

*Anal.* Calcd. for  $C_{23}H_{32}O_2$ : C, 81.13; H, 9.47; O, 9.40. Found: C, 81.00; H, 9.22; O, 9.58.

**Action of Sulfuric Acid on 6 $\beta$ -Vinylprogesterone (IVe).**—To 0.20 g. of 6 $\beta$ -vinylprogesterone (IVe) in 2 ml. of acetic acid was added 2 drops of concentrated sulfuric acid. After 20 min. at room temperature the solution was diluted with water and extracted with ethyl acetate. The extracts were then washed with water, dried and evaporated to leave a

crystalline residue, 0.17 g., m.p. 130–133°, which was further purified by recrystallization from ether-hexane, m.p. 136–138°,  $[\alpha]_D^{25} +435^\circ$ ,  $\lambda_{max}^{EtOH}$  244 and 278–280 m $\mu$ ,  $\log \epsilon$  3.95 and 4.04, unaltered by the addition of a drop of 0.1 N alkali;  $\lambda_{max}^{KBr}$  5.87(s), 6.00(s) and 6.23(m) $\mu$ .

*Anal.* Calcd. for  $C_{23}H_{32}O_2$ : C, 81.13; H, 9.47; O, 9.40. Found: C, 81.00; H, 9.44; O, 9.91.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND BIOCHEMISTRY DEPARTMENTS OF SCHERING CORP.]

## Halogenated Progesterones. I. 9 $\alpha$ ,11 $\beta$ -Dihaloprogesterones

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A number of 9 $\alpha$ ,11 $\beta$ -dihaloprogesterones and 9 $\alpha$ ,11 $\beta$ -dihalo-1-dehydroprogesterones have been prepared from the corresponding 9(11)-dehydro compounds by the addition of chlorine and mixed halogens. The parenteral progestational activity of these compounds, measured in rabbits, is reported.

In recent years a number of analogs of progesterone, some of which have shown interesting physiological activity, have been prepared. These have included the 6 $\alpha$ -methyl,<sup>1</sup> 17 $\alpha$ -methyl,<sup>2</sup> 6-fluoro,<sup>3</sup> 21-fluoro,<sup>4</sup> 17 $\alpha$ -bromo,<sup>5</sup> 17 $\alpha$ -acetoxy<sup>6</sup> and 11-dehydro<sup>7</sup> derivatives of progesterone, and various combinations thereof. Some 9 $\alpha$ -halo-11 $\beta$ -hydroxy- and 11-keto-progesterones<sup>8</sup> have also shown progestational activity.<sup>9</sup> This paper describes a new class of steroids which are active in the McPhail progestin assay in rabbits, 9 $\alpha$ ,11 $\beta$ -dihaloprogesterones.<sup>10</sup>

When 9(11)-dehydroprogesterone (I)<sup>12</sup> was chlorinated with one mole of chlorine (gaseous or derived from N-chlorosuccinimide and hydrogen chloride) either in acetic acid containing an excess of chloride ion or in carbon tetrachloride containing several moles of pyridine<sup>13</sup> a dichloroprogesterone was isolated which was assigned the structure 9 $\alpha$ ,11 $\beta$ -dichloroprogesterone (II). Similarly, treatment of I with one mole of N-bromoacetamide

in the presence of hydrogen chloride and excess chloride ion in acetic acid<sup>11a</sup> or with one mole of N-bromoacetamide in the presence of hydrogen fluoride in diethylacetic acid<sup>11a</sup> resulted in the formation, respectively, of 9 $\alpha$ -bromo-11 $\beta$ -chloroprogesterone (III) and 9 $\alpha$ -bromo-11 $\beta$ -fluoroprogesterone (IV). These structural assignments are based, in addition to analogy with similar additions in other series,<sup>11,14</sup> on the following considerations.

