mμ), it was presumed to be 4-bromo-16α,17α-isopropylidenedioxyprogesterone (VIII).[17] Structure VIII was confirmed by ozonolysis which removed C-4 and furnished the bromine-free lactol IV. Moreover, treatment of VIII with lithium chloride in refluxing collidine afforded the 4,6-pregnadiene IX in 23% yield; similar behavior has been previously noted for 4-bromocholestenone.[18] Finally, the 4-bromoketones VI and VIII were prepared by the reaction of III and II, respectively, with bromine in the presence of collidine. It has been previously established that halogenation of a Δ⁴-3-ketone by this procedure yields a 4-halo derivative.[18]

Having established the structure of the dibromide as VI, it was reasonable to assume that the monobromoketone A, which had been obtained from VI on treatment with refluxing collidine, was the 4-bromo-Δ¹,⁴-3-ketone X. Unfortunately, confirmation for this structure could not be obtained from infrared spectral or polarographic evidence. However, structure X was established by partial hydrogenation of monobromoketone A which furnished 4-bromo-16α,17α-isopropylidenedioxyprogesterone (VIII).[19] It is noteworthy that the ultraviolet spectral properties of the 4-bromodieneone X (λ_{max} 252 mμ) and its semicarbazone (λ_{max} 296 mμ) differ from those reported for 4-bromoprednisone (λ_{max} 243 mμ) and its semicarbazone (λ_{max} 275 mμ).[20]

The fact that either monobromoketone III or dibromoketone VI can be obtained from the same ethoxalyl preparation in 65% yield requires that each is derived, at least in part, from a common precursor. This suggested the possibility that III was an intermediate for VI. Consequently, III was treated with one molar equivalent of bromine using the conditions whereby the ethoxalyl derivative had first afforded VI. This treatment was ineffective, and ketone III was recovered to the extent of 92–94% (two experiments). This observation also shows that the dibromide VI does not result from the rearrangement of a 2,2-dibromide, since the latter can only result from the halogenation of III. It is possible that the dibromide VI may be formed by the direct bromination at C-4 of a 2-bromo-2-ethoxalyl derivative such as B, which presumably is an intermediate in the conversion of a 2-ethoxalyl-Δ⁴-3-ketone into a 2α-bromo-Δ⁴-3-ketone. An alternate possibility



B

for the common precursor is a 2,4-bis-ethoxalyl derivative[21]; however, this possibility is considered less likely.[22] Other explanations, dependent upon

(13) L. Dorfman, *Chem. Revs.*, **53**, 85 (1953).

(14) (a) A 2β,6β-dibromo-Δ⁴-3-ketone structure has been reported [B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956)] to show specific absorption at 257 mμ. (b) Preferential dehydrobromination of 2,6-dibromo-2-methyl-4-androstene-3,17-dione by collidine to give 6-bromo-2-methyl-1,4-androstadiene-3,17-dione has been reported by J. Iriarte and H. J. Ringold [*Tetrahedron*, **3**, 28 (1958)]. Moreover, Fieser and co-workers (ref. 10a) have recorded the fact that collidine may react selectively with 2α,6β-dibromocholestenone to give 2α-bromo-4,6-cholestadiene-3-one. However, when each of these 2,6-dibromo-ketones was treated with collidine using conditions comparable to those utilized in the dehydrobromination of our dibromoketone, the corresponding heteroannular Δ¹,⁴,⁶-3-ketone was obtained.

(15) In an initial attempt to effect selective debromination, dibromoketone VI was treated with chromous chloride[16]; from this experiment the bromine-free II was isolated in 73% yield.

(16) (a) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950); (b) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(17) In addition there was isolated from this experiment a 19% yield of monobromoketone A. Presumably this compound originated from unreacted 2α,4-dibromide present in the crude 4-bromo-2-iodoketone preparation. It may be noted that this result is another example of the striking difference in behavior exhibited by 2-bromo- and 2-iodo-3-ketones toward refluxing collidine.[16a]

(18) D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.*, 627 (1956).

(19) A similar partial reduction has been reported for a 4-chloro-Δ¹,⁴-3-ketone [D. N. Kirk and V. Petrow, *ibid.*, 1334 (1958)].

(20) E. P. Oliveto, L. Weber, C. Gerold, M. M. Pechet and E. B. Hershberg, *J. Org. Chem.*, **22**, 1720 (1957).

(21) Base-catalyzed alkylations at C-4 of Δ⁴-3-ketosteroids are well known [(a) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, THIS JOURNAL, **76**, 2852 (1954); (b) F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957); (c) N. W. Atwater, *ibid.*, **79**, 5315 (1957)].

(22) A 2,4-bis-ethoxalyl derivative would have to have been formed initially as a monosodio-Δ⁴-derivative, since the ultraviolet spectra in neutral and alkaline media indicated a Δ⁴-3-keto moiety. For bromination at C-4 to have occurred *via* an ethoxalyl group at this position it is necessary to postulate a shift to a Δ⁵-derivative. In view of the spectral evidence, this shift presumably would have taken place after the ethoxalyl group at C-2 had been converted to a 2-bromo-2-ethoxalyl

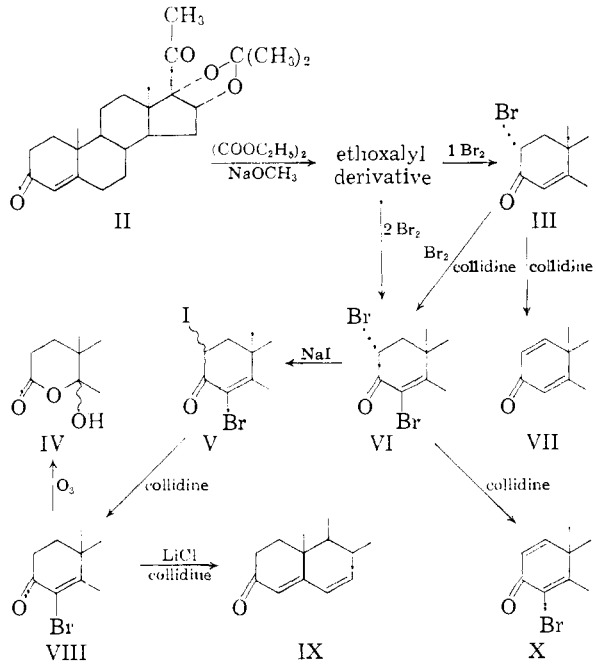
the positive character of the C-2 bromine, are also under consideration. An investigation of the mechanism of this reaction is at present in process in this Laboratory.[23]

