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.

Acknowledgment.—The authors are indebted to Dr. R. I. Dorfman for the endocrinological assays.

Steroidal [17,16-c]Pyrazoles

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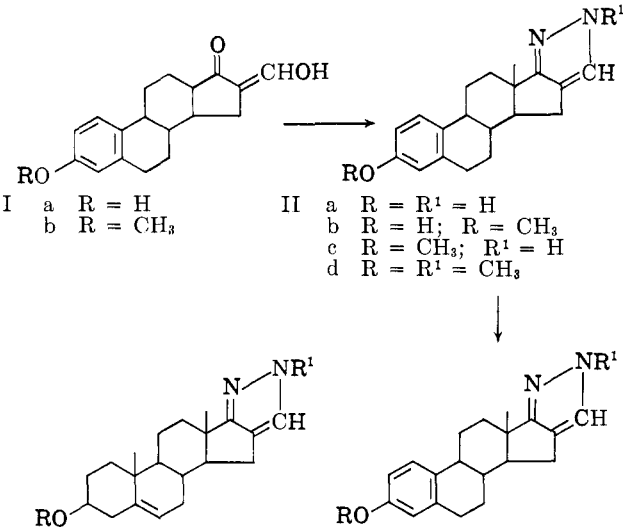
Some years ago, as part of a search for modified estrogens which might show useful lipid-shifting activity and a minimum of feminizing properties, a number of estrogen analogs bearing heterocyclic rings fused at positions 16 and 17 were synthesized in these Laboratories. The purpose of this article is 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



I a R = H; b R = CH_3

II a R = R^1 = H; b R = H; R^1 = CH_3; c R = CH_3; R^1 = H; d R = R^1 = CH_3

IV a R = R^1 = H; b R = R^1 = CH_3CO

III a R = CH_3; R^1 = CH_3CO; b R = CH_3CO; R^1 = CH_3CO; c R = CH_3CO; R^1 = CH_3

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=NN^{1}COR 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 RCON^1 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 N^1 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.

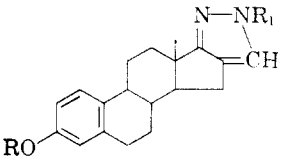
(10) Huttel and Kratzer[4] report $\lambda_{max}^{dioxane}$ 251 mμ (14,160) for N-acetyl-4-ethylpyrazole, compared with $\lambda_{max}^{dioxane}$ 218 mμ (ε 3,450) for the parent 4-ethylpyrazole.

(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).

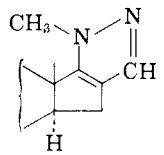
(13) W. Ried and F. J. Konigstein, *Ann.*, **625**, 53 (1959).

TABLE I

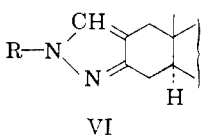


R	R'	M.p., °C.	$[\alpha]D^{c}$	λ_{max}^{EtOH}, mμ	ε	Molecular formula	Analytical data: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	309–313	+101	222	14,000	$C_{19}H_{22}N_2O$	77.51	7.53	9.52	77.03	7.63	9.88
CH_3	H	110 dec.	+98	222	15,500	$C_{20}H_{24}N_2O$	77.88	7.84	9.08	77.82	8.06	9.18
CH_3	CH_3	160–162	+89	223	14,000	$C_{21}H_{26}N_2O$	78.22	8.13	8.69	78.08	8.27	8.50
H	CH_3	312–319	+81 (py)	223	12,900	$C_{20}H_{24}N_2O$	77.88	7.84	9.08	77.64	7.89	9.24
CH_3	CH_3CO	163–165	+81	255	21,000	$C_{22}H_{26}N_2O_2$	75.40	7.48	8.0	75.57	7.78	8.03
CH_3CO	CH_3CO	144–146	+73	255	21,600	$C_{23}H_{26}N_2O_3$	72.99	6.93	7.40	73.42	7.42	7.33
CH_3CO	CH_3	194–198	+85	218	13,100	$C_{22}H_{26}N_2O_2$	75.40	7.48	8.00	75.10	7.44	8.14

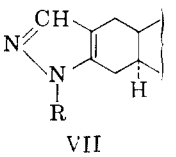
workers that the systems VI and VII show λ_{max}^{MeOH} 223 and 229 mμ, respectively, would seem to support quite firmly the structures shown for the [17,16-c]N-methylpyrazoles.



V

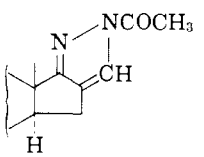


VI

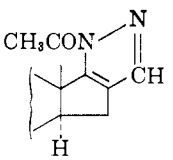


VII

In the case of the N-acetyl[17,16-c]pyrazole system, we propose the structure VIII, rather than the alternative structure IX.



VIII



IX

The n.m.r. spectra of the pyrazoles indicate that the C-18 methyl resonance is shifted relatively little on N-acetylation (Table II) and we infer from this that the pyrazole ring system has remained unchanged. However, without the other isomer, and more model compounds, this conclusion must of course be tentative.

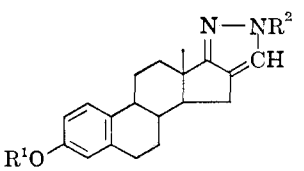
In addition to the foregoing compounds, we prepared hydrochlorides of the [17,16-c] pyrazoles II, IIc, and IVa, either by the action of hydrogen chloride in ether or in ether-dioxane, or by the action of hydrochloric acid in methanol. The products showed the correct analyses, and could be titrated with base to regenerate the parent pyrazoles. The infrared spectra of these hydrochlorides showed absorptions at 3.70–3.88 and at about 5.3 μ, which can be attributed to the $=\overset{+}{N}H$ system.[14]

The n.m.r. spectrum of IIc hydrochloride showed that the C-18 methyl resonance had been shifted considerably (to 1.24 p.p.m.) compared with the unsubstituted and N-substituted pyrazoles (Table II).

The estrogenic and hypocholesterolemic activities of the modified estrogens described earlier were determined by Drs. Tolksdorf, Eisler, Steinberg, Watnick, and co-workers of the Endocrinology Department, Schering Corporation; details will be published by them elsewhere. We note here, however, that compound IIc showed hypocholesterolemic activity[15] approximately equal to that shown by estradiol, while the estrogenic potency, measured in the mouse uterotrophic assay[15] was less than 0.0001 times that of estradiol.

TABLE II

N.M.R. DATA FOR [17,16-c] PYRAZOLES[a]



R'	R²	C-18 methyl	R¹	R²
CH_3	H	1.08	3.84	
CH_3	CH_3	1.00	3.84	3.81
CH_3CO	CH_3	1.00	2.27	3.83
CH_3CO	CH_3CO	1.09	2.30	2.68
CH_3	H·HCl	1.24		

[a] N.m.r. spectra were measured in $CDCl_3$ solution, at 60 Mc., with tetramethylsilane as internal reference, using a Varian A-60 spectrometer. Positions of methyl resonances are given in parts per million (p.p.m.), tetramethylsilane = 0. We thank Dr. Leon Mandell, Emory University, Atlanta, Georgia, for these measurements.

Experimental[16]

General Method of Preparation of 1,3,5(10)-Estratrieno[17,16-c]pyrazoles (IIa-IId).—These compounds were prepared using essentially the procedure of de Ruggieri, *et al.*,[2] but the time of reflux was 3 hr. Yields of recrystallized products fell within the range 50–70%.

(14) B. Witkop, *J. Am. Chem. