gating liquid disclosed two components with R_f 0.74 and 0.65. The slower moving component was the major constituent and migrated at the same rate as linocaffein (I). The location of the components was determined by spraying the chromatogram with bis-diazotized benzidine.[4]

The crude product from the deacetylation reaction was fractionated on a cellulose column using the above irrigating liquid. Evaporation of the fractions which contained the slower moving component gave linocaffein which crystallized from hot water as needles, $[\alpha]^{24}D$ −88° (*c* 1, methanol), m.p. 206–208° alone or in admixture with the linocaffein (I) obtained from the flax hulls.

The faster moving component was not characterized but was probably an isomer of linocaffein with the glucose residue attached to the ring in the 3-position.

FARGO, N. DAK.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

A New Class of Potent Anti-inflammatory Agents; Synthesis of 9α,11β-Dihalocorticosteroids

BY C. H. ROBINSON, L. FINCKENOR, EUGENE P. OLIVETO AND DAVID GOULD

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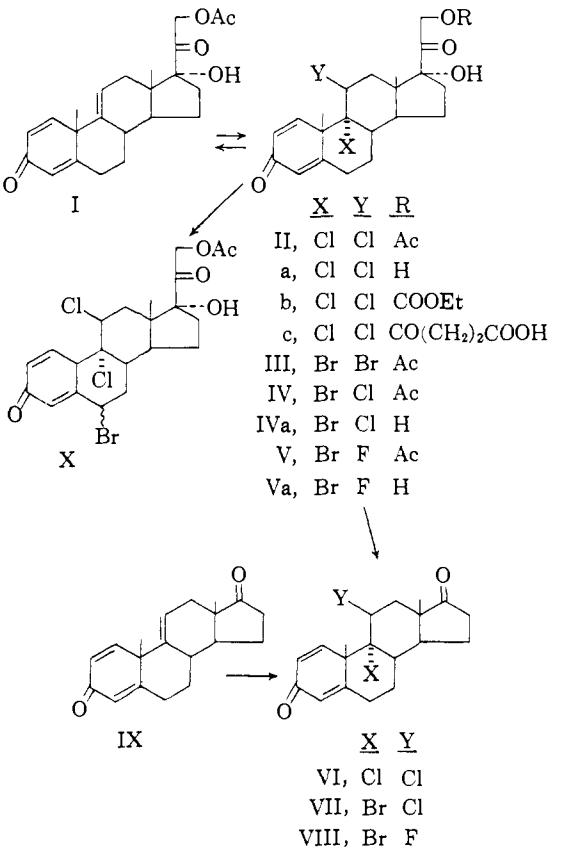
A number of 9α,11β-dihalo steroids have been prepared by the addition of halogens and mixed halogens to the 9(11)-double bond of some 1,4,9(11)-steroidal trienes. Certain of the dihalides are powerful anti-inflammatory agents, as measured by the granuloma pouch test.

The enhancement of anti-inflammatory and glucocorticoid activity associated with the insertion of a chlorine or fluorine atom at C-9 in 11-oxygenated corticoids is well established.[1-3] This increased activity shown by compounds containing *trans*-9,11-chlorohydrin and fluorohydrin systems led us to speculate that *trans*-9,11-dihalocorticoids might also show anti-inflammatory activity, and the ready addition of hypobromous acid to 9(11)-olefins[1,3,4] encouraged us to study the addition of halogens and mixed halogens to 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione-21-acetate[3] (I).

When a solution of the triene I and lithium chloride[5] in acetic acid was treated with 1.1 moles of chlorine (preferably derived from N-chlorosuccinimide and hydrogen chloride, although solutions of chlorine in organic solvents can also be successfully employed) a halogen-containing compound was isolated in 58% yield. Elemental analysis indicated that this compound had resulted from the addition of 1 mole of chlorine to the triene I. We formulate this product as 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione-21-acetate (II) on the following grounds.

The infrared spectrum of II showed that both the 1,4-diene-3-one system and the cortical side chain were intact, and the ultraviolet absorption (λ_{max} 237 mμ, ε 15,000) and positive tetrazolium reaction of II provided supporting evidence. Chromous chloride in acetone at room temperature (sodium iodide in acetone provoked no reaction) smoothly converted II into the triene I, demonstrating that no skeletal rearrangement had occurred in the formation of II.