Attempts to prepare 2,21-bis-ethoxalyl-16α,17α-isopropylidenedioxyprogesterone were apparently unsuccessful.[24] The product obtained was a crude, amorphous ethoxalyl derivative which on treatment with bromine gave monobromoketone III and/or dibromoketone VI. Although these ketones were formed in relatively low yields, there was no evidence for the formation of the desired 2,21-dibromo derivative. These results are in contrast to those observed with the 9-dehydro analog of II from which a 2,21-dibromide was obtained in 56% yield.[2a]

Thus, it may be concluded that 16α,17α-isopropylidenedioxyprogesterone (II) reacts with ethyl oxalate preferentially at C-2 or, as is less likely, at C-2 and C-4. In view of these results and those cited above *it would appear that the 16α,17α-isopropylidenedioxy grouping inhibits acylation at C-21.*

It is of interest to indicate certain qualitative differences noted in the infrared spectra of the various halogenated derivatives prepared in this investigation (see Table I). The introduction of a 2α-bromo substituent into 16α,17α-isopropylidenedioxyprogesterone (II) produces the expected shift in position and lowering of intensity of the 3-carbonyl absorption band.[19] The same effects are noted upon the introduction of a 4-bromo group into II. However, in contrast to the saturated ring A series,[25] introduction of a second bromine atom (equatorially substituted) at C-2 in the 4-bromo compound VIII fails to produce an additional shift in the position of the 3-carbonyl absorption band. This observation is analogous to the finding that the introduction of a 4-bromo substituent into a 2-bromo-Δ^1-3-ketone causes only a slight shift (5 cm.$^{-1}$) in the position of the carbonyl band.[12c] The introduction of a 4-bromo substituent into 16α,17α-isopropylidenedioxyprogesterone (II) and its 1-dehydro derivative VII also effects the position of the double bond absorption band(s). Introduction of bromine at C-4 into II displaces the position of this absorption to a lower frequency by about 36 cm.$^{-1}$. The dieneone VII exhibits the expected double bond absorption at 1637 and 1611 cm.$^{-1}$,[12] whereas its 4-bromo derivative shows only a *single* absorption maximum at 1601 cm.$^{-1}$. This observation indicates that the higher frequency band in VII owes its origin to the 4-ene and that substitution by bromine on the double bond shifts the position of its absorption maximum to a lower frequency by about 36 cm.$^{-1}$.

Finally, during this investigation it was found that deacetonation of certain 16α,17α-isopropylidenedioxysteroids could be effected conveniently with 60% formic acid or 45% acetic acid.[26] Thus, treatment of 16α,17α-isopropylidenedioxyprogesterone (II) with 60% formic acid on the steam-bath for 30 minutes gave 16α,17α-dihydroxyprogesterone in 63% yield; it may be noted that Petrow and his co-workers reported that compound I was recovered essentially unchanged after refluxing for 2.5 hours with 70% acetic acid.[9,27] Dieneone VII gave 16α,17α-dihydroxy-1,4-pregnadiene-3,20-dione in 45% yield when treated with 60% formic acid, whereas this diol was isolated in only 26% yield when hydrolysis was attempted with 45% acetic acid for six hours. However, the same acetic acid treatment when applied to 4-bromo-16α,17α - isopropylidenedioxy - 1,4 - pregnadiene-3,20-dione (X) gave the corresponding diol in 50% yield. In the above examples the diols were reconverted into the original isopropylidene derivatives, thus precluding any rearrangement during or subsequent to the hydrolysis.



Acknowledgment.—We are indebted to Mr. Anthony Pellicano for the large-scale preparation of

or a 2-bromo group. Thus, in considering a 2,4-bis-ethoxalyl precursor it must be assumed that acetate at 0° will catalyze the required shift of the double bond. This behavior must be contrasted with what would have to be the ability of the 4-ethoxalyl group to undergo facile cleavage under almost the same conditions, since it has been demonstrated that the ethoxalyl precursor after monobromination and treatment with acetate at room temperature for about 30 minutes affords a 60% yield of monobromoketone III.

(23) Pertinent to this problem is the fact that 2-ethoxalyl-16α,17α-isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XI) on treatment with two molar equivalents of bromine gave, in 83% yield, the corresponding 2α-bromo derivarive; formation of a dibromide was not observed. Reaction of XI with one molar equivalent of bromine gave the same monobromide in 95% yield.[2a]

(24) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman [THIS JOURNAL, **77**, 4438 (1955)] report the preparation of 2,21-ois-ethoxalyl-11-ketoprogesterone. For 2,21-bis-ethoxalylprogesterone see ref. 3.

(25) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *ibid.*, **74**, 2828 (1952).

(26) It was independently observed by L. L. Smith and M. Marx of the Chemical Process Improvement Department of these laboratories that 60% formic acid converted 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione into the corresponding 16α,17α-glycol. Similar results have since been reported by J. S. Mills and co-workers, THIS JOURNAL., **81**, 1264 (1959).

(27) Fried and his co-workers [*ibid.*, **80**, 2338 (1958)] have also recorded the resistance of certain steroidal acetonides toward hydrolysis with mineral acid, and results from these laboratories[2] have further illustrated the difficulty in hydrolyzing such ketals.