The ultraviolet and infrared spectra are in accord with the proposed structures, showing evidence for an intact 4-ene-3-one system. Treatment of II with chromous chloride in acetone resulted in ready transformation to I; under these conditions a 2-chloro-4-ene-3-one is essentially inert.<sup>15</sup> Further evidence of addition (necessarily at 9(11) in view of the spectroscopic evidence) rather than substitution (at 2,6,17 or 21) taking place lies in the isolation of the mixed dihalo compounds (if an ionic mechanism is assumed). While it is possible to ascribe the formation of the bromochloro compound III to substitution by chlorine and bromine via the equilibrium  $2BrCl \rightleftharpoons Br_2 + Cl_2$ , this pathway appears to be impossible in the case of the bromofluoro compound IV in which case only  $F^-$  is available.<sup>16</sup> It seems reasonable to extend this result to the other compounds in the series.

The assigned stereochemistry is based on initial attack by the positive halogen from the less hindered  $\alpha$ -side<sup>17</sup> followed by the attack of the negative ion to give the *trans*-diaxial addition product.<sup>18</sup> The ultraviolet spectra of dihaloprogesterones show the expected lower absorption

(1) (a) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (b) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(2) H. H. Günthard, E. Beriger, C. R. Engel and H. Heusser, *Helv. Chim. Acta*, **35**, 2437 (1952), and references cited there.

(3) (a) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); (b) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(4) P. Tannhäuser, R. J. Pratt and E. V. Jensen, *THIS JOURNAL*, **78**, 2658 (1956).

(5) C. R. Engel and H. Jahuke, *Canad. J. Biochem. Physiol.*, **35**, 1047 (1957).

(6) R. B. Turner, *THIS JOURNAL*, **75**, 3489 (1953).

(7) C. Meystre, E. Tschopp and A. Wettstein, *Helv. Chim. Acta*, **31**, 1463 (1948).

(8) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *THIS JOURNAL*, **77**, 1068 (1955).

(9) J. Fried, W. B. Kessler and A. Borman, *Ann. N. Y. Acad. Sci.*, **71**, 494 (1958).

(10) 9 $\alpha$ ,11 $\beta$ -Dihalo-11-desoxycorticosteroids<sup>11a,b</sup> and 9 $\alpha$ ,11 $\beta$ -dihalo-1,4-androstadiene-3,17-diones<sup>11a</sup> have recently been described.

(11) (a) C. H. Robinson, L. Fincklenor, E. P. Oliveto and D. Gould, *THIS JOURNAL*, **81**, 2191 (1959); (b) S. K. Figdor, Abstracts of the Meeting of the American Chemical Society, Chicago, Ill., Sept. 11, 1958, p. 66-P.

(12) (a) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943); (b) G. Rosenkranz, O. Mancera and F. Sondheimer, *THIS JOURNAL*, **76**, 2227 (1954).

(13) We wish to thank Dr. C. H. Robinson for suggesting this procedure.

(14) R. E. Buckles (*THIS JOURNAL*, **71**, 1157 (1949)) used N-bromoacetamide with hydrogen bromide to convert olefins to dibromides and later studied similar additions using N-bromoacetamide and hydrogen chloride to give bromochloro compounds (R. E. Buckles and J. W. Long, *ibid.*, **73**, 998 (1950)). J. B. Ziegler and A. C. Shabica (*ibid.*, **74**, 4891 (1952)) employed N-bromoacetamide and hydrogen chloride to convert cholesterol to 5 $\alpha$ -bromo-6 $\beta$ -chlorocholestanol.

(15) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *ibid.*, **75**, 3500 (1953).

(16) The possibility of disubstitution by bromine, followed by replacement of one bromide by fluoride, is considered very unlikely under the reaction conditions.

(17) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(18) Cf. the addition of hypohalous acid (ref. 8 and 19) and of acyl hypohalite (ref. 20 and S. G. Levine and M. E. Wall, *THIS JOURNAL*, **81**, 2826 (1959)) to 9(11)-dehydro steroids

maxima for the 9 $\alpha$ -chloro than for the 9 $\alpha$ -bromo compounds.<sup>11a,19</sup>

An attempt to prepare the bromofluoro compounds IV from I by the use of N-bromoacetamide and potassium fluoride in acetic acid resulted in the formation of 9 $\alpha$ -bromo-11 $\beta$ -acetoxyprogesterone (VI) as the only isolated product. The structure of VI was demonstrated by its synthesis from 9(11)-dehydroprogesterone (I) using N-bromoacetamide and sodium acetate in acetic acid.<sup>20</sup>

For comparison purposes it was of interest to prepare some 1-dehydro-9 $\alpha$ ,11 $\beta$ -dihaloprogesterones. Microbial dehydrogenation of 11 $\alpha$ -hydroxyprogesterone,<sup>21</sup> using *Corynebacterium simplex* (A. T.C.C. 6946)<sup>22b</sup> resulted in the formation of 1,4-pregnadiene-3,20-dione-11 $\alpha$ -ol (VIII).<sup>22a,b,c</sup> Compound VIII was converted to the required intermediate 1,4,9(11)-pregnatriene-3,20-dione (X) by esterification to the 11-*p*-toluenesulfonate IX followed by treatment with sodium acetate in acetic acid.<sup>12b,23</sup> The triene X was readily converted to 9 $\alpha$ ,11 $\beta$ -dichloro-1,4-pregnadiene-3,20-dione (XI) by reaction with one mole of chlorine in carbon tetrachloride in the presence of excess pyridine. When the triene X was treated with N-chlorosuccinimide and hydrogen fluoride in carbon tetrachloride-methylene chloride containing an excess of pyridine, 9 $\alpha$ -chloro-11 $\beta$ -fluoro-1,4-pregnadiene-3,20-dione (XIX) was obtained. The structures of these compounds are based on physical data and analogy with the 1,2-saturated compounds.

An attempt was made to prepare 9 $\alpha$ -chloro-11 $\beta$ -fluoroprogesterone by a modified procedure, using dimethylformamide as the solvent. When compound I was treated with N-chlorosuccinimide and hydrogen fluoride in dimethylformamide a mixture was obtained from which starting material I and 9 $\alpha$ -chloro-11 $\beta$ -formyloxyprogesterone (V) could be isolated by crystallization. The structure of the latter was established by its analysis, infrared

spectrum and independent synthesis from I by reaction with N-chlorosuccinimide and sodium formate in formic acid.<sup>20</sup> The formation of V can be explained by attack of the carbonyl oxygen of dimethylformamide on the chloronium complex A to give the intermediate B, which is hydrolyzed to V and dimethylamine during the work-up.

Ultraviolet absorption maxima and rotational data are summarized in Table I. It is of interest to note that an 11 $\beta$ -fluoro substituent (compounds IV and XII) appears to have a rather large levorotatory contribution compared to the other 11 $\beta$ -substituents.

TABLE I  
ROTATIONAL AND ULTRAVIOLET ABSORPTION DATA

Compound	Ring A	Substituent-9 $\alpha$ -	11 $\beta$ -	$[\alpha]_D^{25}$ CHCl <sub>3</sub>	M <sub>D</sub>	$\lambda_{max}$ , m $\mu$ CH <sub>3</sub> OH
I	1,2-Satd.	9(11)-Dehydro		+174°	+542	239
II	1,2-Satd.	Cl	Cl	+243	+930	238
III	1,2-Satd.	Br	Cl	+226	+968	242
IV	1,2-Satd.	Br	F	+170	+698	240
V	1,2-Satd.	Cl	HCOO	+216	+849	238
VI	1,2-Satd.	Br	CH <sub>3</sub> COO	+197	+888	241
X	1-Dehydro	9(11)-Dehydro		+75.5	+234	240
XI	1-Dehydro	Cl	Cl	+184	+701	237
XII	1-Dehydro	Cl	F	+141	+515	236

Progestational activity of the compounds was determined according to the method of McPhail.<sup>24</sup> Immature rabbits weighing approximately 1-1.5 kg. were injected subcutaneously with 3.3 micrograms of estradiol benzoate on alternate days for a total of three injections. After this period of estrogen priming, the rabbits were injected subcutaneously once daily with various doses of the test compound dissolved in sesame oil for five days, and sacrificed twenty-four hours after the last injection.

