Steroid Homolog Containing a Pyrazole Nucleus¹

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Many reports have appeared recently which record² the syntheses and activities of steroids possessing a heterocycle fused to carbons 2 and 3, as steroidal (3,2-c) pyrazoles, (3,2-c) isoxazoles, (3,2-c) pyrimidines, and (3,2-b) thiazoles. A large number of ring A-azasteroids² have been prepared and known to be active.

In the course of a study of the relationship between structure and biological activity, it appeared desirable to prepare a steroid which had a heterocycle instead of an isocyclic A-ring.⁴

This note records the synthesis of an A-nor-2,3-diazasteroid. 17β -Acetoxyandrost-1,4-dien-3-one⁵ (I) was obtained in 70% yield by dehydrogenation of testosterone acetate with 2,3-dichloro-5,6dicyanobenzoquinone.⁶ Ozonolysis of I under conditions similar to those of Barton and Taylor⁷ afforded 17β -acetoxy-1-oxo-1,5-sec-2,3,4-trisnorandrostan-5-one (II) in 40% yield. The keto aldehyde II was converted to A-nor-2,3-diazaandrosta-1,3-dien-17 β -ol (III) by condensation with hydrazine hydrate in ethanol, followed by hydrolysis with potassium hydroxide in aqueous methanol.

Compound III was inactive as an androgen, an anabolic agent, an estrogen, and as an antiestrogen under the conditions employed. In the castrated rat androgenic-anabolic assay the compound indicated less than 5% the activity of testosterone when administered by injection.⁸ In the chick's comb inunction test,⁹ the compound was less than 2% as active as testosterone. The compound, when administered subcutaneously, possessed less than 0.05% the estrogenicity

(6) D. Burn, D. N. Kirk, and V. Petrow, Proc. Chem. Soc., 14 (1960).

(7) D. H. R. Barton and W. C. Taylor, J. Chem. Soc., 2500 (1958).

of estrone¹⁰ and was inactive as an antiestrogen at a total dose of 0.5 mg, in a mouse uterine assay.¹¹



Experimental¹²

17β-Acetoxyandrosta-1,4-dien-3-one⁵ (I).—A solution of 4 g of 17β-acetoxyandrost-4-en-3-one and of 3.5 g, of 2,3-dichloro-5,6dicyanobenzoquinone in 120 ml. benzene was refluxed for 24 hr. The reaction nixture was cooled and filtered, the filtrate washed several times with $1\frac{C}{6}$ aqueous potassium hydroxide solution, and then with water to neutrality. The dried solution was concentrated and then passed through a column of 100 g, of neutral alumina (Woelm, activity I). After evaporation and repeated recrystallizations from ether–hexane, the ethyl acetate eluate furnished 2.8 g, (70% 2) yield) of I; m.p. 155°; infrared absorption maxima ν_{max} 1748, 1658, 1607 cm.⁻¹; ultraviolet absorption λ_{nax} 244 (15,250) and 305 mµ (shoulder) (ϵ 1,880).

 17β -Acetoxy-1-oxo-1,5-sec-2,3,4-trisnorandrostan-5-one (II). -A solution of 200 mg, of 17β -acetoxyandrosta-1,4-dien-3-one in 20 ml. ethyl acetate was ozonized at -70° until the solution had a deep blue color (15 min.) and then kept at -70° until the the ultraviolet maximum of $244 \text{ m}\mu$ had disappeared, which was usually the case in about 30 min. (it is desirable to have the ratio of optical density at 210 m μ to that at 244 m μ greater than 4). The ozonide was decomposed by addition of 2 ml, of water, followed by evaporation of the solvent under reduced pressure. The residue was dissolved in ethyl acetate, the solution washed with an aqueous sodium hydrogen carbonate solution, dried, and evaporated to give 160 mg. of a neutral fraction, which was chromatographed on 16 g. of silica gel. The fractions with 2 and 5% ethyl acetate in benzene gave 40 mg, of I. Elution with 10% ethyl acetate in benzene gave, after recrystallization from ether-pentane, 60 mg. (40%) of II, m.p. 129-130°; infrared absorption maxima ν_{max} 2725, 1745, 1695, and 1200 cm.⁻¹: ultraviolet absorption $\lambda_{\max} 292 \ \mathrm{m}\mu \ (\epsilon 38)$.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.77; H, 8.68.

