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]

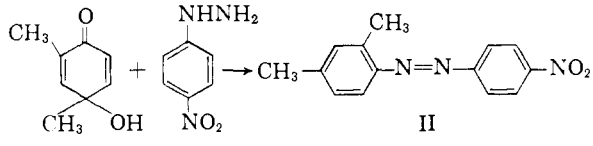
The Reaction of Steroidal *p*-Quinol Acetates with Benzylamine: Amine Analogs of Estrone and Estradiol[1]

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

RECEIVED NOVEMBER 7, 1958

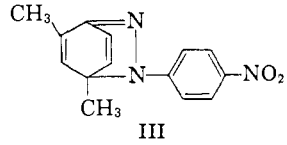
The steroidal *p*-quinol acetates 10ξ-acetoxy-1,4-estradiene-3,17-dione (VI) and 10ξ-acetoxy-17β-hydroxy-1,4-estradiene-3-one (IX), on refluxing with benzylamine followed by treatment with dilute sulfuric acid, yield 3-amino-1,3,5(10)-estratriene-17-one (VII) and 3-amino-1,3,5(10)-estratriene-17β-ol (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.



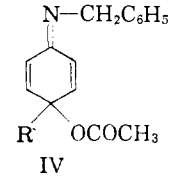
I

II

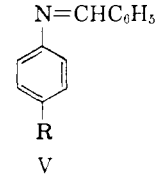


III

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

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(3) (a) E. Schinzel and F. Wessely, *Monatsh.*, **86**, 912 (1955); (b) F. Langer and F. Wessely, *ibid.*, **88**, 298 (1957); (c) W. Metlesics, F. Wessely and Budzikiewicz, *ibid.*, **89**, 102 (1958).

(4) S. Goodwin and B. Witkop, THIS JOURNAL, **79**, 179 (1957).

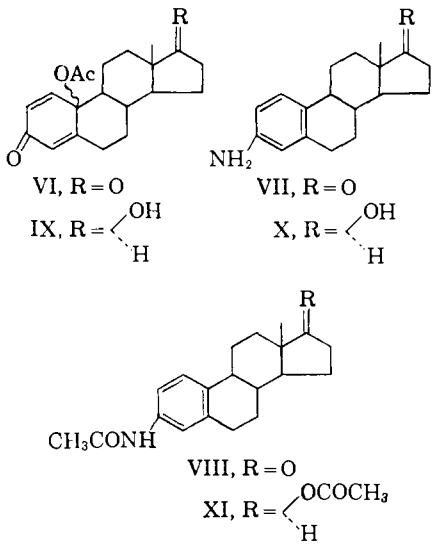
(5) D. H. R. Barton and G. Quinkert, *Proc. Chem. Soc.*, 197 (1958).

(6) E. Bamberger, *Ber.*, **33**, 3600 (1900).

(7) E. Bamberger, *ibid.*, **35**, 1424 (1902).

(8) F. Wessely and F. Sinwel, *Monatsh.*, **81**, 1055 (1950).

(9) A. M. Gold and E. Schwenk, THIS JOURNAL, **80**, 5683 (1958).



ketone VII was diazotized and the resulting diazonium salt was hydrolyzed by heating in acid. The product was shown to be estrone by the usual physical methods.

The nature of the products also was shown by independent synthesis, making use of the long-known reaction of cyclohexene oximes with acetic anhydride.[10] When 19-nortestosterone oxime was boiled with acetic anhydride a fair yield of 3-acetamido-1,3,5(10)-estratriene-17β-ol-acetate (XI) could be isolated. This substance was shown to be identical to the product of acetylation of X.

The choice of benzylamine as reactant and solvent was dictated by the high boiling point, high basicity and relatively unhindered nature of this amine. More important, however, was the activation of the α-hydrogen atoms by the phenyl group. Loss of acetic acid by the intermediate IV will depend partly upon the ease with which an α-hydrogen can be abstracted by base. When cyclohexylamine was substituted for benzylamine in the reaction with IX only a trace of cyclohexanone and no X could be detected.