That both chlorine atoms were located in the nucleus became apparent from the following reaction sequence. Hydrolysis of II using methanolic perchloric acid[4] gave the 21-alcohol IIa which was degraded with sodium bismuthate[6] to a dichloroandrostadienedione. The latter compound also could be prepared by the addition of chlorine to 1,4,9(11)-androstatriene-3,17-dione (IX) and

(1) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953); **76**, 1455 (1954).

(2) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955).

(3) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955).

(4) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(5) Without added chloride ions, mixtures of 9α,11β-dichloride and 9α-chloro-11β-acetate resulted. When lithium acetate was substituted for lithium chloride the 9α-chloro-11β-acetate was isolated as the major product. The literature contains several examples of the addition of the elements of acyl hypohalite to double bonds, and pertinent references are given the accompanying paper (C. H. Robinson, L. Finckenor, M. Kirtley, D. H. Gould and E. P. Oliveto) which describes the preparation of a series of 9α-halo-11β-acyloxy corticoids.

(6) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

is formulated as 9α,11β-dichloro-1,4-androstadiene-3,17-dione (VI).

At this point, chlorine substitution at C-6 in II had not been excluded. We therefore subjected II to Ziegler bromination, using 1.3 moles of N-bromosuccinimide. The product was a monobromo-dichloro compound (X) showing $\lambda_{max.}$ 243 mμ. The shift of the ultraviolet absorption maximum associated with the conversion of II ($\lambda_{max.}$ 237 mμ) to X is similar to the shift previously observed[7] when 1,4-diene-3-ones were converted to the 6-bromo derivatives. In the case of Δ^4-3-ketones, the bathochromic effect of a 6β-bromo substituent has been noted.[8]

We believe X to be the 6-bromo derivative of the dichloride II with the 6-bromine substituent probably in the β-configuration. Prolonged treatment of X with silver fluoride in acetone provided, in poor yield, a substance showing ultraviolet absorption maxima at 225 (10,000), 248 (8,000) and 297 mμ (10,400). This absorption spectrum is characteristic of 1,4,6-triene-3-one chromophores.[7]

Analogy with the addition of hypobromous acid and of the elements of acyl hypohalite[5] to I, together with the evidence just described, provides the basis for our formulation of II as a 9,11-dichloride. The stereochemical assignment (9α,-11β) rests on analogy with the *trans*-diaxial addition of hypobromous acid and acyl hypohalites to I and with the results of previous additions of halogens to steroid olefins.[9]

Before turning from the dichloro compounds it should be mentioned that the 21-alcohol IIa was converted readily into the 21-acetate II, 21-carbethoxylate IIb and 21-hemisuccinate IIc using the standard procedures (the appropriate acid anhydride or acid chloride in pyridine).

We also observed that a mixture of N-bromoacetamide,[10] potassium bromide and I in acetic acid yielded a dibromo compound in 53% yield. This product is formulated as 9α,11β-dibromo-1,4-pregnadiene-17α,21-diol-3,20-dione-21-acetate (III) on the bases of elemental analysis, ultraviolet and infrared spectra, molecular rotation (see Table I) and analogy with the formation of the dichloro compound II.

The dibromo compound III decomposed in the solid state at room temperature with evolution of hydrogen bromide, and no further studies were attempted.

We had originally envisaged the addition of mixed halogens, as well as halogens, to I. The use of N-bromoacetamide and hydrogen chloride by Buckles and Long[11] to convert olefins to bromochloro compounds (giving in all the cases studied, the product predicted as a result of ionic *trans* addition of $Br^{\ominus}$ and $Cl^{\ominus}$), and by Ziegler and Shabica[12] to prepare 5α-bromo-6β-chlorocholesterol from cholesterol, encouraged us to extend the method to I.

When a solution of I and lithium chloride in acetic acid was treated with N-bromoacetamide and hydrogen chloride, the product IV had the correct analysis for addition of bromine chloride to I. The reaction of IV with zinc and acetic acid led to the triene I. Hydrolysis of IV with methanolic perchloric acid furnished the 21-alcohol IVa, which upon sodium bismuthate degradation gave uncrystallizable oils. Attempts to prepare the 17-ketone VII from IX led in poor yield to a substance which contained halogen and was probably an impure specimen of VII.

The findings of Buckles and Long,[11] and of Ziegler and Shabica,[12] suggest that IV had resulted from ionic *trans* addition of $Br^{\ominus}$ and $Cl^{\ominus}$ to I, and should therefore be formulated as the 9α-bromo-11β-chloro derivative.

