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.

Acknowledgment.—The authors are grateful to Miss M. Kirtley for assistance with some of the experiments, and to Mr. R. Wayne for much helpful advice on the interpretation of infrared spectra.

BLOOMFIELD, N. J.

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

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

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

RECEIVED SEPTEMBER 8, 1958

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-

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

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

(3) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956).

(4) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoft, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, *ibid.*, **80**, 3161 (1958).

(5) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4431 (1958).

(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.

(7) See for example P. D. Bartlett, THIS JOURNAL, **57**, 224 (1935).

(8) H. J. Backer and J. S. Strating, *Rec. trav. chim.*, **53**, 525 (1934).

(9) W. Bockemüller and F. W. Hoffman, *Ann.*, **519**, 165 (1935).

(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.

ence of intact 1,4-dien-3-one system and cortical side chain) of II.

If the reaction is accepted as proceeding through ionic species, analogy with the addition of hypobromous acid to the 9(11)-double bond[11] would lead to the prediction that II is a 9α-bromo-11β-acetate (formed by attack of $Br^{\oplus}$ on the 9(11)-double bond to give the intermediate 9,11-α-bromonium ion which on β-face attack by acetate ion opens diaxially).

Proof that our formulation of II was indeed correct came from the conversion of II to authentic 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-11β,17α,21-triacetate[12] (IIa) on acetylation with a *p*-toluenesulfonic acid–acetic acid–acetic anhydride mixture at room temperature. Identity was confirmed by melting point, mixed melting point, comparison of infrared spectra and paper chromatography.

Similarly we were able to prepare 9α-chloro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-11β,21-diacetate (III) by the action of N-chlorosuccinimide, in acetic acid containing lithium acetate, on the triene I.

Extension of this reaction, substituting formic acid and sodium formate for acetic acid and lithium acetate, furnished, in good yields, 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-11β-formate 21-acetate (IV) and the corresponding 9α-chloro compound V. Similarly, using trifluoroacetic acid, 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-11β-trifluoroacetate 21-acetate (VI) was obtained.

The structural assignments are based on elemental analyses, ultraviolet and infrared spectra, and analogy with the formation of the 9α-bromo-11β-acetate II.

We also observed (interestingly, in view of the size of the diethylacetate group and the hindered nature of the 11β-position) that the action of N-bromoacetamide, in diethylacetic acid containing *p*-toluenesulfonic acid, on the 1,4,9(11)-triene I furnished a bromine-containing compound, the infrared spectrum and analysis of which strongly suggested the 9α-bromo-11β-diethylacetate VII. This supposition received strong support when hydrolysis at C-21, using perchloric acid in methanol[11] at room temperature, yielded the corresponding 21-alcohol VIIIa which gave a strong positive tetrazolium reaction, and showed infrared bands (5.78 and 8.88 μ) clearly attributable only to the diethylacetate group. Elemental analysis again supported the 9α-bromo-11β-diethylacetate structure VIIa.

Acetylation of the 21-alcohol VIIa in pyridine–acetic anhydride at room temperature proceeded smoothly to give the original 21-acetate VII. (Identity was confirmed by melting point, mixed melting point, infrared spectrum and paper chromatography.) Attempts to hydrolyze the 11β-ester grouping to furnish the known 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione[2] were unsuccessful, but the evidence cited above, while not conclusive, strongly supports our formulations of VII and VIIa.

We next turned our attention to the action of base on the 9α-bromo-11β-formate IV and the 9α-bromo-11β-trifluoroacetate VI. Since 11β-formates[13–15] and 11β-trifluoroacetates[13] are known to hydrolyze under fairly mild conditions, it was anticipated that conversion of IV and VI directly to the 9β,11β-oxide VIII should be possible under conditions congenial to the cortical side chain. A new alternative route to 9α-chloro- and 9α-fluoro-11β-hydroxy corticoids would then be available.

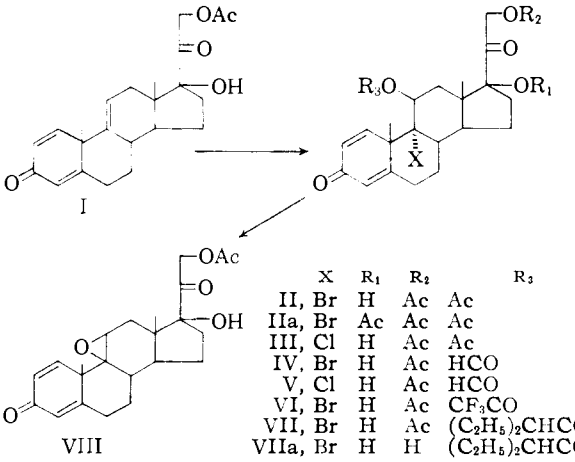
Indeed, treatment of 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-formate 21-acetate (IV) with aqueous sodium hydroxide in methanol at room temperature, with later re-acetylation at C-21, gave the known[2] 9β,11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (VIII).