TABLE I

INFRARED SPECTRA OF 16α,17α-ISOPROPYLIDENEDIOXYPROGESTERONE (II), 16α,17α-ISOPROPYLIDENEDIOXY-1,4-PREGNADIENE-3,20-DIONE (VII) AND CERTAIN OF THEIR BROMINATED DERIVATIVES[a]

Compound	3-Carbonyl, cm.$^{-1}$	Δν on bromination	C=C, cm.$^{-1}$	Δν on bromination
16α,17α-Isopropylidenedioxyprogesterone (II)	1684		1620	
2α-Bromo- (III)	1694[b]	10	1625	
4-Bromo- (VIII)	1697[b]	13	1584	~36
2α,4-Dibromo- (VI)	1694[b]	10	1627	
16α,17α-Isopropylidenedioxy-1,4-pregnadiene-3,20-dione (VII)	1675		1637, 1611	
4-Bromo- (X)	1667		1601	~36

[a] All spectra are for pressed potassium bromide disks. [b] The intensity of this band is less than that of the 20-carbonyl band.

certain intermediates. Analyses were performed by Mr. L. Brancone and his staff and spectral and optical rotation determinations were made by Mr. W. Fulmor and his associates. Polarographic assays were kindly determined and interpreted by Dr. M. Halwer of the Chemical Process Improvement Department of these laboratories.

Experimental[28]

16α,17α-Isopropylidenedioxyprogesterone (II) was prepared as described previously[9] in 88–89% yield. It was obtained as flat white needles, m.p. 206–208°, after recrystallization from benzene–petroleum ether. The product had $[\alpha]^{25}D$ +121° (*c* 2.1, methanol), +132° (*c* 1.4, chloroform); λ_{max} 240 mμ (ε 17,300); λ_{max} 5.82, 5.94, 6.18, 7.26, 7.29 μ. Reported[9] values are m.p. 210° and $[\alpha]^{25}D$ +137° (*c* 0.7, chloroform).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.66; H, 9.00.

A solution of 0.386 g. (1.0 mmole) of the above product and 0.218 g. (1.1 mmoles) of 2,4-dinitrophenylhydrazine in 5 ml. of glacial acetic acid was warmed on the steam-bath for 2 minutes. The solid which separated was recrystallized from chloroform–ethanol to give the 3-(2,4-dinitrophenylhydrazone) as orange needles, m.p. 282–283° dec., $[\alpha]^{25}D$ +217° (*c* 0.52, chloroform); λ_{max} 218, 255, 389 mμ (ε 21,000, 20,100, 31,600).

Anal. Calcd. for $C_{30}H_{38}N_4O_7$: N, 9.89. Found: N, 9.35.

Condensation of 16α,17α-Isopropylidenedioxyprogesterone (II) with Ethyl Oxalate, Using 1.1 Moles of Sodium Methoxide.—A solution of 22 ml. of 1 *N* methanolic sodium methoxide in 90 ml. of benzene was distilled until 65 ml. of distillate was collected. The cooled residual mixture was treated with 4.82 g. (0.034 mole, 4.6 ml.) of ethyl oxalate with magnetic stirring; all of the solid dissolved. To this solution was added a solution of 7.72 g. of 16α,17α-isopropylidenedioxyprogesterone (II) in 50 ml. of benzene. The resulting orange solution was stirred at room temperature for 21 hours. The solvent was removed, and the residual gum was triturated with 100 ml. of dry ether to give a gelatinous solid that was collected by filtration. This material was dissolved in 250 ml. of water to give a slightly turbid, orange solution which was filtered through a bed of Celite[29] diatomaceous earth. The filtrate was acidified with 5% hydrochloric acid solution; the precipitated amorphous, ivory-colored solid was collected by filtration to give 6.956 g. (72% yield when calculated as a monoethoxalyl derivative) of material which had λ_{max} 242 ($E^{1\%}_{1cm}$ 246), 330 mμ ($E^{1\%}_{1cm}$ 95), λ^{NaOH}_{max} 251 ($E^{1\%}_{1cm}$ 240), 335 mμ ($E^{1\%}_{1cm}$ 100),[30] and λ_{max} 5.74, 5.82, 6.10, 7.21, 7.25, 7.92 (broad) μ.

Anal. Calcd. for $C_{28}H_{28}O_7$ (mono): C, 69.11; H, 7.87. Calcd. for $C_{32}H_{42}O_{10}$ (bis): C, 65.51; H, 7.22. Found: C, 66.64, 66.73; H, 7.74, 7.96.

The ether filtrate from the removal of the gelatinous solid was taken to dryness, and the residue was dissolved in about 15 ml. of benzene. This solution was adsorbed onto a column prepared from silica gel[31] (column size: 1.6 × 16.5 cm.). The column was eluted with 20% ether-in-benzene solution; 250-ml. fractions were collected. The solid contained in the first fraction was recrystallized from benzene–petroleum ether to give 0.555 g. (7% recovery) of **16α,17α-isopropylidenedioxyprogesterone** (II) as flat, white needles, m.p. 206–208° alone or when mixed with an authentic sample.

When the time of reaction was decreased to 3 hours, the yield of ethoxalyl derivative was 51 and 47%, whereas starting material was recovered to the extent of 35 and 47%, respectively (two experiments).

Bromination Experiments with the Ethoxalyl Derivative Formed under Monoacylation Conditions. A. Treatment with One Molar Equivalent of Bromine.—A mixture of 0.730 g. (1.5 mmoles if calculated as a monoethoxalyl derivative) of ethoxalyl derivative A, 0.294 g. (3.0 mmoles) of potassium acetate and 12 ml. of methanol was chilled in an ice-bath with magnetic stirring. A 0.58 *M* solution of bromine in carbon tetrachloride was added dropwise until a water-white solution resulted; this required 2.9 ml. of the solution (equivalent to 1.68 mmoles). An additional 2–3 drops of the bromine solution resulted in the presistence of bromine color for 1–2 minutes. The addition required 15 minutes, and all of the solid dissolved during the addition. The solution was then allowed to stir for another 5 minutes and concentrated on the steam-bath to remove the carbon tetrachloride. Water was added slowly until a faint turbidity persisted. The solution was chilled, and the walls of the container were scratched. The crystals that were deposited were recrystallized from acetone–petroleum ether to give 0.444 g. (62% yield) of **2α-bromo-16α,17α-isopropylidenedioxyprogesterone** (III) as a white solid, m.p. 193–195° dec., $[\alpha]^{25}D$ +118° (*c* 1.1, methanol), λ_{max} 243 mμ (ε 11,100), and λ_{max} 5.85, 5.92 (less intense than 5.85 band), 6.16, 7.24, 7.28 μ.

Anal. Calcd. for $C_{24}H_{33}BrO_4$: C, 61.93; H, 7.15; Br, 17.17. Found: C, 61.96; H, 7.40; Br, 17.31.

This material showed a tendency to separate as a gel from acetone–petroleum ether; however, this gel could be dried to give material with acceptable analytical values. On occasion it separated from acetone–petroleum ether as white needles, m.p. 187–189° dec. Although the infrared spectra of the two forms were identical, completely satisfactory analytical values could not be obtained for the needle form.

Anal. Calcd. for $C_{24}H_{33}BrO_4$: C, 61.93; H, 7.15; Br, 17.17. Found: C, 62.41; H, 7.26; Br, 17.65.

In a preliminary experiment the addition of bromine was followed by the addition of a molar equivalent of sodium methoxide. From this experiment the bromoketone III was isolated in 64% yield. Subsequent to the experiment detailed above the ketone III was obtained in 60% yield; in this experiment heat was not used in the removal of the carbon tetrachloride.

B. **Treatment with Two Molar Equivalents of Bromine.**—A mixture of 1.460 g. (3.0 mmoles if calculated as a monoethoxalyl derivative) of ethoxalyl derivative A, 0.588 g. of potassium acetate and 25 ml. of methanol was chilled in an ice-bath with continuous stirring. This mixture was treated by dropwise addition over 14 minutes with 7.3 ml. of a 0.82 *M* solution of bromine in carbon tetrachloride; all of the solid dissolved during the addition. The yellow solution

(28) All melting points were determined in a capillary tube and are uncorrected. The ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer. The infrared spectra (pressed potassium bromide disk) were determined with a Perkin–Elmer spectrophotometer (model 21). Optical rotations were determined in a 1-dm. semi-micro tube, and all evaporations were carried out under reduced pressure unless otherwise specified. Except where otherwise noted, the petroleum ether used was that fraction boiling at 60–70°.

(29) Celite is Johns–Manville's registered trademark for diatomaceous silica products.

(30) For the base spectrum a methanolic solution was diluted 1:1 with 0.1 *N* sodium hydroxide solution.

(31) Davison Silica Gel, mesh size 200, a product of the Davison Chemical Co., was used as such.

was stirred for an additional 6 minutes, and 6.0 ml. of a 1 *N* solution of sodium methoxide in methanol was then added. A precipitate of white solid separated immediately; the mixture was filtered, and the solid was washed with water to give 0.881 g. (52% yield) of **2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI)**, as white crystals, m.p. 164–165° dec. (gas bubbles). A mixture of this material with an analytical specimen (see below) melted at 167–170° dec. (gas bubbles). Moreover, the infrared spectrum of this material was identical with that of an analytical sample.

The filtrate was concentrated to a volume of about 10 ml. and diluted with water. The amorphous solid was dissolved in the minimum amount of benzene and sorbed onto a column that was prepared from 60 g. of silica gel[31] (column size: 2.8 × 17 cm.). The column was washed with a 5% ether-in-benzene solution; 125-ml. fractions were collected. The material contained in fractions 5–10 was combined and recrystallized from acetone–petroleum ether to give 0.235 g. (17% yield) of **2α-bromo-16α,17α-isopropylidenedioxyprogesterone** (III) as a white solid, m.p. 188–190° dec. A mixture of this material with the analytical sample melted at 189–193° dec.; moreover, the infrared spectra of this material and that obtained previously were identical.

In a second experiment the solution of the potassium acetate, ethoxalyl derivative A, methanol and the bromine in carbon tetrachloride was allowed to stir for 4 hours before the addition of the methanolic sodium methoxide. In this manner a 65% yield of the dibromoketone VI was obtained. Chromatography of the amorphous material in the mother liquor failed to give any of the bromoketone III.

16α,17α-Isopropylidenedioxy-1,4-pregnadiene-3,20-dione (VII).—A solution of 0.935 g. (2.0 mmoles) of 2α-bromo-16α,17α-isopropylidenedioxyprogesterone (III) and 5 ml. of redistilled collidine was allowed to reflux during 45 minutes; the solution became quite black in color and solid separated when the reflux temperature was reached. The cooled mixture was diluted with 10 ml. of ether and filtered. The residue was washed with two 10-ml. portions of ether. The combined filtrate and washings were diluted with an additional 20 ml. of ether, and the ethereal solution was washed with 10% sulfuric acid solution (2 × 50 ml.) and water (50 ml.) and then dried over magnesium sulfate. The solid obtained on removal of the ether was recrystallized from ether to give 0.564 g. (74% yield) of white rods and prisms, m.p. 202–204°. An additional recrystallization from ether did not alter this melting range. The material had $[\alpha]^{25}D$ +83° (*c* 1.1, methanol), λ_{max} 243 mμ (ε 15,200), and λ_{max} 5.82, 5.97, 6.11, 6.21, 7.24, 7.28 μ.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.62; H, 8.43.

In polarographic assays a solution of VII (*c*, 1 mg./ml.) in 90% methanol and 0.1 *N* tetramethylammonium bromide gave a single wave with a half-wave potential of −1.04 volts, whereas its Δ⁴-3-keto counterpart II under the same conditions gave a single wave with a half-wave potential of −1.20 volts.

16α,17α-Isopropylidenedioxy-1,4-pregnadiene-3,20-dione 3-(2,4-Dinitrophenylhydrazone).—A solution of 0.100 g. (0.26 mmole) of 16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (VII) and 0.060 g. (0.30 mmole) of 2,4-dinitrophenylhydrazine in 3 ml. of glacial acetic acid was allowed to reflux for 4 hours. The solution was diluted with 15 ml. of methanol and poured into 50 ml. of water–cracked ice. The amorphous solid was collected by filtration to give 85 mg. of solid which was dissolved in 50 ml. of 15% chloroform-in-benzene and adsorbed onto 20 g. of silica gel[31] (column size: 1.5 × 18 cm.). The column was washed with 100 ml. of 15% chloroform-in-benzene solution, 200 ml. of 25% chloroform-in-benzene solution, and 200 ml. of 40% chloroform-in-benzene solution; these washings were discarded. The column was then washed with 50% chloroform-in-benzene solution; 50 ml. fractions were collected. The material in fractions 6–10 was combined and crystallized from chloroform–methanol to give 52 mg. of deep orange crystals, m.p. 245–249° dec., $[\alpha]^{25}D$ +129° (*c* 0.11, chloroform); λ_{max} 255, 303, 396 mμ (ε 16,900, 10,700, 37,000).

Anal. Calcd. for $C_{30}H_{36}N_4O_7$: N, 9.92. Found: N, 9.48.

Monobromoketone A [4-Bromo-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (X)].—A mixture of 0.544 g. (1.0 mmole) of 2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI) and 5 ml. of redistilled collidine was allowed to reflux for one hour. The mixture was never free of undissolved solid; however, the originally water-white mixture was dark at the end of the reflux period. Xylene (5 ml.) was added, and the mixture was allowed to reflux for 3 hours. The hot mixture was filtered, and the filtrate was allowed to cool. The residual solid was washed with three 10-ml. portions of ether and dried to give 0.192 g. (95% yield) of collidine hydrobromide as a gray solid. The ether washings and the filtrate were combined, and this solution was diluted with an additional 50 ml. of ether. The ethereal solution was washed with 10% sulfuric acid solution (2 × 50 ml.) and water (2 × 50 ml.), dried over magnesium sulfate, and taken to dryness. The residue was recrystallized from acetone–petroleum ether to give 0.352 g. (76% yield) of hard crystals, m.p. 218–221°. An additional recrystallization gave hard crystals, m.p. 221–223°, $[\alpha]^{25}D$ +22.8° (*c* 1.1, chloroform), λ_{max} 252 mμ (ε 16,500); λ_{max} 5.85, 6.00, 6.25, 7.24, 7.28 μ.

Anal. Calcd. for $C_{24}H_{31}BrO_4$: C, 62.20; H, 6.74; Br, 17.25. Found: C, 62.15; H, 6.90; Br, 17.14.

A slurry of 0.463 g. (1.0 mmole) of the above product in 25 ml. of methanol was treated with a solution of 0.790 g. (7.0 mmoles) of semicarbazide hydrochloride and 0.605 g. (7.7 mmoles, 0.4 ml.) of pyridine in 4 ml. of water. The solution was allowed to reflux for 20 hours. After 18 hours had elapsed, solid began to separate. The cooled mixture was filtered to furnish 0.487 g. of white crystals, m.p. 230–235° (gas). A sample was recrystallized from methanol to give the 3-semicarbazone as white needles, m.p. 230–232° (gas); λ_{max} 250, 296 mμ (ε 9,250, 32,200).

Anal. Calcd. for $C_{25}H_{34}BrN_3O_4$: Br, 15.42; N, 8.11. Found: Br, 15.67; N, 7.93.

The bromoketone X was recovered to the extent of 91% after treatment with potassium acetate in refluxing isobutyl methyl ketone for 24 hours. Moreover, the ketone X was recovered essentially unchanged after treatment with either lithium chloride in refluxing collidine (23 hours) or chromous chloride.

In polarographic assays a solution of X (*c* 1 mg./ml.) in 90% methanol and 0.1 *N* tetramethylammonium bromide gave *two* waves of equal intensity with half-wave potentials of −1.03 and −1.32 volts, whereas a solution of the 4-bromo-Δ⁴-3-ketone VIII exhibited a *single* wave with a half-wave potential of −1.27 volts under the same conditions.

Reduction of 2α,4-Dibromo-16α,17α-isopropylidenedioxyprogesterone with Chromous Chloride.—A suspension of 0.272 g. (0.5 mmole) of 2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI) in 20 ml. of glacial acetic acid was swept thoroughly with carbon dioxide. The mixture was treated with 25 ml. of 0.4 *N* chromous chloride solution and kept under a carbon dioxide atmosphere for 20 minutes. Filtration of the reaction mixture gave 0.078 g. (29% recovery) of the starting material, m.p. 168–170° dec. alone or when mixed with an authentic specimen.

The green filtrate was diluted with 50 ml. of water and extracted with methylene chloride (2 × 50 ml.). The combined organic solutions were washed with water (50 ml.), saturated sodium bicarbonate solution (2 × 50 ml.) and finally with water (50 ml.). The organic solution was dried over magnesium sulfate and taken to dryness to give a solid residue which was recrystallized from acetone–petroleum ether to give 0.100 g. (73% yield based on unrecovered starting material) of flat, white needles, m.p. 206–208° alone or when mixed with an authentic sample of **16α,17α-isopropylidenedioxyprogesterone (II)**, $[\alpha]^{25}D$ +120° (*c* 1.0, methanol), λ_{max} 240 mμ (ε 17,300); its infrared spectrum was identical with that of an authentic sample.

4-Bromo-16α,17α-isopropylidenedioxyprogesterone (VIII). A. From 2α,4-Dibromo-16α,17α-isopropylidenedioxyprogesterone (VI).—A solution of 0.485 g. (0.9 mmole) of 2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI), 0.600 g. of sodium iodide and 100 ml. of acetone was allowed to reflux during 6 hours. The solution had deposited a small amount of solid and an iodine-like color had developed. The mixture was diluted with sodium thiosulfate solution, chilled and filtered to give 0.420 g. of pink-colored solid, m.p. 145–150° dec. after previous darkening.

A solution of 0.250 g. of this material in 5 ml. of collidine was allowed to reflux for 30 minutes. The solution became black when the reflux temperature was reached, and a dark solid separated from the solution. The mixture was sus-

pended in 50 ml. of methylene chloride, and this suspension was washed with 10% sulfuric acid solution (2 × 50 ml.) and water (2 × 50 ml.). The organic solution was dried over magnesium sulfate and taken to dryness. The residue was dissolved in 10 ml. of petroleum ether–benzene (1:1), and this solution was adsorbed onto 3 g. of neutral alumina[32] (column size: 0.6 × 20 cm.). The column was washed with petroleum ether–benzene (1:1); 25-ml. fractions were collected.

Fractions 1–3 were combined and the solid contained therein was recrystallized from acetone–petroleum ether to give 46 mg. (19%, adjusted yield from V) of **4-bromo-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (X)**, m.p. 219–221°. A mixture with an authentic sample melted at 219–222°. The material had λ_{max} 252 mμ (ε 15,700) and its entire infrared spectrum was identical with that of an analytical sample.

Fractions 4–12 were taken to dryness and the solids therein were combined and recrystallized from methanol to give 69 mg. (28%, adjusted yield from V) of **4-bromo-16α,17α-isopropylidenedioxyprogesterone** (VIII), m.p. 227–228° dec. alone or when mixed with a sample prepared by method B. The material had $[\alpha]^{24}D$ +149° (*c* 2.1, chloroform), λ_{max} 260 mμ (ε 11,400) and its infrared spectrum was identical with that of a sample obtained by method B.

B. **From 16α,17α-Isopropylidenedioxyprogesterone.**—A solution of 3.86 g. (0.010 mole) of 16α,17α-isopropylidenedioxyprogesterone (II), 40 ml. of propylene oxide and 10 ml. of a 1 *M* bromine in acetic acid solution was stored at −20° in the dark for 20 hours.[18] The solution was dissolved in 100 ml. of methylene chloride and the organic solution was washed with water (100 ml.), sodium thiosulfate solution (100 ml.), saturated sodium bicarbonate solution (100 ml.) and finally again with water (100 ml.). The organic solution was then dried over magnesium sulfate and taken to dryness. The solid residue was dissolved in 30 ml. of petroleum ether–benzene (1:1) and this solution was adsorbed onto 11 g. of alkaline alumina[32] (column size: 0.9 × 16 cm.). The column was then washed with petroleum ether–benzene (1:1); 125-ml. fractions were collected. The material eluted in fraction three was recrystallized from acetone–petroleum ether to give 1.75 g. (38% yield) of white needles, m.p. 229–230° dec., $[\alpha]^{24}D$ +155° (*c* 2.0, chloroform), λ_{max} 260 mμ (ε 12,000); λ_{max} 5.81, 5.90, 6.32, 7.24, 7.26, 8.25, 9.55 μ.

Anal. Calcd. for $C_{24}H_{33}BrO_4$: C, 61.93; H, 7.15; Br, 17.17. Found: C, 61.90; H, 7.49; Br, 17.08.

When ether—collidine was substituded for propylene oxide, the yield of the bromo compound dropped to 32%.

4-Bromo-16α,17α-isopropylidenedioxyprogesterone was recovered to the extent of 92% after treatment with chromous chloride.

When this ketone was treated with 2,4-dinitrophenylhydrazine in acetic acid on the steam-bath for 3 minutes, orange crystals separated. This material was recrystallized twice from chloroform–ethanol to give orange needles, m.p. 290–292° dec., λ_{max} 378 mμ ($E^{1\%}_{1cm}$ 500). Analyses showed that a portion of the bromine was removed during this brief treatment.

Anal. Calcd. for $C_{30}H_{37}BrN_4O_7$: Br, 12.48; N, 8.68. Found: Br, 8.67, 8.75; N, 8.47, 8.79.

5ε-Hydroxy-16α,17α-isopropylidenedioxy-4-oxapregnane-3,20-dione (IV).—A solution of 0.930 g. (2.0 mmoles) of 4-bromo-16α,17α-isopropylidenedioxyprogesterone (VIII) in 40 ml. of ethyl acetate–acetic acid (1:1) was chilled to −10° in a salt–ice-bath. Ozone (4.2 molar equivalents) was introduced. After the solution was treated with 5 ml. of water and 0.5 ml. of 30% hydrogen peroxide, it was allowed to stand at room temperature for 21 hours.

The solution was diluted with 100 ml. of ether and washed with water (9 × 100 ml.). The ethereal solution was then extracted with 0.5 *N* sodium hydroxide solution (3 × 50 ml.), and the combined alkaline extracts were acidified with 5% hydrochloric acid solution. The resulting aqueous mixture was extracted with ether (2 × 100 ml.), and the combined ethereal solutions were washed with water (100 ml.) and then with a saturated sodium chloride solution. The solution was dried over magnesium sulfate, and the solvent was removed to give a gummy residue which on crystallization from ether–petroleum ether gave 0.584 g. of white crystals, m.p. 180–187°. Recrystallization (3X) from acetone–petroleum ether gave 0.516 g. (62% yield) of white prisms, m.p. 202–204°. This material gave a negative Beilstein test, and had $[\alpha]^{24}D$ +62° (*c* 1.0, methanol); λ_{max} 230 (ε 970), 297 mμ (ε 750); λ_{max} 3.12, 5.73, 5.82, 7.19, 7.24 μ; and $\lambda^{KBr-NaOH}_{max}$ 2.95 (broad), 5.85, 6.35, 7.30 (broad) μ.

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 67.95; H, 8.43. Found: C, 67.57; H, 8.43; H_2O (Karl Fischer), 0.0.

16α,17α-Isopropylidenedioxy-4,6-pregnadiene-3,20-dione (IX).—A mixture of 1.000 g. (2.15 mmoles) of 4-bromo-16α,17α-isopropylidenedioxyprogesterone (VIII), 0.360 g. (8.5 mmoles) of anhydrous lithium chloride and 10 ml. of collidine was allowed to reflux for two hours. The mixture was never free of undissolved solid, but when reflux temperature was reached additional solid separated and the mixture became darker in color. The cooled mixture was filtered after dilution with 5 ml. of ether, and the residue was washed thoroughly with 50 ml. of ether. The combined ethereal solutions were washed with 10% sulfuric acid solution (2 × 50 ml.) and water (50 ml.), dried over magnesium sulfate and taken to dryness. The residue was dissolved in the minimum necessary amount of benzene–petroleum ether (1:1) and adsorbed onto a column prepared from 10 g. of neutral alumina[32] (column size: 0.9 × 14 cm.). The column was washed with benzene–petroleum ether (1:1); 50 ml. fractions were collected. The material contained in fractions 1–5 was combined and recrystallized from acetone–petroleum ether to give 0.189 g. (23% yield) of crystals, m.p. 211–214°. One additional recrystallization raised the melting range to 214–216°, $[\alpha]^{25}D$ +84° (*c* 1.30, chloroform), λ_{max} 282 mμ (ε 23,800); λ_{max} 5.85, 6.00, 6.17, 6.31, 7.24, 7.28 μ.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.92; H, 8.39. Found: C, 75.02; H, 8.19.