The uterus was dissected out, trimmed of fat and connective tissue and weighed. Pieces of both uterine horns were removed and fixed in 10% formalin for 24 hours. Sections were cut at 5 microns, and stained with hematoxylin-eosin.

Sections were scored for the degree of endometrial proliferation from 0 (estrogen primed controls) to 4+ (McPhail). Comparisons with standard slides of progesterone-treated rabbits at high, medium and low doses were used as the reference standard.

The progestational activities of the dihaloprogesterones, given parenterally, are shown in Table II.

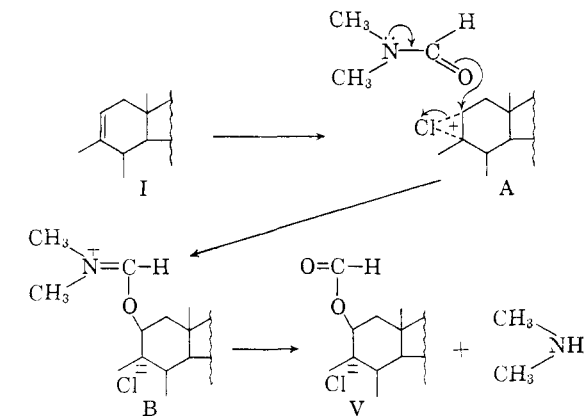
TABLE II  
PROGESTATIONAL ACTIVITY OF DIHALOPROGESTERONES

Compound	Activity <sup>a</sup>
II	5.5
III	~1.0
IV	0.7
XI	3.0
XII	~2.0

<sup>a</sup> Progesterone = 1.

The synthesis of 17 $\alpha$ -oxygenated and 6-substituted derivatives of this new class of progestins will be described in forthcoming publications.

(24) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).



(19) J. Fried and E. F. Sabo, *THIS JOURNAL*, **79**, 1130 (1957).

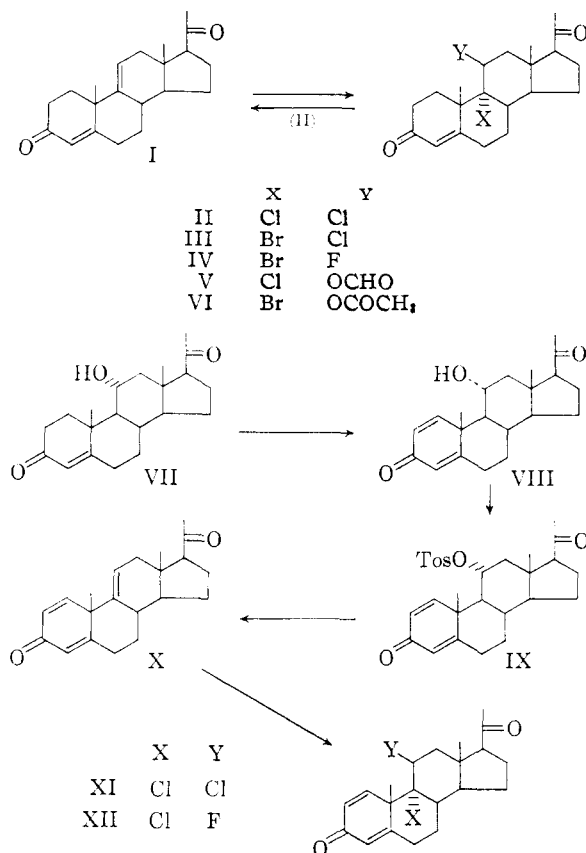
(20) C. H. Robinson, L. Fincknor, M. Kirtley, D. Gould and E. P. Oliveto, *ibid.*, **81**, 2195 (1959).

(21) (a) D. H. Peterson and H. C. Murray, *ibid.*, **74**, 1891 (1952); (b) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

(22) (a) H. A. Kroll, J. F. Pagano and R. W. Thoma, U. S. Patent 2,822,318, Feb. 4, 1958; (b) R. W. Thoma and J. Fried, U. S. Patent 2,880,217, March 31, 1959; (c) S. H. Eppstein, P. D. Meister and A. Weintraub, U. S. Patent 2,883,400, April 21, 1959.