Similarly the 9α-bromo-11β-trifluoroacetate VI, after subjection to refluxing ethanolic potassium acetate for 17 hours and re-acetylation at C-21, gave the 9β,11β-oxido compound VIII in good yield.

TABLE I

MOLECULAR ROTATIONS AND ULTRAVIOLET ABSORPTION MAXIMA OF 9α-HALO-11β-ACYLOXY-DERIVATIVES OF 1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 21-ACETATE

Substituent 9α	Substituent 11β	[M]D, dioxane	MeOH λmax, mμ
Br	HCOO–	+794°	239
Br	CH_2COO–	+832	240
Br	CF_2COO–	+814	240
Br	$(C_2H_5)_2CHCOO$–	+847	240
Cl	HCOO–	+753	237
Cl	CH_3COO–	+781	236



	X	R_1	R_2	R_3
II,	Br	H	Ac	Ac
IIa,	Br	Ac	Ac	Ac
III,	Cl	H	Ac	Ac
IV,	Br	H	Ac	HCO
V,	Cl	H	Ac	HCO
VI,	Br	H	Ac	CF_3CO
VII,	Br	H	Ac	$(C_2H_5)_2CHCO$
VIIa,	Br	H	H	$(C_2H_5)_2CHCO$

Experimental[16]

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (II).—To a solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) in glacial

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

(12) The triacetate IIa was prepared from the known 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione (ref. 2) by Mr. E. L. Shapiro and Dr. D. H. Gould of these laboratories (see ref. 6).

(13) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 443 (1954).

(14) E. P. Oliveto, C. Gerold and E. B. Hershberg, *Arch. Biochem. Biophys.*, **49**, 244 (1954).

(15) E. P. Oliveto, C. Gerold, R. Rausser and E. B. Hershberg, THIS JOURNAL, **77**, 3564 (1955).

(16) Melting points were obtained on the Kofler block. Rotations were measured at 25° in dioxane solution, unless otherwise stated, at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infra-

acetic acid (40 ml.) containing lithium acetate (4 g.) was added N-bromoacetamide (395 mg.), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was then poured into water (400 ml.). Filtration, followed by water washing and drying of the residue, yielded the crude product (1.3 g., 95%). Crystallization from acetone–hexane furnished pure 9α-bromoprednisolone 11β,21-diacetate (II, 1.0 g.), m.p. 208–210° dec., $[\alpha]_D$ +159°, λ_{max}^{MeOH} 240 mμ (14,000); λ_{max}^{Nujol} 2.98, 5.72, 5.76, 5.80, 6.03, 6.18, 6.28 and 8.15 μ.

Anal. Calcd. for $C_{25}H_{31}O_7Br$ (523.41): C, 57.36; H, 5.97; Br, 15.27. Found: C, 57.38; H, 6.03; Br, 15.96.

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β,17α,21-Triacetate (IIa).—To a stirred suspension of the foregoing diacetate (II, 500 mg.) in glacial acetic acid (10 ml.) and acetic anhydride (10 ml.) was added *p*-toluenesulfonic acid monohydrate (100 mg.), at room temperature. Stirring was continued for 48 hours at room temperature, and the reaction mixture then was poured into cold water (200 ml.), stirred for 1 hour and filtered. The residue was washed with water, and dried, resulting in 490 mg. (90%) of crude product. Crystallization from acetone–hexane furnished 9α-bromoprednisolone-11β,17α,21-triacetate (IIa), m.p. 197–204° dec. (m.p. undepressed on admixture with an authentic specimen[11] of IIa prepared from 9α-bromoprednisolone 21-acetate by the above procedure which had m.p. 197–205° dec., $[\alpha]_D$ +99°, λ_{max}^{MeOH} 241 mμ (14,300)); λ_{max}^{Nujol} 5.72, 5.77, 6.03, 6.16, 6.23 and 8.15 μ, identical with the Nujol spectrum of authentic IIa.

Anal. Calcd. for $C_{27}H_{33}O_8Br$: C, 57.34; H, 5.88; Br, 14.13. Found: C, 56.91; H, 5.79; Br, 14.40.