A-Nor-2,3-diazaandrosta-1,3-dien-17 β -ol (III).—To a solution of 186 mg, of II in 30 ml, of ethanol was added 300 mg, of freshly distilled hydrazine hydrate (95%) and the mixture was refluxed under nitrogen for 24 hr. The solution was then evaporated to dryness under reduced pressure, the residue dissolved in methylene chloride, and washed several times with N hydrochloric acid and then with water to neutrality. The solution was dried, the solvent evaporated, and the residue recrystallized from etherpentane; yield 140 mg, of A-nor-2,3-diazaandrosta-1,3-dien-17 β -ol acetate. The acetate was dissolved in 10 ml, of methanol and 1 ml, of a 30% aqueous potassium hydroxide solution was added. The resulting solution was refluxed under nitrogen for 3 hr. and then concentrated, whereby 111 mg. (65%) of crude III could be

⁽¹⁾ . This research was supported, in part, by a National Institutes of Health Grant H-5266.

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⁽³⁾ For review see G. Rosseels, Ingr. Chimiste, 43, 73 (1961); Chem. Abstr., 56, 14935 (1961).

⁽⁴⁾ Compare the synthesis of a steroidal pyridazinone by F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, J. Am. Chem. Soc., **76**, 552 (1954).

⁽⁵⁾ H. H. Inhoffen, G. Zühlsdorff, and H. Minlon, Chem. Ber., 73, 451 (1940).

⁽⁸⁾ R. I. Dorfman and F. A. Kinel, Endocrinology, 72, 259 (1963).

⁽⁹⁾ R. I. Dorfman and A. S. Dorfman, Acta Endocrinol., Suppl., 74, 3 (1963).

⁽¹⁰⁾ B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endo-crinology*, **49**, 429 (1951).

⁽¹¹⁾ R. I. Dorfman, F. A. Kinel, and H. J. Ringold, *ibid.*, **68**, 17 (1961).
(12) Melting points are corrected. Ultraviolet absorption spectra were determined in methanol on a Cary Model 14 recording spectrophotometer. Infrared spectra were recorded from a pressed potassium bromide pellet on a Perkin-Elmer Infracord. Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

separated off. Repeated recrystallizations from ether-hexane gave an analytical sample: m.p. 246°; infrared absorption maxima $\nu_{\rm max}$ 1621, 1600, 1567, 1471 (shoulder), 1445, and 1420 (shoulder) cm.⁻¹; ultraviolet absorption $\lambda_{\rm max}$ 256 m μ , (ϵ 5700). Anal. Calcd. for C₁₆H₂₄ON₂: C, 73.80; H, 9.29; N, 10.76.

Anal. Caled. for $C_{16}H_{24}ON_2$: C, 73.80; H, 9.29; N, 10.76. Found: C, 73.60; H, 9.20; N, 10.60.

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Steroidal [17,16-c]Pyrazoles

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Some years ago, as part of a search for modified estrogens which might show useful lipid-shifting activity and a minimum of feminizing properties, a number of estrogen analogs bearing heterocyclic rings fused at positions 16 and 17 were synthesized in these Laboratories. The purpose of this article is to describe the preparation and properties of one such group of modified estrogens, the 1,3,5(10)-estratrieno [17,16-c]pyrazoles.

After this manuscript was completed, a publication² appeared in which compounds IIa-d (Chart I) were



described. The experimental procedures involved² [the action of hydrazine or methylhydrazine in ethanol on 16-hydroxymethylene estrone³ (Ia) or the corresponding 3-methyl ether⁴ Ib] were essentially the same as those used in our work.

The compounds IIa-c could each be methylated (dimethyl sulfate-potassium hydroxide) to give one and the same [17,16-c]N-methylpyrazole (IId).

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(2) P. de Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. chim. ital.*, **93**, 269 (1963).