The success of this reaction caused us to consider next the use of N-bromoacetamide and hydrogen fluoride, which should yield products resulting from *ionic trans* addition of $Br^{\ominus}$ and $F^{\ominus}$. Indeed, when compound I was dissolved in diethylacetic acid and treated with N-bromoacetamide and a solution of hydrogen fluoride in tetrahydrofuran–chloroform, the product of the reaction showed the correct analysis for the addition of bromine fluoride to I. This product, V, was hydrolyzed with methanolic perchloric acid to the 21-alcohol Va, which also showed the correct analysis for a bromofluoro compound.

Using the same procedure by which V was prepared, 1,4,9(11)-androstatriene-3,17-dione (IX) was converted into the bromofluoro derivative VIII. Chromous chloride regenerated IX from VIII and I from V.

Compounds V and VIII are formulated as 9α-bromo-11β-fluoro derivatives of I and IX, respectively, by analogy with the other dihalides. In addition, comparison of ultraviolet absorption maxima supports the view that the bromine substituent in V is at C-9. Thus V and the bromochloride IV both show $\lambda_{max.}$ 239 mμ and the dibromide III shows $\lambda_{max.}$ 240 mμ. The dichloride II shows $\lambda_{max.}$ 237 mμ, and a 9-fluoro-11-bromo compound would be expected to show a maximum about 237 mμ.[13]

We were unable to obtain a crystalline product from the reaction of I with iodine chloride other than unchanged starting material.

The ultraviolet absorption maxima and molecular rotations of some of the compounds described in this paper are collected in Table I.

In the granuloma pouch test, in rats, compounds IV, II and IIa showed anti-inflammatory activities,

(7) D. H. Gould, E. L. Shapiro, H. L. Herzog, M. Gentles, E. B. Hershberg, W. Charney, M. L. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, THIS JOURNAL, **79**, 502 (1957).

(8) C. W. Bird, R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 3675 (1956), and references cited therein.

(9) See G. H. Alt and D. H. R. Barton (*ibid.*, 2484 (1954)) who studied the addition of halogens to cholest-2-ene and cholest-3-ene, and noted that in these cases and in earlier studies with Δ^4-steroids (D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 370, 1066 (1950)) and Δ^{11}-steroids (R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1956)) the predominant or sole product isolated was the diaxial dihalide.

(10) *Cf.* R. E. Buckles, THIS JOURNAL, **71**, 1157 (1949), who used N-bromoacetamide–hydrogen bromide to convert olefins to dibromides in high yields.

(11) R. E. Buckles and J. W. Long, *ibid.*, **73**, 998 (1950).

(12) J. B. Ziegler and A. C. Shabica, *ibid.*, **74**, 4891 (1952).

(13) The ultraviolet maxima shown by 9α-bromo-, 9α-chloro- and 9α-fluoroprednisolone acetate (all from ref. 3) are, respectively, 241, 238 and 238 mμ.

TABLE I

MOLECULAR ROTATIONS AND ULTRAVIOLET ABSORPTION MAXIMA OF 9α,11β-DIHALO-1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 21-ACETATES

Substituent 9α-	Substituent 11β-	[M]D dioxane	MeOH λmax, mμ
Br	Br	+1006°	240
Br	Cl	+ 860	239
Br	F	+ 594	239
Cl	Cl	+ 737	237

respectively, 1.2, 4.0 and 8.5 times the activity of prednisolone acetate.

Compounds II and IIa were studied for eosinopenic activity in intact and adrenalectomized dogs, and found to be only slightly active.[14]

Until now, 11-oxygenation of the steroid nucleus has been regarded as one of the prerequisites for glucocorticoid activity in its various aspects.[15] Modification of this view is necessary as a consequence of the anti-inflammatory effects shown by 11-halogenated steroids.

Experimental[16]

9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (II).[16a]—To a stirred, cooled (0–5°) solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (*I*, 1.0 g.) and lithium chloride (4.0 g.) in glacial acetic acid (40 ml.) was added N-chlorosuccinimide[17] (383 mg., 1.1 equiv.), followed immediately by an anhydrous solution of hydrogen chloride (104 mg.) in tetrahydrofuran (1.0 ml.). Stirring was continued at room temperature for 3 hours, and the reaction mixture then was poured into water (400 ml.). The resulting mixture was filtered, and the residue was washed with water and dried, giving 1.18 g. (99%) of crude product. Crystallization from acetone furnished analytically pure 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (II, 700 mg.), m.p. 246–253° dec., [α]D +162°, λ_{max}^{MeOH} 237 mμ (15,000); λ_{max}^{Nujol} 2.94, 5.72, 5.80, 6.04, 6.22, 8.12 μ.