9α-Chloro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (III).[16a]—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.) containing lithium acetate (4 g.) was added N-chlorosuccinimide (1.1 equiv.) and hydrogen chloride (104 mg.) dissolved in tetrahydrofuran (2.5 ml.). Stirring was continued at room temperature for 2 hours, and the reaction mixture then was poured into water (400 ml.) and filtered. The residue, after washing with water and drying, weighed 1.05 g. (85%). Crystallization from acetone–hexane afforded 9α-chloroprednisolone 11β,-21-diacetate (III), m.p. 278–281° dec., $[\alpha]_D$ +163°, λ_{max}^{MeOH} 236 mμ (15,600); λ_{max}^{Nujol} 2.98, 5.75, 5.81, 6.02, 6.18 and 8.12 μ.

Anal. Calcd. for $C_{25}H_{31}O_7Cl$ (478.95): C, 62.69; H, 6.52; Cl, 7.40. Found: C, 62.66; H, 6.60; Cl, 7.01.

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Formate 21-Acetate (IV).—To a stirred solution of 1,4,-9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) in formic acid (40 ml., 98–100%) containing sodium formate (4 g.) was added N-bromoacetamide (395 mg.). Stirring was continued for 3 hours; the reaction mixture then was poured into water (400 ml.), filtered, and the residue washed with water and dried (1.26 g., 95%). Crystallization from acetone–hexane yielded the 11β-formate IV, m.p. 210–213° dec., $[\alpha]_D$ +156°, λ_{max}^{MeOH} 239 mμ (13,800); λ_{max}^{Nujol} 2.95, 3.02, 5.75, 5.82, 6.04, 6.18, 6.24, 8.10, 8.64, 8.80 μ.

Anal. Calcd. for $C_{24}H_{29}O_7Br$ (509.39): C, 56.58; H, 5.73; Br, 15.69. Found: C, 56.27; H, 5.68; Br, 14.12.

9α-Chloro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Formate 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 formic acid (40 ml., 98–100%) containing sodium formate (4 g.) was added *N*-chlorosuccinimide (1.1 equiv.), followed immediately by *N* hydrochloric acid (2.7 ml.). Stirring was continued for 3 hours, at room temperature, and the reaction mixture now was poured into water (400 ml.). Filtration and then water washing and drying of the residue gave solid (1.14 g., 95%). Crystallization from acetone–hexane gave the 11β-formate V, m.p. 258–262° dec., $[\alpha]_D$ +162°, λ_{max}^{MeOH} 237 mμ (14,500); λ_{max}^{Nujol} 2.86, 3.02, 3.12, 5.75, 5.82, 6.04, 6.18, 6.22, 8.10, 8.64 and 8.8 μ.

Anal. Calcd. for $C_{24}H_{29}O_7Cl$ (464.93): C, 61.99; H, 6.28; Cl, 7.64. Found: C, 61.64; H, 6.58; Cl, 7.36.

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Trifluoroacetate 21-Acetate (VI).—To a stirred solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 1.0 g.) in tetrahydrofuran (20 ml.) and trifluoroacetic acid (20 ml.) was added N-bromoacetamide (400 mg.), the temperature being maintained at about 25° by cooling. Stirring at room temperature was continued for 3 hours, and the reaction mixture was then poured into water (400 ml.) and filtered. The residue was washed with water, dried (1.05 g.) and crystallized from acetone–hexane, giving the trifluoroacetate VI, m.p. 205–210° dec., $[\alpha]_D$ +141° λ_{max}^{MeOH} 240 mμ (13,900); λ_{max}^{Nujol} 2.97, 5.63, 5.69, 5.78, 6.02, 6.18, 6.23, 8.09 μ.

Anal. Calcd. for $C_{25}H_{28}O_7BrF_3$ (577.39): C, 52.00; H, 4.89; Br, 13.84; F, 9.87. Found: C, 52.20; H, 4.89; Br, 13.76; F, 10.09.

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Diethylacetate 21-Acetate (VII). (A).—To a stirred solution of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I, 200 mg.) in diethylacetic acid (50 ml.) was added N-bromoacetamide (395 mg.) and *p*-toluenesulfonic acid monohydrate (50 mg.) at room temperature. Stirring was continued for 17 hours, and the reaction mixture was then poured into saturated sodium carbonate solution (500 ml.). The steroid was isolated by extraction with methylene chloride, and the extracts were washed with water. Evaporation of the dried (Na_2SO_4) extracts *in vacuo* and crystallization of the residue from acetone–hexane furnished the diethylacetate (VII, 120 mg.), m.p. 211–213° dec., $[\alpha]_D$ +147°, λ_{max}^{MeOH} 240 mμ (14,600); λ_{max}^{Nujol} 2.88, 5.74, 5.82, 5.85, 6.05, 6.18, 6.24, 8.10, 8.56 μ.

