Notes

Steroid Homolog Containing a Pyrazole Nucleus[1]

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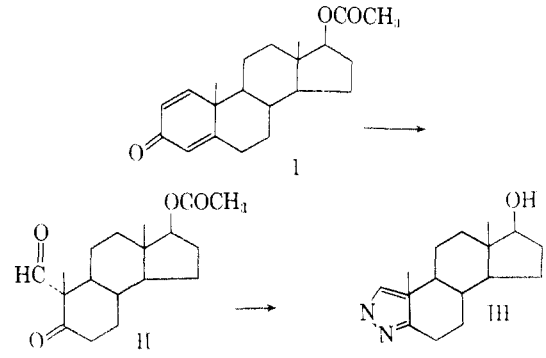
Many reports have appeared recently which record[2] the syntheses and activities of steroids possessing a heterocycle fused to carbons 2 and 3, as steroidal (3,2-c) pyrazoles, (3,2-c) isoxazoles, (3,2-c) pyrimidines, and (3,2-b) thiazoles. A large number of ring A-azasteroids[3] have been prepared and 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-one[5] (I) was obtained in 70% yield by dehydrogenation of testosterone acetate with 2,3-dichloro-5,6-dicyanobenzoquinone.[6] Ozonolysis of I under conditions similar to those of Barton and Taylor[7] afforded 17β-acetoxy-1-oxo-1,5-*seco*-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-17β-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 of estrone[10] and was inactive as an antiestrogen at a total dose of 0.5 mg. in a mouse uterine assay.[11]



Experimental[12]

17β-Acetoxyandrosta-1,4-dien-3-one[5] (I).—A solution of 4 g. of 17β-acetoxyandrost-4-en-3-one and of 3.5 g. of 2,3-dichloro-5,6-dicyanobenzoquinone in 120 ml. benzene was refluxed for 24 hr. The reaction mixture was cooled and filtered, the filtrate washed several times with 1% 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% yield) of I; m.p. 155°; infrared absorption maxima ν_{max} 1748, 1658, 1607 cm.$^{-1}$; ultraviolet absorption λ_{max} 244 (15,250) and 305 mμ (shoulder) (ϵ 1,880).

17β-Acetoxy-1-oxo-1,5-*seco*-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 mμ had disappeared, which was usually the case in about 30 min. (it is desirable to have the ratio of optical density at 210 mμ to that at 244 mμ 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 λ_{norm} 292 mμ (ϵ 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-17β-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 ether–pentane; yield 140 mg. of A-nor-2,3-diazaandrosta-1,3-dien-17β-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.

(2) (a) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, K. F. Jennings, and D. K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962), and preceding communications; (b) P. de Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. Chim. Ital.*, **92**, 768 (1962); (c) J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 236 (1963); (d) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960); (e) N. J. Doorenbos and C. P. Dorn, *J. Pharm. Sci.*, **51**, 414 (1962); (f) P. G. Holton and E. Necoechea, *J. Med. Pharm. Chem.*, **5**, 1352 (1962); (g) E. Caspi and D. M. Piatak, *Chem. Ind.* (London), 1984 (1962); (h) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(3) For review see G. Rosseels, *Inyg. Chimiste*, **43**, 73 (1961); *Chem. Abstr.*, **56**, 14933*b* (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).

(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).

(8) R. I. Dorfman and F. A. Kincl, *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, *Endocrinology*, **49**, 429 (1951).

(11) R. I. Dorfman, F. A. Kincl, 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 ν_{max} 1621, 1600, 1567, 1471 (shoulder), 1445, and 1420 (shoulder) cm.$^{-1}$; ultraviolet absorption λ_{max} 256 mμ, (ε 5700).

Anal. Calcd. 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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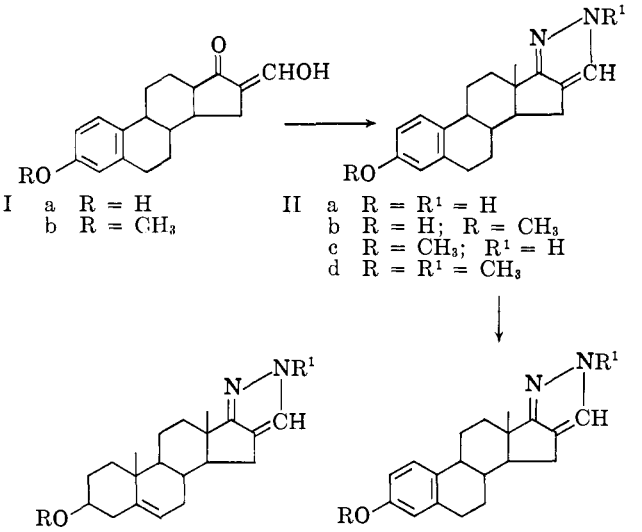
Some years ago, as part of a search for modified estrogens which might show useful lipid-shifting activity and a minimum of feminizing properties, a number of estrogen analogs bearing heterocyclic rings fused at positions 16 and 17 were synthesized in these Laboratories. The purpose of this article is 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 publication[2] appeared in which compounds IIa–d (Chart I) were

CHART I



described. The experimental procedures involved[2] [the action of hydrazine or methylhydrazine in ethanol on 16-hydroxymethylene estrone[3] (Ia) or the corresponding 3-methyl ether[4] 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).

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 reported[6] to show λ_{max}^{EtOH} 223 mμ (ε ~ 5,000) in accord with the absorption shown by simple pyrazoles.[7,8] In the cases at hand, the maximum at 222–223 mμ (ε ~ 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]pyrazole[9] [IVa; λ_{max}^{MeOH} 223 mμ (ε 6,500)] showed the same maximum at 222 mμ (ε 15,500) as did 3-methoxy-1,3,5(10)-estratrieno[17,16-c]-pyrazole (IIc), along with the normal 278 and 288 mμ 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 mμ (ε ~ 21,000), in good agreement with the values recorded for an N-acetyl androstano[3,2-c]-pyrazole[6] [λ_{max}^{EtOH} 258 mμ (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 μ, and in the case of compound IVb at 5.75 μ. These absorption peaks differ quite markedly from those due to the >NCOR system[11] (~6.0–6.14 μ) and the >C=NN¹COR system[12] (~6.0 μ). However, the C=O absorptions of a number of N-acylpyrazoles have been recorded by Ried and Konigstein[13] who found, for example, that N-propionyl-3,5-dimethylpyrazole showed λ_{max} 1722 cm.$^{-1}$ (5.81 μ).

The shift to lower wave length of the C=O absorption in going from the system >NCOR to systems of the type RCON¹⟨N⟩ can be plausibly attributed[13] to the change in double bond character of the C=O group in the latter case where the electron pair on N¹ is committed to the electron system of the heterocyclic ring.

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 disclosure[6] by these

(1) Dept. of Pharmacology, The Johns Hopkins Medical School, Baltimore 5, Maryland.

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

(3) L. Ruzicka, V. Prelog, and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948).

(4) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

(5) No spectroscopic data were reported for compounds IIa–d by the Italian workers[2] 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 Kratzer[4] report $\lambda_{max}^{dioxane}$ 251 mμ (14,160) for N-acetyl-4-ethylpyrazole, compared with $\lambda_{max}^{dioxane}$ 218 mμ (ε 3,450) for the parent 4-ethylpyrazole.

(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 ($\lambda_{max}^{CS_2}$ 1668 cm.$^{-1}$; 6.00 μ).

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