Conversion of 2α-Bromo-16α,17α-isopropylidenedioxyprogesterone (III) into 2α,4-Dibromo-16α,17α-isopropylidenedioxyprogesterone (VI).—A solution of 0.755 g. (1.62 mmoles) of 2α-bromo-16α,17α-isopropylidenedioxyprogesterone (III) in 15 ml. of ether and 5 ml. of collidine was treated with 6.5 ml. of 1 *M* bromine in acetic acid solution and allowed to stand in the dark at room temperature for 50 hours. The resulting mixture was distributed between 75 ml. of methylene chloride and 75 ml. of water. The organic solution was washed successively with 50 ml. of 5% hydrochloric acid solution, 50 ml. of saturated sodium bicarbonate solution, 50 ml. of saturated sodium thiosulfate solution and 50 ml. of water. The organic layer was taken to dryness after drying over magnesium sulfate to give a residue which crystallized when triturated with 20 ml. of ether. The solid was recrystallized from benzene–petroleum ether to give 0.508 g. (58% yield) of crystals, m.p. 168–170° dec. alone or when mixed with the dibromoketone prepared by bromination of the ethoxalyl derivative. To decolorize this material it was dissolved in benzene and adsorbed onto a column prepared from 15 g. of silica gel[31] (column size: 1.4 × 14.5 cm.). The column was eluted with a 3% ether-in-benzene solution; 100-ml. fractions were collected. The material contained in fractions 1–4 was combined and recrystallized from benzene–petroleum ether to give 0.458 g. of white prisms, m.p. 170–172° dec., λ_{max} 255 mμ (ε 13,100) and $[\alpha]^{25}D$ +23.8° (*c* 1.05, chloroform); its infrared spectrum was identical with that of the dibromoketone prepared from the ethoxalyl derivative.

Catalytic Hydrogenation of 4-Bromo-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (X).—A mixture of 0.926 g. (2.0 mmoles) of bromodieneone X and 80 mg. of 5% palladium-on-barium carbonate catalyst in 80 ml. of methanol was magnetically stirred under an atmosphere of hydrogen until one molar equivalent of the gas was consumed. The mixture was filtered, and the solvent was removed from the filtrate. Trituration of the gummy residue with ether gave 162 mg. of water-soluble, non-ultraviolet-absorbing inorganic halide; this material was discarded. Concentration of the ether filtrate gave 0.120 g. of crude starting material as needles, m.p. 192–215° dec. Recrystallization of this material from acetone–petroleum ether gave needles, m.p. 215–218°, λ_{max} 252 mμ (ε 15,700). The infrared spectrum of the material was the same as that of the starting material, and a mixture of this material with the starting ketone (m.p. 221–223°) melted at 215–218°.

(32) A product of M. Woelm Eschwege and distributed in this country by Alupharm Chemicals.

The ether was removed from the reaction filtrate, and the residue was dissolved in the minimum quantity of benzene–petroleum ether (1:1) and adsorbed onto a column prepared from 6 g. of neutral alumina[32] and petroleum ether (column size: 0.6 × 20 cm.). The column was eluted with benzene–petroleum ether (1:1), 10-ml. fractions being collected. Fractions 1–4 were combined and the material contained therein was crystallized from acetone–petroleum ether. Two recrystallizations from this solvent pair gave 56 mg. of needles, m.p. 212–214°, λ_{max} 252 mμ (ε 13,400). A mixture of this material with starting ketone X melted at 212–215°, and its infrared spectrum was essentially the same as that of the starting material. However, the appearance of a shoulder at 5.88 μ in its spectrum indicated the presence of an impurity.

Fractions 5–11 were combined and taken to dryness. The residual gum crystallized upon seeding with 4-bromo-16α,17α-isopropylidenedioxyprogesterone (VIII). This material was recrystallized four times from acetone–petroleum ether to give 0.213 g. (22% yield) of needles, m.p. 227–229° dec. alone or in mixture with a sample of VIII prepared from II (see above). The material had λ_{max} 259 mμ (ε 10,700) and an infrared spectrum which was identical with that of a sample of VIII which was prepared from II.

Condensation of 16α,17α-Isopropylidenedioxyprogesterone with Ethyl Oxalate, Using 2.2 Moles of Sodium Methoxide.—A solution of 22 ml. of 1 *N* methanolic sodium methoxide in 100 ml. of benzene was distilled until 80 ml. of distillate was collected. The cooled residual mixture was treated with 4.82 g. (0.034 mole, 4.6 ml.) of ethyl oxalate with magnetic stirring; all of the solid dissolved. To this solution was added 3.86 g. (0.010 mole) of 16α,17α-isopropylidenedioxyprogesterone (II), 10 ml. of benzene being used to aid in the transfer. The resulting orange solution was stirred at room temperature for 24 hours. The solution was diluted with 150 ml. of ether; an amorphous solid separated. The mixture was stirred at room temperature for one hour and filtered to give 5.26 g. of amorphous sodio derivative. The filtrate was taken to dryness, and the residue was triturated with ether to give 0.781 g. of crude sodio derivative. The combined solids were dissolved in 300 ml. of water to give a turbid, orange solution which was filtered through a bed of Celite. The clear orange filtrate was acidified with 5% hydrochloric acid solution, and the precipitated amorphous solid was collected by filtration to give 3.417 g. of ethoxalyl derivative (57% yield calculated as a bis-derivative and 70% yield calculated as a mono-derivative), λ_{max} 252 mμ ($E^{1\%}_{1cm}$ 175) and 310 mμ ($E^{1\%}_{1cm}$ 145); λ^{NaOH}_{max} 252 mμ ($E^{1\%}_{1cm}$ 230), 310 mμ (shoulder) ($E^{1\%}_{1cm}$ 155) and 348 mμ ($E^{1\%}_{1cm}$ 192)[30]; λ_{max} 5.73, 5.82 (more intense than 5.73 band), 6.11, 6.95, 8.90 μ (broad).