Anal. Calcd. for $C_{29}H_{39}O_7Br$ (579.5): C, 60.10; H, 6.78; Br, 13.79. Found: C, 60.12; H, 6.94; Br, 13.89.

(B) By Acetylation of the 21-Alcohol VIIa.—Acetylation of the 21-alcohol VIIa in pyridine and acetic anhydride at room temperature for 7 hours yielded, after water precipitation, filtering and drying of the water-washed residue, the 21-acetate VII, m.p. 204–207° dec. (undepressed on admixture with authentic VII prepared as in A), λ_{max}^{MeOH} 240 mμ (14,900). The infrared spectrum (Nujol) completely matched the spectrum of authentic VII.

9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Diethylacetate (VIIa).—A suspension of the 21-acetate (VII, 1.0 g.) in 0.27 *N* methanolic perchloric acid[12] (60 ml.) was stirred at room temperature for 17 hours. The reaction mixture then was poured into water (500 ml.) and filtered. The water-washed, dried product (820 mg.) was crystallized from acetone–hexane, furnishing the 21-alcohol VIIa, m.p. 185–187° dec., $[\alpha]_D$ +130°, λ_{max}^{MeOH} 240 mμ (14,600); λ_{max}^{Nujol} 2.98, 5.78, 5.86, 6.04, 6.20, 6.24 and 8.88 μ.

Anal. Calcd. for $C_{27}H_{37}O_6Br$ (537.47): C, 60.33; H, 6.94; Br, 14.87. Found: C, 60.63, 60.49; H, 6.88, 7.00; Br, 14.75, 15.14.

Conversion of 9α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-Formate 21-Acetate (IV) to the 9β,11β-Oxide VIII.—To a suspension of the 11β-formate (IV, 570 mg.) in methanol (35 ml.) was added, dropwise, with stirring, *N* aqueous sodium hydroxide (2.85 ml.). Stirring was continued at room temperature for 16 hours, and the reaction mixture was then poured into water (400 ml.). The steroid was isolated by methylene chloride extraction, and the methylene chloride extracts were evaporated *in vacuo* to yield crude 9β,11β-oxido-21-alcohol (350 mg.). This material was acetylated in pyridine–acetic anhydride at room temperature for 1.5 hours, and the acetylated product was isolated by water precipitation and filtration. The water-washed, dried residue (350 mg., 78% from IV) was crystallized from acetone–hexane, furnishing 9β,11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate[2] (VIII), m.p. 209–210° (m.p. undepressed on admixture with authentic VIII of m.p. 218°). The identity was confirmed by comparison of infrared spectra, and by paper chromatography.

Conversion of 1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (I) to 9β,11β-Oxido-1,4-pregnadiene-17α,-21-diol-3,20-dione 21-Acetate (VIII) through the 9α-Bromo-11β-trifluoroacetate (VI).—The 1,4,9(11)-triene (I, 1.0 g.) was

red spectra and rotations. Microanalyses were performed by Mr. Conner (Microanalytical Laboratory, Schering Corp.), Schwarzkopf Microanalytical Laboratory, Woodside, L. I., and Galbraith Laboratories, Knoxville, Tenn.

(16a) After this paper was submitted, the preparation of the 1,2-dihydro analogs of III and V by somewhat different technique, and the conversion of 1,2-dihydro V to the 9β,11β-oxido derivative, were described by Dr. S. K. Figdor at the American Chemical Society Meeting, Chicago, Ill., Sept. 11, 1958.

converted to 9α-bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-trifluoroacetate 21-acetate (VI) as described previously, except that the reaction mixture was water precipitated and extracted with methylene chloride, the extracts being washed with sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated *in vacuo*. The crude yellow solid (1.5 g.) was dissolved in absolute ethanol (100 ml.) containing potassium acetate (4 g.), and the solution was refluxed for 17 hours. The reaction mixture was concentrated to small volume, water was added, and the mixture was extracted with methylene chloride. The extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*, giving a solid (750 mg.). (Paper chromatography (propylene glycol–dioxane–toluene system) demonstrated that this solid contained at least 80% of the 9β,11β-oxido 21-acetate VIII. A more polar substance also was present, the migration rate of which strongly suggested the 9β,11β-oxido 21-alcohol.) This material was re-acetylated at C-21 (pyridine and acetic anhydride at room temperature) and the acetylated product (750 mg., 73% from I) was filtered through a Florisil column in methylene chloride–ether (1:9) to yield 9β,11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (VIII) identical with authenic VIII as evidenced by melting point, mixed melting point and comparison of infrared spectra.