Anal. Calcd. for $C_{23}H_{28}O_5Cl_2$: C, 60.66; H, 6.20; Cl, 15.57. Found: C, 60.24; H, 6.14; Cl, 15.99.

9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIa).—A suspension of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (II, 1.0 g.) in 0.27 *N* methanolic perchloric acid[4] (70 ml.) was stirred at room temperature for 17 hours. The reaction mixture then was poured into water (200 ml.), filtered, and the residue was washed with water and dried, giving a quantitative yield of crude product. Crystallization from acetone yielded pure IIa, m.p. 238–241° dec., [α]D +134° (pyridine), λ_{max}^{MeOH} 237 mμ (15,400); λ_{max}^{Nujol} 3.0, 5.86, 6.04, 6.22, 6.24 μ.

Anal. Calcd. for $C_{21}H_{26}O_4Cl_2$: C, 61.02; H, 6.34; Cl, 17.15. Found: C, 61.26; H, 6.30; Cl, 16.66.

The foregoing compound (IIa, 50 mg.) was acetylated in pyridine and acetic anhydride at room temperature for 17 hours to yield the pure 21-acetate (II, 37 mg.) identical with authentic II as evidenced by melting point, mixed melting point and comparison of infrared spectra.

9α,11β-Dichloro-1,4-prgnadiene-17α,21-diol-3,20-dione 21-Carbethoxylate (IIb).—A solution of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIa, 1.0 g.) in pyridine (25 ml.) was chilled in an ice-bath, and ethyl chlorocarbonate (0.5 ml.) was added, with stirring. Stirring was continued for 15 minutes and a further portion (0.5 ml.) of ethyl chlorocarbonate was added. After stirring for an additional 15 minutes the reaction mixture was poured into cold dilute aqueous sulfuric acid and filtered. The residue was washed with water and dried to give a quantitative yield of crude product. Crystallization twice from acetone–hexane afforded pure IIb, m.p. 238–242° dec., [α]D +149°, λ_{max}^{MeOH} 237 mμ (14,800); λ_{max}^{Nujol} 2.88, 5.68, 5.78, 6.02, 6.14, 6.22, 7.98 μ.

Anal. Calcd. for $C_{24}H_{30}O_6Cl_2$: C, 59.38; H, 6.23; Cl, 14.61. Found: C, 59.61; H, 6.29; Cl, 14.71.

9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Hemisuccinate (IIc).—A stirred solution of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIa, 3.0 g.) and succinic anhydride (3.0 g.) in pyridine (75 ml.) was heated to 70° for 5 minutes. Stirring was continued for 20 hours at room temperature, and the reaction mixture was then poured into cold dilute aqueous sulfuric acid (700 ml.) and filtered. The residue was washed with water, dried and crystallized from ethyl acetate, giving 2.1 g. of IIc, m.p. 234–236° dec., [α]D +150°, λ_{max}^{MeOH} 237 mμ (14,600); λ_{max}^{Nujol} 2.98, 3.88, 5.75, 5.78, 5.88, 6.02, 6.22, 8.50, 8.70 μ.

Anal. Calcd. for $C_{25}H_{30}O_7Cl_2$: C, 58.48; H, 5.89; Cl, 13.81. Found: C, 58.79; H, 5.84; Cl, 13.54.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (I) from 9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (II).—To a suspension of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (II, 200 mg.) in acetone (20 ml.) was added, at room temperature under carbon dioxide, a solution of chromous chloride[18] (5 ml.). The mixture was shaken and after 2 minutes all the suspended steroid had dissolved. A further portion (5 ml.) of chromous chloride solution was added, and the mixture was shaken for an additional 5 minutes. The reaction mixture then was diluted with water, extracted with methylene chloride and the extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was crystallized from acetone–hexane, yielding pure I (150 mg., 88%), m.p. 221–225° (m.p. undepressed on admixture with authentic I), [α]D +54°, λ_{max}^{MeOH} 238 mμ (15,000); the infrared spectrum (Nujol) was identical with that of authentic I.

6-Bromo-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (X).—To a refluxing suspension of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (II, 1.0 g.) in chlorobenzene (160 ml.) and carbon tetrachloride (95 ml.) was added N-bromosuccinimide (590 mg.) and benzoyl peroxide (20 mg.). The mixture then was refluxed for 3 minutes over a G. E. 500-watt photoflood lamp (RFL-2), then cooled, filtered, and diluted with methylene chloride. The solution was washed twice with water and evaporated *in vacuo*. The crude product was crystallized twice from acetone–hexane, yielding pure X (485 mg., 41%), m.p. 193–196° dec., λ_{max}^{MeOH} 243 mμ (14,000); $\lambda_{max}^{CHCl_3}$ 2.94, 5.74, 5.78, 6.02, 6.15 μ.

Anal. Calcd. for $C_{23}H_{27}O_5BrCl_2$: C, 51.70; H, 5.09; Br, 14.96; Cl, 13.27. Found: C, 52.01; H, 5.15; Br, 14.80; Cl, 13.49.

Dehydrobromination of 6-Bromo-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (X).—To a solution of X (1.5 g.) in acetone (40 ml.) was added silver fluoride (3.0 g.), and the resulting suspension was stirred at room temperature for 65 hours. The reaction mixture was diluted with water, extracted with methylene chloride and the extracts were washed with water, then aqueous 10% sulfuric acid, then water, followed by drying ($MgSO_4$) and evaporating *in vacuo*. The crude product was chromatographed on Florisil, elution with ether–hexane (3:1) furnishing a substance, m.p. *ca.* 225° dec.; λλ$_{max}^{MeOH}$ 225 (10,000), 248 (8,600) and 297 mμ (10,400).

1,4,9(11)-Androstatriene-3,17-dione (IX).—A stirred solution of 11β-hydroxy-1,4-androstadiene-3,17-dione (93.5

(14) A detailed description of these and other findings will be given in a forthcoming publication by S. Tolksdorf, M. Eisler and P. L. Perlman of these laboratores.

(15) See, for example, I. E. Bush, *Experientia*, **12**, 325 (1956), and references cited therein.

(16) Melting points were obtained on the Kofler block. Rotations were measured at 25° in dioxane solution at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corporation, for measurement of ultraviolet and infrared spectra and rotations. Microanalyses were performed by Mr. Conner (Microanalytical Laboratory, Schering Corporation), by the Schwarzkopf Microanalytical Laboratory, Woodside, L. I., by Galbraith Laboratories, Knoxville, Tenn., and by V. Tashinian, Berkeley, Calif.

(16a) After this paper was submitted, the preparation of the 1,2-dihydro analog of II was described by Dr. S. K. Figdor at the American Chemical Society Meeting, Chicago, Ill., Sept. 11, 1958, but no specific biological data were presented.

(17) Unpurified commercial N-chlorosuccinimide also can be successfully used, provided the active chlorine content (usually in the range 60–80%) is determined (potassium iodide–sodium thiosulfate method).

(18) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

g.) in dimethylformamide (1.1 l.) and pyridine (100 ml.) was cooled to 0°, and methanesulfonyl chloride (78.4 g.) was added dropwise. Stirring was continued for 27 hours at room temperature, the reaction mixture then was diluted with water and extracted with methylene chloride. The extracts were washed with aqueous 10% sodium bicarbonate solution, then water, and dried ($MgSO_4$). Evaporation *in vacuo* gave 77 g. (88%) of crude product. Filtration through a Florisil column in ether, and crystallization from acetone–hexane yielded 48 g. (55%) of pure IX, m.p. 164–167°, $[\alpha]D$ +104°, λ_{max}^{MeOH} 238 mμ (15,200); λ_{max}^{Nujol} 5.75, 6.01, 6.15, 6.22 μ.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.71; H, 7.89.

9α,11β-Dichloro-1,4-androstadiene-3,17-dione (VI). (A) From 9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIa) with Sodium Bismuthate.—To a solution of IIa (1.0 g.) in 50% aqueous acetic acid (800 ml.) was added sodium bismuthate (18 g.) and the suspension was stirred at room temperature for 20 hours. The reaction mixture then was filtered, and methylene chloride was added to the filtrate. Water was added to the resulting mixture, the organic phase was separated and washed successively with water, 10% aqueous sodium bicarbonate solution and water. The methylene chloride solution now was dried ($MgSO_4$) and evaporated *in vacuo* to yield the crude product. Crystallization from acetone–hexane furnished pure VI (684 mg., 80%), m.p. 222–230° dec., $[\alpha]D$ +178°, λ_{max}^{MeOH} 235 mμ (15,600); λ_{max}^{Nujol} 5.75, 6.02, 6.16, 6.24 μ.