(23) J. Fried and E. F. Sabo, *THIS JOURNAL*, **75**, 2273 (1953).

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### Experimental<sup>25</sup>

**9 $\alpha$ ,11 $\beta$ -Dichloroprogestosterone (II).** (a) **In Acetic Acid Solvent.**—To a stirred solution of 1.000 g. of 9(11)-dehydroprogesterone and 4.0 g. of lithium chloride in 50 ml. of glacial acetic acid was added a solution of 250 mg. of hydrogen chloride in one ml. of tetrahydrofuran followed by 500 mg. of 93% N-chlorosuccinimide. The mixture was stirred in the dark for 20 minutes,<sup>26</sup> then poured with stirring into ice-water. The precipitate was collected, washed with water and dried, giving 1.064 g. of crude product. Crystallization from ether gave 527 mg. of II, m.p. 160–170° dec. The analytical sample was recrystallized twice from acetone–hexane; m.p. 174–177° dec.,  $[\alpha]_D^{25} +243^\circ$ ,  $\lambda_{max}^{MeOH}$  238 m $\mu$  ( $\epsilon$  16,200);  $\lambda_{Nujol}^{max}$  5.88, 5.98, 6.14  $\mu$ .

*Anal.* Calcd. for C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>Cl<sub>2</sub>: C, 65.79; H, 7.36; Cl, 18.50. Found: C, 65.46; H, 7.59; Cl, 18.66.

Compound II could also be prepared from I in somewhat lower yield, by the use of a solution of chlorine in glacial acetic acid, in the presence of a large excess of lithium chloride.

(b) **In Carbon Tetrachloride Solvent.**—To a stirred solution of 1.000 g. of I in 30 ml. of carbon tetrachloride containing 0.75 ml. of dry pyridine at –20° was added 2.1 ml. of a solution of chlorine in carbon tetrachloride (111 mg. of chlorine/ml.). The mixture was stirred at –20° for 15 minutes,

(25) Melting points were determined on the Kofler block. Rotations were measured at 25° in chloroform at about 1% concentration. Rotational and spectral data were obtained by the Physical Chemistry Department, Schering Corporation. Microanalyses were performed by Mr. E. Connor and staff (Microanalytical Laboratory, Schering Corporation), Galbraith Laboratories, Knoxville, Tenn., and the Schwarzkopf Microanalytical Laboratory, Woodside, L. I.

(26) The addition reactions were generally allowed to proceed until a negative test with potassium iodide–starch paper indicated complete consumption of halogenating agent.

then allowed to come to room temperature over a period of 30 minutes. The solution was washed with 5% hydrochloric acid, sodium bicarbonate solution and water, then concentrated to an oil. The oily residue was triturated with ether to give 465 mg. of crude II. Crystallization from acetone–hexane afforded II, 382 mg., m.p. 173–180° dec., with an infrared spectrum identical with that of II prepared in (a).

**9(11)-Dehydroprogesterone (I) from 9 $\alpha$ ,11 $\beta$ -Dichloroprogestosterone (II).**—To a solution of 50 mg. of the dichloro compound II in 10 ml. of acetone, under carbon dioxide, was added 5 ml. of chromous chloride solution.<sup>27</sup> The mixture was allowed to stand at room temperature for 15 minutes, then poured into water and extracted with methylene chloride. The extracts were washed with water, dried and evaporated to an oil which was crystallized from ether–pentane to give 29 mg. of I, Beilstein test negative,  $\lambda_{max}^{MeOH}$  238 m $\mu$  ( $\epsilon$  16,100), infrared spectrum identical with that of an authentic sample.