Anal. Calcd. for $C_{32}H_{42}O_{10}$ (bis): C, 65.51; H, 7.22. Found: C, 65.77, 65.77; H, 7.41, 7.47.

Bromination of the Ethoxalyl Derivative Formed under Bis-acylation Conditions.—To a solution of 3.92 g. (0.040 mole) of potassium acetate in 50 ml. of methanol was added 3.86 g. (0.6 mmole calculated as a bis-ethoxalyl derivative) of ethoxalyl derivative (described immediately above) with magnetic stirring. The resulting solution was chilled in an ice-bath and treated by dropwise addition over a period of 45 minutes with 23 ml. of 0.87 *M* bromine in carbon tetrachloride solution. The resulting mixture was stirred for an additional 10 minutes, and treated with 20 ml. of 1 *N* methanolic sodium methoxide. The mixture was filtered and the water-soluble residue was discarded. The filtrate was concentrated to a volume of about 25 ml. and filtered to give 2.800 g. of solid which was dissolved in benzene and adsorbed onto a column prepared from 300 g. of silica gel[31] (column size: 4.8 × 32 cm.). The column was washed with 1500 ml. of a 3% ether-in-benzene solution and this washing was discarded. The column was then eluted with a 5% ether-in-benzene solution, 500-ml. fractions being collected. Fractions 3–7 were combined and the solid contained therein was recrystallized from benzene–petroleum ether to give 0.697 g. of **2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone VI**) as white prisms, m.p. 169–170° dec. Two additional ecrystallizations raised the melting range to 170–172° dec., $\alpha]^{25}D$ +19.7° (*c* 1.0, chloroform), λ_{max} 256 mμ (ε 12,000) and λ_{max} 5.83, 5.92 (less intense than 5.83 μ band), 6.15, 7.23, 7.26 μ.

Anal. Calcd. for $C_{24}H_{32}Br_2O_4$: C, 52.96; H, 5.93; Br, 29.37. Found: C, 53.02; H, 6.20; Br, 29.07.

Fractions 9–15 were combined and the solid contained therein was recrystallized from acetone–petroleum ether to give 0.776 g. of **2α-bromo-16α,17α-isopropylidenedioxyprogesterone** (III) as a white solid, m.p. 185–187° dec. Three additional recrystallizations raised the melting range to 192–193° dec., $[\alpha]^{25}D$ +112° (*c* 1.1, methanol) λ_{max} 243 mμ (ε 11,100), same infrared spectrum as that of the analytical sample. A mixture of this material and the analytical sample melted at 193–195° dec.

In another experiment treatment of 3.86 g. of the ethoxalyl derivative with 15.3 ml. of 0.87 *M* bromine in carbon tetrachloride solution as described above gave 0.259 g. of the dibromoketone VI and 1.263 g. of the monobromoketone III.

Finally treatment of 1.46 g. of this ethoxalyl derivative with 3.2 ml. of 0.93 *M* bromine in carbon tetrachloride by the above procedure gave only 0.236 g. of the monobromoketone III.

Hydrolysis of Certain 16α,17α-Isopropylidenedioxysteroids. Method A.—The appropriate steroid (1.0 g.) and 30 ml. of 60% formic acid were heated on the steam-bath for 30 minutes. The hot solution was diluted to turbidity with water and cooled to give the product which was recrystallized from the appropriate solvent(s).

Method B.—The steroid (1.0 g.) and 55 ml. of acetic acid–water (5:4) were allowed to reflux for 6 hours, after which the reaction solution was processed as described above.

16α,17α-Dihydroxyprogesterone was obtained by method A (63% yield) as white platelets after recrystallization from methylene chloride–petroleum ether; m.p. 219–223°, $[\alpha]^{25}D$ +92° (*c* 1.04, chloroform) and λ_{max} 241 mμ (ε 16,100).[33] The infrared spectrum of this material was identical with that of an authentic sample. Treatment of 100 mg. of this diol with 5 ml. of acetone and one drop of 37% hydrochloric acid gave 112 mg. (100% yield) of 16α,17α-isopropylidenedioxyprogesterone as white needles, m.p. 206–208°, λ_{max} 240 mμ (ε 16,300), $[\alpha]^{25}D$ +119° (*c* 1.0, methanol), +131° (*c* 1.4, chloroform). The identity with a known sample was further confirmed by the sameness of the infrared spectra of the two samples.

16α,17α-Dihydroxy-1,4-pregnadiene-3,20-dione was obtained in 45% yield by method A and 26% yield by method B. Recrystallization of the diol from acetone–petroleum ether gave white needles, m.p. 209–211°, $[\alpha]^{25}D$ +28.2° (*c* 0.4, methanol), λ_{max} 244 mμ (ε 15,300); λ_{max} 2.97, 5.86, 6.03, 6.19, 6.26 μ.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.84; H, 8.43.

This diol, on treatment with acetone and perchloric acid, gave a quantitative yield of 16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (VII), m.p. 198–200°, $[\alpha]^{25}D$ +79.5° (*c* 0.88, methanol), λ_{max} 243 mμ (ε 14,600). Identity with a known sample was further indicated by mixed melting point and infrared spectral comparisons.

4-Bromo-16α,17α-dihydroxy-1,4-pregnadiene-3,20-dione was obtained by method B (50% yield) as white needles, m.p. 227–229°, $[\alpha]^{25}D$ −21.5° (*c* 1.1, chloroform), λ_{max} 244 mμ (ε 15,300); λ_{max} 3.00, 5.88, 6.02, 6.26 μ.

Anal. Calcd. for $C_{21}H_{27}BrO_4$: C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.83; H, 6.56; Br, 18.95.

Reaction of this diol with acetone and perchloric acid gave, in 78% yield, 4-bromo-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione as hard white crystals, m.p. 221–223° alone or in mixture with an analytical specimen. Identity was further established by infrared spectral evidence.

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(33) Cooley and co-workers (ref. 9) report m.p. 225° and $[\alpha]^{22}D$ +95° (chloroform), whereas Allen and Bernstein [THIS JOURNAL, **78**, 1909 (1956)] record m.p. 219–223°, $[\alpha]^{24}D$ +97° (chloroform) and λ^{EtOH}_{max} 241–242 mμ (ε 15,200).