Anal. Calcd. for $C_{19}H_{22}O_2Cl_2$: C, 64.59; H, 6.28; Cl, 20.07. Found: C, 64.24; H, 6.58; Cl, 19.67.

(B) From 1,4,9(11)-Androstatriene-3,17-dione (IX).—To a stirred solution of IX (1.32 g.) in diethylacetic acid (60 ml.) containing lithium chloride (5.0 g.) was added N-chlorosuccinimide (684 mg.) and then immediately *N* aqueous hydrochloric acid (5.0 ml.). Stirring was continued at room temperature for 17 hours, and the reaction mixture then was poured into saturated aqueous sodium carbonate solution. The resulting mixture was extracted with methylene chloride, and the extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to yield the crude product.

Crystallization from acetone–hexane gave VI (475 mg., 29%), m.p. 227–231° dec. The identity of this material with VI prepared as in (A) was confirmed by mixed melting point and comparison of infrared spectra.

9α,11β-Dibromo-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (III).—To a stirred solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) in glacial acetic acid (40 ml.) was added potassium bromide (6.0 g.) followed by N-bromoacetamide (395 mg.). Stirring was continued at room temperature for 2 hours, and the reaction mixture then was poured into water (400 ml.) and filtered. The *wet* solid was dissolved in methylene chloride and the solution was dried ($MgSO_4$) and concentrated to about 20 ml. Ether now was added, and the solution was concentrated further until crystallization ensued. The dibromo compound III (748 mg., 53%) thus was obtained, m.p. *ca.* 140° (chars above 110°), $[\alpha]D$ +185°, λ_{max}^{MeOH} 240 mμ (14,100); λ_{max}^{Nujol} 2.90, 5.72, 5.78, 6.02, 6.18, 8.12 μ.

Anal. Calcd. for $C_{23}H_{28}O_5Br_2$: C, 50.75; H, 5.18; Br, 29.37. Found: C, 51.00; H, 5.04; Br, 28.82.

9α-Bromo-11β-chloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (IV).—To a stirred, cooled (0–5°) solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) and lithium chloride (4.0 g.) in glacial acetic acid (40 ml.) was added N-bromoacetamide (395 mg.) followed immediately by an anhydrous solution of hydrogen chloride (104 mg.) in tetrahydrofuran (1.0 ml.). Stirring was continued at room temperature for 3 hours, and the reaction mixture was water precipitated and filtered. The residue was washed with water, and dried to yield 1.2 g. (92%) of crude product. Crystallization from acetone gave analytically pure IV, m.p. 190–195° dec., $[\alpha]D$ +172°, λ_{max}^{MeOH} 239 mμ(14,500); λ_{max}^{Nujol} 2.88, 5.79, 5.87, 6.02, 6.20, 8.1 μ.

Anal. Calcd. for $C_{23}H_{28}O_5BrCl$: C, 55.26; H, 5.65; Br, 15.99; Cl, 7.09. Found: C, 55.28; H, 5.34; Br, 15.60; Cl, 7.01.

9α-Bromo-11-β-chloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IVa).—A suspension of IV (1.0 g.) in 0.27 *N* methanolic perchloric acid (70 ml.) was stirred at room temperature for 17 hours. The reaction mixture then was water precipitated and filtered. The residue was washed with water, and dried, giving 912 mg. (quantitative yield) of crude product. Crystallization from acetone yielded pure IVa (455 mg., 50%), m.p. >320° (chars above 110°), $[\alpha]D$ +142° (pyridine), λ_{max}^{MeOH} 240 mμ (13,500); λ_{max}^{Nujol} 3.00, 5.86, 6.06, 6.18, 6.26 μ.

Anal. Calcd. for $C_{21}H_{26}O_4BrCl$: C, 55.09; H, 5.73; Br, 17.46; Cl, 7.74. Found: C, 55.05; H, 5.89; Br, 17.31; Cl, 7.88.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (I) from 9α-Bromo-11β-chloro-1,4-pregnadiene-17α,-21-diol-3,20-dione 21-Acetate (IV).—To a solution of IV (100 mg.) in glacial acetic acid (5 ml.) was added zinc dust (100 mg.) and the mixture was heated on the steam-bath for 20 minutes. The reaction mixture then was filtered, and the zinc dust on the filter was washed with methanol. The combined filtrate and washings were diluted with water and extracted with methylene chloride. The methylene chloride extract was dried ($MgSO_4$), evaporated *in vacuo*, and the resulting solid was crystallized from acetone–hexane, furnishing I (27 mg., 35%), identical with authentic I as evidenced by melting point, mixed melting point and comparison of infrared spectra.