**9 $\alpha$ -Bromo-11 $\beta$ -chloroprogestosterone (III).**—To a stirred solution of 1.005 g. of 9(11)-dehydroprogesterone and 4.0 g. of lithium chloride in 50 ml. of glacial acetic acid was added 490 mg. of 95% N-bromoacetamide. A slow stream of gaseous hydrogen chloride was passed over the surface of the stirred solution for about 30 seconds, giving a deep red solution. After stirring at room temperature with exclusion of light for 10 minutes the solution was poured into ice-water. The resulting suspension was filtered and the crude product washed with water, dried and immediately triturated with ether. The resulting solid was crystallized from methylene chloride–pentane to give a total of 625 mg. of III, m.p. 107–110° dec. The analytical sample was recrystallized from methylene chloride–pentane, m.p. 111–113° dec.,  $[\alpha]_D^{25} +226^\circ$ ,  $\lambda_{max}^{MeOH}$  242 m $\mu$  ( $\epsilon$  15,900);  $\lambda_{Nujol}^{max}$  5.86, 5.99, 6.14  $\mu$ .

*Anal.* Calcd. for C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>BrCl: C, 58.92; H, 6.60; Br, 18.68; Cl, 8.29. Found: C, 59.10; H, 6.25; Br, 18.36; Cl, 8.23.

Compound III could be kept in the freezer but decomposed to a black solid on standing at room temperature.

**9 $\alpha$ -Bromo-11 $\beta$ -fluoroprogestosterone (IV).**—To a stirred solution of 1.000 g. of 9(11)-dehydroprogesterone in 50 ml. of diethylacetic acid contained in a polyethylene bottle was added 5 ml. of a solution of hydrogen fluoride in chloroform–tetrahydrofuran (about 250 mg. HF/ml.) followed by 487 mg. of 95% N-bromoacetamide. The reaction mixture was stirred at room temperature for 100 minutes, then poured into aqueous potassium carbonate solution (50 g. K<sub>2</sub>CO<sub>3</sub> in one l. of water). The mixture was stirred for 30 minutes, then extracted with methylene chloride. The organic extracts were washed with 5% aqueous sodium hydroxide solution and water and dried over magnesium sulfate. The solution was concentrated and the product crystallized by the addition of pentane, to give 380 mg. of IV. This was recrystallized from methylene chloride–pentane; m.p. 145–150° dec.,  $[\alpha]_D^{25} +170^\circ$ ,  $\lambda_{max}^{MeOH}$  240 m $\mu$  ( $\epsilon$  15,300);  $\lambda_{Nujol}^{max}$  5.86, 5.96, 6.14  $\mu$ .

*Anal.* Calcd. for C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>BrF: C, 61.31; H, 6.86; Br, 19.43; F, 4.62. Found: C, 60.66; H, 6.94; Br, 19.95; F, 4.52.

**9 $\alpha$ -Bromo-11 $\beta$ -acetoxyprogesterone (VI).** (a) **Attempted Preparation of IV Using Potassium Fluoride in Acetic Acid.**—To a solution of 1.000 g. of 9(11)-dehydroprogesterone and 5.0 g. of potassium fluoride in 50 ml. of glacial acetic acid contained in a polyethylene bottle was added 486 mg. of 95% N-bromoacetamide and the mixture stirred at room temperature for 4.5 hours. It was then poured into ice-water and the resulting precipitate isolated, washed with water and dried. The crude product was crystallized from ether, giving 473 mg. of VI. A further crystallization from acetone–hexane gave analytically pure material, m.p. 147–151° dec.,  $[\alpha]_D^{25} +205^\circ$ ,  $\lambda_{max}^{MeOH}$  241 m $\mu$  ( $\epsilon$  15,800);  $\lambda_{Nujol}^{max}$  5.74, 5.90, 6.02, 6.17, 8.10  $\mu$ .

*Anal.* Calcd. for C<sub>23</sub>H<sub>30</sub>O<sub>3</sub>Br: C, 61.19; H, 6.92; Br, 17.70. Found: C, 61.17; H, 7.07; Br, 17.31.