The reaction of quinol derivatives with benzylamine may be of general applicability in the synthesis of aromatic amines. Conversely, it is possible that quinol acetates will be useful reagents for the conversion of amines, having activated α-hydrogen atoms, to aldehydes or ketones.

Experimental[11]

3-Amino-1,3,5(10)-estratriene-17-one (VII).—A solution of 10ξ-acetoxy-1,4-estradiene-3,17-dione (0.50 g.) in 5.0 ml. of benzylamine was refluxed for 2.5 hours. Most of the benzylamine was removed by warming in a stream of nitrogen and the residue was refluxed with 50 ml. of 2 *N* H_2SO_4 for two hours. The cooled mixture, smelling strongly of benzaldehyde, was extracted with ether, made alkaline with solid Na_2CO_3, and extracted with methylene chloride. The latter extract was dried with Na_2SO_4 and evaporated to a semi-crystalline material which smelled strongly of benzylamine. Cyclohexane (10 ml.) was added to the product and, after standing at room temperature for a short time, the mixture was filtered. The crude product consisted of 0.27 g. (66% yield) of dark reddish crystals.

The crude product was sublimed at 140° (0.01 mm.). The resulting white powder could be recrystallized repeatedly from benzene–cyclohexane mixtures, but no satisfactory microanalysis was obtained. The best product showed m.p. 192.0–192.6° in an evacuated capillary when introduced into the bath at 188°; $\lambda\lambda_{max}^{CH_3OH}$ 238 mμ (9,100), 292 mμ (1,900); $[\alpha]^{25}D$ + 160° (*c* 1.1, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{23}ON$: N, 5.20. Found: N, 5.62.

3-Acetamido-1,3,5(10)-estratriene-17-one (VIII).—A solution of 3-amino-1,3,5(10)-estratriene-17-one (80 mg.) in 1.0 ml. of pyridine was treated with 0.20 ml. of acetic anhydride and allowed to stand at room temperature for one hour. Water (10 drops) was added and after one hour 10 ml. of 2 *N* H_2SO_4 was added. The white precipitate was filtered, washed with water and recrystallized from aqueous methanol. After sublimation at 195° (0.02 mm.) the product was twice recrystallized from aqueous methanol. The analytical sample showed m.p. 255–256.0° (evacuated capillary); $\lambda\lambda_{max}^{CH_3OH}$ 247 mμ (15,500), 289 mμ (1,100); $[\alpha]^{23}D$ +161° (*c* 0.9, dimethylformamide).

Anal. Calcd. for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.43, 77.61; H, 8.12, 8.24; N, 4.59.

Estrone Acetate from 3-Amino-1,3,5(10)-estratriene-17-one (VIII).—The amino ketone (50 mg.) was dissolved in 3.0 ml. of 0.7 *N* H_2SO_4, cooled in ice-water (the amine sulfate crystallized) and treated with 39 mg. of solid $NaNO_2$. The amine sulfate dissolved rapidly and the solution was allowed to stand at 0° for 15 minutes. Urea (58 mg.) was added and the resulting solution was warmed to room temperature in about 10 minutes. The solution was diluted with 10 ml. of water and boiled for 10 minutes. After cooling, the precipitate was isolated by filtration, dried and sublimed at 160° (0.03 mm.). The sublimate was recrystallized from methanol to yield 23 mg. of white crystals which were identified as estrone by their ultraviolet spectrum, melting point and mixture melting point. The infrared spectrum, however, showed slight discrepancies.

The product was dissolved in 1.0 ml. of pyridine containing 0.10 ml. of acetic anhydride and allowed to stand overnight at room temperature. The solution was worked up in the usual way and the product was crystallized from cyclohexane, sublimed at 115° (0.03 mm.) and recrystallized. This product, m.p. 124–125°, had an infrared spectrum identical to that of estrone acetate and showed no melting point depression on admixture with the authentic material.

3-Amino-1,3,5(10)-estratriene-17β-ol (X).—A solution of 10ξ-acetoxy-17β-hydroxy-1,4-estradiene-3-one (0.30 g.) in 3.0 ml. of benzylamine was refluxed for two hours. Most of the benzylamine was evaporated by warming in a stream of nitrogen and the residue was treated with 5 ml. of 2 *N* H_2SO_4 and 25 ml. of water. This mixture was distilled down to half its original volume and the distillate was set aside for isolation of benzaldehyde. The residue was refluxed for another 1.5 hours. The cooled mixture precipitated a quantity of tan solid which was isolated by filtration, washed with water and dry ether and dried. Recrystallization of the crude product from methanol gave 0.15 g. of cotton-like crystals of amine sulfate. A quantity of the sulfate was shaken with benzene and aqueous Na_2CO_3 solution until dissolved, and the organic phase was dried over Na_2SO_4 and evaporated. The free amine could, with difficulty, be recrystallized from benzene–cyclohexane, but no preparation could be obtained free of the highly colored oxidation product characteristic of aromatic amines. The best preparation showed m.p. 143°; $\lambda\lambda_{max}^{CH_3OH}$ 237 mμ (7,900), 292 mμ (1,500); $[\alpha]^{21}D$ +71° (*c* 1.0, $CHCl_3$).

The steam distillate was treated with excess 2,4-dinitrophenylhydrazine reagent[12] and the precipitated derivative was isolated and recrystallized from ethyl acetate. The product weighed 0.23 g. (88% yield) and melted at 241.4–242.2°. Authentic benzaldehyde 2,4-dinitrophenylhydrazone melted at 240.5–241.6°.

Sulfate of X.—The amine sulfate was recrystallized from methanol three times to prepare an analytical sample which decomposed at 320° (evacuated capillary).

(10) F. M. Beringer and I. Ugelow, THIS JOURNAL, **75**, 2635 (1953).

(11) All melting points below 270° were determined with a Hershberg apparatus, using Anschütz thermometers. Ultraviolet spectra were taken with a Cary recording spectrophotometer, model 11MS. The authors are indebted to Mr. E. Connor of the Analytical Department of the Schering Corp. for part of the microanalyses.

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," third edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

Anal. Calcd. for $C_{18}H_{25}ON \cdot 1/2\ H_2SO_4$; N, 4.37; S, 4.99. Found: N, 4.32; S, 5.10.

Hydrochloride of X.—A quantity of the free amine was converted to its hydrochloride and recrystallized from methanol–water three times. The salt was treated with active charcoal in methanol solution, filtered and again recrystallized. The product melted at 274° (evacuated capillary).

Anal. Calcd. for $C_{18}H_{25}ON \cdot HCl$: C, 70.22; H, 8.51; N, 4.55; Cl, 11.53. Found: C, 70.32; H, 8.58; N, 4.00; Cl, 11.61.

3-Acetamido-1,3,5(10)-estratriene-17β-ol-acetate (XI). From 19-Nortestosterone.—A solution of 19-nortestosterone (2.42 g.) in 30 ml. of methanol was treated with a solution of 1.86 g. of hydroxylamine hydrochloride and 5.0 g. of sodium acetate hydrate in 10 ml. of water. The mixture was boiled on the steam-bath for 3 hours and the concentration of methanol was adjusted to give a saturated solution. The solution was seeded and slowly cooled. The product, isolated by filtration and dried *in vacuo*, was 2.32 g. of crude 19-nortestosterone oxime.

The crude oxime was refluxed for 3 hours with 25 ml. of acetic anhydride and the reaction mixture was decomposed by pouring into 250 ml. of cold water. After one hour, with occasional agitation, the mixture was extracted with chloroform. The organic extract was washed with water and $KHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residue could not be crystallized even when seeded, so it was chromatographed on 80 g. of neutral alumina (Woelm, activity III). The material was introduced onto the column in benzene solution and eluted with 500 ml. each of benzene, 10% chloroform–benzene and 30% chloroform–benzene; the eluate was collected in 250-ml. fractions which were distilled to dryness *in vacuo*. All the crystalline fractions were combined and dissolved in 30 ml. of hot benzene. Cyclohexane (30 ml.) was added and the solution was heated to boiling, although crystallization began almost at once. After cooling, the product was filtered, dried and recrystallized from absolute methanol. The product consisted of 1.47 g. (45% yield, based on 19-nortestosterone) of heavy platelets.