Attempted Preparation of 9α-Bromo-11β-chloro-1,4-androstadiene-3,17-dione (VII) from 1,4,9(11)-Androstatriene-3,17-dione (IX).—To a stirred solution of IX (1.0 g.) and lithium chloride (5 g.) in glacial acetic acid (40 ml.) at room temperature was added N-bromoacetamide (700 mg.) and *N* aqueous hydrochloric acid (5.0 ml.). Stirring was continued for 3 hours, the reaction mixture then was poured into water, filtered, and the residue was washed with water and dried. No pure product could be obtained by crystallization, so the total crude material was chromatographed on a silica gel column. Elution with hexane–ether (4:1) yielded solid (140 mg.). Crystallization from acetone–hexane gave a substance, m.p. 151–155° dec., $[\alpha]D$ +171°, λ_{max}^{MeOH} 239 mμ (13,000); λ_{max}^{Nujol} 5.75, 6.04, 6.15, 6.22 μ. We were unable to obtain a satisfactory analysis for this material.

Anal. Calcd. for $C_{19}H_{22}O_2BrCl$: C, 59.77; H, 5.82; Br, 20.93; Cl, 9.29. Found: C, 58.68; H, 5.79; Br, 19.73; Cl, 8.33.

9α-Bromo-11β-fluoro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (V).—To a stirred solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) in diethylacetic acid (50 ml.) contained in a polyethylene bottle, was added a solution of hydrogen fluoride in chloroform–tetrahydrofuran (5 ml., 270 mg. of hydrogen fluoride per ml. of solution), followed by N-bromoacetamide (395 mg.). Stirring was continued for 17 hours, and the solution then was poured into 10% aqueous sodium carbonate solution (500 ml.). The mixture was extracted with methylene chloride and the extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give 1.15 g. (91%) of crude product. Crystallization from acetone–hexane yielded pure V (660 mg., 51%), m.p. 225–228° dec., $[\alpha]D$ +123°, λ_{max}^{MeOH} 240 mμ (13,800); λ_{max}^{Nujol} 2.95, 3.02, 5.75, 5.80, 6.02, 6.20, 8.10 μ.

Anal. Calcd. for $C_{23}H_{28}O_5BrF$: C, 57.15; H, 5.84; Br, 16.53; F, 3.93. Found: C, 57.41; H, 6.12; Br, 16.38; F, 3.64.

9α-Bromo-11β-fluoro-1,4-pregnadiene-17α,21-diol-3,20-dione (Va).—A solution of V (1.0 g.) in 0.27 *N* methanolic perchloric acid (70 ml.) was left at room temperature for 17 hours. The reaction mixture then was poured into water (500 ml.), filtered, and the residue was washed with water and dried, giving 400 mg. of solid. The filtrate and washings were extracted with methylene chloride, the extracts were washed with aqueous sodium bicarbonate solution, then water, and dried ($MgSO_4$). Evaporation *in vacuo* furnished solid (495 mg.), the total yield of crude product was therefore 895 mg. (96%). These solids were combined and crystallized from acetone–hexane to give pure Va, m.p. >300° (chars above 210°), $[\alpha]D$ +88° (pyridine), λ_{max}^{MeOH} 239 mμ (14,300); λ_{max}^{Nujol} 3.00, 5.85, 6.04, 6.22 μ.

Anal. Calcd. for $C_{21}H_{26}O_4BrF$: C, 57.15; H, 5.94; Br, 18.11; F, 4.30. Found: C, 57.13; H, 6.10; Br, 18.35; F, 4.26.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (I) from 9α-Bromo-11β-fluoro-1,4-pregnadiene-17α,21-diol-

3,20-dione 21-Acetate (V).—A solution of V (200 mg.) in acetone (20 ml.), under a carbon dioxide atmosphere, was treated with chromous chloride solution[18] (5 ml.). After 10 minutes the solution was poured into water, and the mixture was extracted with methylene chloride. Evaporation of the dried ($MgSO_4$) extract and crystallization of the resulting solid from acetone–hexane gave I (90 mg., 56%), m.p. 209–217°, $[\alpha]_D$ +62°; infrared spectrum identical with that of authentic I.