(b) **Using Sodium Acetate in Acetic Acid.**—To a stirred solution of 500 mg. of 9(11)-dehydroprogesterone and 2.0 g. of anhydrous sodium acetate in 20 ml. of glacial acetic acid was added 230 mg. of N-bromoacetamide. The solution was stirred at room temperature for 35 minutes, then poured

(27) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *This Journal*, **72**, 4077 (1950).

into ice-water. The suspension was filtered and the gummy solid washed with water and triturated with ether to give 206 mg. of VI, m.p. 149–154° dec.,  $[\alpha]_D +197^\circ$ , infrared spectrum identical to that of the compound obtained in (a). From the aqueous mother liquor an additional 89 mg. of crystalline VI, m.p. 149–155° dec., with an identical infrared spectrum was obtained.

**9 $\alpha$ -Chloro-11 $\beta$ -formyloxyprogesterone (V).** (a) **Attempted Preparation of 9 $\alpha$ -Chloro-11 $\beta$ -fluoroprogesterone Using Hydrogen Fluoride in Dimethylformamide.**—To a stirred solution of 1.005 g. of 9(11)-dehydroprogesterone in 50 ml. of dimethylformamide contained in a polyethylene bottle was added 4 ml. of a solution of hydrogen fluoride in chloroform-tetrahydrofuran followed by 460 mg. of 98% N-chlorosuccinimide. The mixture was stirred at room temperature for 18 hours, then poured into ice-water and made slightly alkaline with potassium carbonate. The precipitate was isolated, washed with water and triturated with ether giving 100 mg. of a solid which was crystallized from methylene chloride-pentane to give V, 59 mg., m.p. 218–225° dec. The analytical sample was recrystallized from methylene chloride-pentane; m.p. 224–227° dec.,  $[\alpha]_D +216^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  238 m $\mu$  ( $\epsilon$  15,900);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  5.80, 5.90, 6.00, 6.15, 8.68  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{36}\text{O}_4\text{Cl}$ : C, 67.25; H, 7.44; Cl, 9.02. Found: C, 67.44; H, 7.62; Cl, 9.32.

From the ethereal mother liquor, by concentration to an oil under reduced pressure and crystallization from ether, 261 mg. of impure starting material I was obtained. Crystallization from acetone-hexane afforded 160 mg. of I,  $\lambda_{\text{max}}^{\text{MeOH}}$  239 m $\mu$  ( $\epsilon$  16,500), infrared spectrum identical with that of authentic I.

(b) **Using Sodium Formate in Formic Acid.**—To a stirred solution of 500 mg. of 9(11)-dehydroprogesterone and 2.0 g. of sodium formate in 20 ml. of 100% formic acid was added 230 mg. of 98% N-chlorosuccinimide and the mixture stirred at room temperature for 65 hours. The solution was poured into ice-water and the precipitate isolated, washed with water and dried. The crude product was triturated with ether to give a total of 110 mg. of solid. Crystallization from methylene chloride-pentane afforded V, m.p. 215–225° dec., infrared spectrum identical with that of V prepared in (a).

**1,4-Pregnadiene-3,20-dione-11 $\alpha$ -ol 11-*p*-Toluenesulfonate (IX).**—To a stirred solution of 5.835 g. of 1,4-pregnadiene-3,20-dione-11 $\alpha$ -ol (VIII, m.p. 226.5–228.5°,  $[\alpha]_D +98^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  247 m $\mu$  ( $\epsilon$  18,100);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  2.95, 5.88, 6.05, 6.18, 6.26  $\mu$ ) in 23.5 ml. of chloroform and 29 ml. of dry pyridine, chilled to 0°, was added 7.0 g. of *p*-toluenesulfonyl chloride. The mixture was stirred in the ice-bath which was allowed to come to room temperature over a period of 18 hours. The solution was poured into ice-water, extracted with methylene chloride and the extracts washed with water, 5% hydrochloric acid and again with water. The organic solution was concentrated and the product crystallized on addition of methanol, giving IX, 4.822 g., m.p. 172–173° dec. A second crop of IX, 1.028 g., m.p. 167–169° dec., was obtained from the mother liquor. The analytical sample was recrystallized from acetone-hexane, m.p. 173–175°,  $[\alpha]_D +119^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  229 m $\mu$  ( $\epsilon$  23,800);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  5.88, 6.05, 6.18, 6.26, 7.54, 8.54, 11.25  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{34}\text{O}_5\text{S}$ : C, 69.69; H, 7.10; S, 6.63. Found: C, 69.57; H, 7.04; S, 6.81.