A sample was recrystallized three times from methanol for analysis. This material was found to contain 5.5% solvent of crystallization by drying at 100° *in vacuo*. The dried product showed a melting point of 207.5–209.8°; $\lambda_{max}^{CH_3OH}$ 249 mμ (15,000) (inflection at 273 mμ); $[\alpha]^{24}D$ + 15° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.27; H, 8.29; N, 3.92.

From 3-Amino-1,3,5(10)-estratriene-17β-ol (X).—The free amino alcohol (10 mg.) was treated with 0.5 ml. of pyridine and 0.10 ml. of acetic anhydride, allowed to stand at room temperature for two hours and worked up in the usual way. The product was recrystallized from a small volume of methanol·and dried at 100° in vacuum. This material, m.p. 210–214°, did not depress the melting point of the product from 19-nortestosterone. The infrared and ultraviolet spectra were also consistent with the identity of the two substances.

SHREWSBURY, MASS.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Nuclear Magnetic Resonance Studies on 6-Methyl Steroids

BY GEORGE SLOMP, JR., AND BRUCE R. MCGARVEY

RECEIVED NOVEMBER 14, 1958

Nuclear magnetic resonance spectra of representative 6-methyl steroids have been measured. The 6α- and 6β-methyl groups were differentiated readily. Some effects of interactions with other substituents are tabulated.

Shoolery and Rogers[1] have tabulated some useful correlations between the chemical shifts of the angular methyl groups of steroids with various functional groups on the molecule. Some 6α- and 6β-methyl steroids were studied in the present work, and it was found that the axial and equatorial conformations were readily distinguishable by nuclear magnetic resonance spectroscopy.

Methyl resonance frequencies were sensitive to configuration and to small changes in the geometry of the rings to which they were attached. It was apparent that changes which tended to increase crowding of the methyl group, by nearby axial hydrogens or other substituents, increased the

TABLE I

EFFECTS OF 6-METHYL GROUPS ON 19-METHYL RESONANCE FREQUENCIES, IN C.P.S.

Compounds compared	No 6-methyl H_0	19-Methyl shift For 6α-methyl subst. H_0	Correction	For 6β-methyl subst. H_0	Correction
11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate[a,b] *vs.*	130				
6-Methyl-11β,17α,21-trihydroxy-1,4-pregnadien-3,20-dione 21-acetate		130	0	..	..
Methyl 3,11-diketo-4,17(20)-[*cis*]-pregnadien-21-oate[c] *vs.*	131				
Methyl 3,11-diketo-6-methyl-4,17(20)-[*cis*]-pregnadien-21-oate		132	+1	128	−4
Methyl 3,11-diketo-4,17(20)-[*trans*]-pregnadien-21-oate[c] *vs.*	131				
Methyl 3,11-diketo-6-methyl-4,17(20)-[*trans*]-pregnadien-21-oate		130	−1	..	..
4-Pregnene-3,11,20-trione *vs.*	132				
6-Methyl-4-pregnene-3,11,20-trione		131	−1	128	−4
4-Pregnene-3,20-dione *vs.*	140				
6-Methyl-4-pregnene-3,20-dione		140	0	138	−2
5α-Pregnane-3,20-dione[d] *vs.*	147				
6-Methyl-5α-pregnane-3,20-dione		146	−1	144	−3

[a] J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, THIS JOURNAL, **77**, 4438 (1955). [b] These compounds were run in dimethyl sulfoxide solvent and the results have been corrected for the solvent shift. [c] 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). [d] W. J. Wechter, these laboratories.

(1) J. N. Shoolery and M. T. Rogers, THIS JOURNAL, **80**, 5121 (1958).