9α-Bromo-11β-fluoro-1,4-androstadiene-3,17-dione (VIII).—To a stirred solution of 1,4,9(11)-androstatriene-3,17-dione (1.0 g.) in diethylacetic acid (50 ml.), contained in a polyethylene bottle, was added a solution of hydrogen fluoride in chloroform–tetrahydrofuran (5 ml., 270 mg. of hydrogen fluoride per ml. of solution), and then the N-bromoacetamide (538 mg.). Stirring was continued for 17 hours, and the solution then was poured into 10% aqueous sodium carbonate solution (500 ml.). The mixture was extracted with methylene chloride, and the extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product (1.21 g., 90%). Crystallization from acetone–hexane gave pure VIII (550 mg., 41%), m.p. 194–196° dec., $[\alpha]_D$ +118°, λ_{max}^{MeOH} 239 mμ (14,000); λ_{max}^{Nujol} 5.74, 6.02, 6.15, 6.22 μ.

Anal. Calcd. for $C_{19}H_{22}O_2BrF$: C, 59.84; H, 5.82; Br, 20.96; F, 4.98. Found: C, 60.00; H, 5.94; Br, 20.92; F, 4.32.

1,4,9(11)-Androstatriene-3,17-dione (IX) from 9α-Bromo-11β-fluoro-1,4-androstadiene-3,17-dione (VIII).—To a solution of VIII (100 mg.) in acetone (5 ml.), under carbon dioxide, was added chromous chloride solution[18] (5 ml.). After 5 minutes the reaction mixture was poured into water, and extracted with methylene chloride. The crude product was crystallized from acetone–hexane, yielding IX (25 mg., 42%), m.p. 163–166°, infrared spectrum identical with the spectrum of authentic IX.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

A Novel Route to 9α-Halo-11β-acyloxycorticosteroids

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A series of hitherto undescribed 11β-esters of 9α-bromo- and 9α-chloro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetates has been prepared by direct addition of the elements of acyl hypohalite to 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I). A new method for converting I to the corresponding 9β,11β-oxide is described.

The interesting biological properties manifested by C-9 fluorinated derivatives of hydrocortisone[1] and prednisolone[2] include considerably enhanced anti-inflammatory activity and concomitantly increased salt retention (by comparison with the non-fluorinated parent compound, in each case). Substantial efforts have been made recently to retain the anti-inflammatory activity of these 9α-fluorinated compounds while diminishing the undesirable salt retention by appropriate modifications[3–5] elsewhere in the molecule.

Until now, 9α-halogenated corticosteroids have been prepared by conversion of the appropriate $\Delta^{9(11)}$-compound to the 9α-bromo-11β-ol, using hypobromous acid, followed by closure with base to the 9β,11β-oxide, which then was transformed to the 9α-chloro- and 9α-fluoro-11β-alcohol by treatment with hydrogen chloride and hydrogen fluoride, respectively.[1,2]

The corresponding 11β-acyl compounds have not been described hitherto, since the sterically hindered 11β-hydroxyl function can be acylated only by procedures which simultaneously esterify the C-17α-hydroxyl group.[6]

We therefore sought a method for the preparation of such esters, which we believed might provide interesting biological data while also furnishing a 9,11-halohydrin system protected for further manipulations (for example oxidations). Also, in view of the ready closure of *trans*-halohydrins to the oxides under basic conditions,[7] we felt such protection using, perhaps, an 11β-acetate group, might prove of value. The literature describes several examples[8–10] of the addition of the elements of acetyl hypohalite to double bonds to yield halo acetates, and this approach indeed proved fruitful.

Thus, when 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate[2] (I) was treated, in glacial acetic acid containing lithium acetate, with N-bromoacetamide, stereospecific conversion (74% yield of pure material) to 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-diacetate (II) occurred.

That II had resulted from the addition of the elements of acetyl hypobromite to the triene I was apparent from elemental analysis. The probability that this addition had taken place at the 9(11)-double bond was strengthened by the ultraviolet ($\lambda_{max.}$ 240 mμ, ε 15,000) and infrared spectra (pres-

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(6) The conversion of 9α-halo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetates to the corresponding 9α-halo-11β,17α,21-triacetates, using *p*-toluenesulfonic acid in acetic acid–acetic anhydride mixtures, at room temperature, has been successfully accomplished by Mr. E. L. Shapiro and Dr. D. H. Gould of these laboratories.

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(10) See especially G. H. Alt and D. H. R. Barton (*J. Chem. Soc.*, 4284 (1954)) who observed the formation of 3α-chloro-2β-acetoxycholestane, as well as the two *trans*-2,3-dichlorocholestanes, when cholest-2-ene was treated with chlorine in a carbon tetrachloride–acetic acid mixture.