BLOOMFIELD, N. J.

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

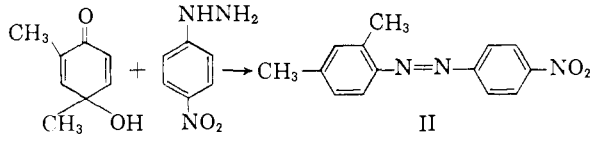
The Reaction of Steroidal *p*-Quinol Acetates with Benzylamine: Amine Analogs of Estrone and Estradiol[1]

BY A. M. GOLD[2] AND E. SCHWENK

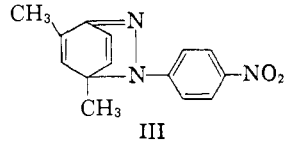
RECEIVED NOVEMBER 7, 1958

The steroidal *p*-quinol acetates 10ξ-acetoxy-1,4-estradiene-3,17-dione (VI) and 10ξ-acetoxy-17β-hydroxy-1,4-estradiene-3-one (IX), on refluxing with benzylamine followed by treatment with dilute sulfuric acid, yield 3-amino-1,3,5(10)-estratriene-17-one (VII) and 3-amino-1,3,5(10)-estratriene-17β-ol (X), respectively. A possible mechanism is presented. The O,N-diacetyl derivative XI of the latter amine was obtained independently by the reaction of 19-nortestosterone oxime with acetic anhydride.

The diversity of reactions undergone by the quinols and their derivatives[3-5] has made them useful intermediates in the synthesis of numerous types of compounds. The reaction of *p*-quinols with hydrazine derivatives was described by Bamberger[6] in 1900 when the first *p*-quinols were reported. The highly colored product resulting from condensation of 4-hydroxy-2,4-dimethyl-2,5-cyclohexadienone (I) and *p*-nitrophenylhydrazine first was formulated as III, but later[7] was corrected to 2,4-dimethyl-4′-nitroazobenzene (II). The reaction also worked well with the non-aromatic hydrazine semicarbazide.

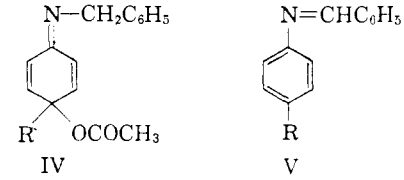


I



III

This procedure appeared to be a potentially useful method for the preparation of aromatic amines *via* reduction of the azo compounds. However, a modification using benzylamine, in place of the hydrazine derivative, and the acetate of the quinol[8] promised to lead to the desired amines through a more direct pathway. The mechanism would involve condensation of the quinol acetate and the amine to a Schiff base IV. Loss of acetic acid with concurrent aromatization then leads to another Schiff base (V) which will yield the amine and benzaldehyde on acid hydrolysis.



IV V

For the first experiments the steroidal quinol acetate VI,[9] 10ξ-acetoxy-1,4-estradiene-3,17-dione, was chosen. The steroid was refluxed in benzylamine and then boiled with aqueous sulfuric acid. On extraction, a fair yield of the free amine VII was isolated. The product had infrared and ultraviolet spectra consistent with the formulation as a disubstituted aniline. The substance could be sublimed and recrystallized, but could not be obtained analytically pure. An N-acetyl derivative (VIII) was prepared to facilitate characterization.

The steroidal quinol monoacetate IX yielded, similarly, the amine X. This substance proved very difficult to purify by crystallization, but formed difficultly soluble, well crystallized salts with hydrochloric and sulfuric acid.

In order to verify the relationship of these aromatic amines to the estrogens, the amino

(1) This work was supported by the United States Public Health Service grant No. C321, an Institutional Grant from the American Cancer Society, and a special grant from the Schering Corp., Bloomfield, N. J. The authors wish to acknowledge gifts of estrone and estradiol from G. D. Searle & Co., Chicago, Ill., and the Schering Corp.; 19-nortestosterone was kindly provided by Prof. Dr. Karl Junkmann, Schering A. G. Berlin.

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