**1,4,9(11)-Pregnatriene-3,20-dione (X).**—To a solution of 4.0 g. of anhydrous sodium acetate in 40 ml. of glacial acetic acid, heated to about 100°, was added 2.886 g. of IX and the mixture heated under reflux for 2.5 hours. The solution was cooled and diluted with water and the resulting precipitate filtered, washed and dried, giving 1.408 g. of slightly impure X. The product was crystallized from acetone-ether to give substantially pure X, m.p. 132–134°. The analytical sample was recrystallized from ethyl acetate-ether and methylene chloride-pentane, m.p. 135–138°, resolidifying and melting at 147–150°.  $[\alpha]_D +75.5^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  240 m $\mu$  ( $\epsilon$  15,500);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  5.88, 6.02, 6.15, 6.24, 10.98, 12.12  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{26}\text{O}_2$ : C, 81.25; H, 8.44. Found: C, 81.23; H, 8.58.

**9 $\alpha$ ,11 $\beta$ -Dichloro-1,4-pregnadiene-3,20-dione (XI).**—To a stirred solution of 500 mg. of X in 20 ml. of carbon tetrachloride containing 0.38 ml. of pyridine, chilled to –20°, was added 1.05 ml. of a solution of chlorine in carbon tetrachloride (110 mg. chlorine/ml.). The mixture was stirred at –20° for 10 minutes, then allowed to come to room temperature and diluted with methylene chloride. The solution was washed with 5% hydrochloric acid, sodium bicarbonate solution and water, then concentrated to an oil under reduced pressure. Trituration with ether afforded impure XI, 240 mg., which was crystallized from acetone-hexane to give XI, 172 mg., m.p. 198–208° dec. From the ethereal mother liquor an additional 61 mg. of XI was obtained. The analytical sample was recrystallized from acetone-hexane; m.p. 199–207° dec.,  $[\alpha]_D +184^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  237 m $\mu$  ( $\epsilon$  15,000);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  5.92, 6.02, 6.14, 6.22, 11.36  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{26}\text{O}_2\text{Cl}_2$ : C, 66.14; H, 6.87; Cl, 18.60. Found: C, 66.32; H, 6.91; Cl, 18.31.

**9 $\alpha$ -Chloro-11 $\beta$ -fluoro-1,4-pregnadiene-3,20-dione (XII).**—To a stirred solution of 500 mg. of X in 20 ml. of carbon tetrachloride containing 3 ml. of dry pyridine in a polyethylene bottle was added 1.5 ml. of a solution of hydrogen fluoride in chloroform-tetrahydrofuran (about 250 mg. HF/ml.) followed by 230 mg. of 98% N-chlorosuccinimide. An oily layer formed and enough methylene chloride was added to give a clear solution. The mixture was allowed to stand at room temperature for 70 hours, then aqueous potassium carbonate solution was added with stirring. The organic layer was separated, washed with water, dilute hydrochloric acid and again water and dried over magnesium sulfate. The solution was treated with decolorizing charcoal, then concentrated to dryness. The solid residue was triturated with ether, giving XII, 350 mg. The crude product was crystallized from acetone-hexane to give 248 mg., m.p. 210–215°. The analytical sample was recrystallized from methylene chloride-pentane; m.p. 215–220°,  $[\alpha]_D +141^\circ$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  236 m $\mu$  ( $\epsilon$  15,100);  $\lambda\lambda_{\text{max}}^{\text{Nujol}}$  5.88, 6.02, 6.15, 6.22  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{36}\text{O}_2\text{ClF}$ : C, 69.12; H, 7.18; Cl, 9.72; F, 5.21. Found: C, 69.21; H, 6.91; Cl, 9.74; F, 5.12.

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