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The N-acetyl compounds (IIIa and b) were prepared by the action of hot acetic anhydride on IIc and IIa, respectively. Acetylation at C-3 of the [17,16-c]-N-methylpyrazole (IIb) gave IIIc. The physical properties of all these compounds are collected in Table I.⁵

The ultraviolet spectra require some comments. Steroidal [3,2-c]pyrazoles with saturated A-rings have been reported⁶ to show $\lambda_{\max}^{\text{EtOH}} 223 \text{ m}\mu$ ($\epsilon \sim 5,000$) in accord with the absorption shown by simple pyrazoles.^{7,8} In the cases at hand, the maximum at 222–223 m μ ($\epsilon \sim 14,000-15,000$) is attributed to summation of the E-band of the aromatic A-ring and the pyrazole absorption. Indeed, this was simply demonstrated as follows: a solution containing equimolar amounts of estrone 3-methyl ether and 3β -hydroxy-5-androsteno[17,16-c]pyrazole⁹ [IVa; $\lambda_{\max}^{\text{MeOH}} 223 \text{ m}\mu$ (ϵ 6,500)] showed the same maximum at 222 m μ (ϵ 15,500) as did 3-methoxy-1,3,5(10)-estratrieno[17,16-c]-pyrazole (IIc), along with the normal 278 and 288 m μ maxima due to the aromatic A-ring.

The N-acetylpyrazoles (IIIa and b) as well as the 5-androsteno [17,16-c]N-acetylpyrazoles IVb showed λ_{\max}^{MeOH} 255 m μ ($\epsilon \sim 21,000$), in good agreement with the values recorded for an N-acetyl androstano[3,2-c]-pyrazole⁶ [λ_{\max}^{EtOH} 258 m μ (ϵ 19,000)] and for simple N-acylpyrazoles.^{8,10}

The infrared absorptions due to the N-acetyl group in IIIa and b appeared at $5.82 \,\mu$, and in the case of compound IVb at 5.75 μ . These absorption peaks differ quite markedly from those due to the >NCOR system¹¹ (~6.0–6.14 μ) and the >C==NN¹COR system¹² (~6.0 μ). However, the C==O absorptions of a number of N-acylpyrazoles have been recorded by Ried and Konigstein¹³ who found, for example, that N-propionyl-3,5-dimethylpyrazole showed λ_{max} 1722 cm.⁻¹ (5.81 μ).

We had assumed that our N-methylpyrazoles had the structures shown, rather than the possible alternative system V for reasons which have since been advanced by Clinton, *et al.*,⁶ when considering the case of steroidal [3,2-c]pyrazoles. The disclosure⁶ by these

(5) No spectroscopic data were reported for compounds IIa-d by the Italian workers² and we show these figures in Table II, together with melting points (corrected) and optical rotations measured in solvents differing from those in ref. 2.

(6) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, J. Am. Chem. Soc., 83, 1478 (1961).

(7) R. Huttel and J. Kratzer, Ber., 92, 2014 (1959).

(8) H. A. Staab, Ann., 622, 31 (1959).

(9) After this work was completed, a publication appeared [K. Bruckner, K. Irmscher, F. Werder, K. H. Bork, and H. Metz, *Ber.*, **94**, 2897 (1961)] in which the preparation of compound IVa was reported. The physical constants recorded for IVa by these workers are in good agreement with those which we observed.

(10) Huttel and Kratzer⁴ report $\lambda_{max}^{dioxane}$ 251 m μ (14,160) for N-acetyl-4ethylpyrazole, compared with $\lambda_{max}^{dioxane}$ 218 m μ (ϵ 3,450) for the parent 4ethylpyrazole.

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 2nd Ed., 1958, p. 205.

(12) J. Elks and G. H. Phillipps, J. Chem. Soc., 4326 (1956), describe the infrared spectra of some steroidal acetylhydrazones and of acetone acetylhydrazone (λ_{max}^{S2} 1668 cm.⁻¹; 6.00 μ).

(13) W. Ried and F. J. Konigstein, Ann., 625, 53 (1959).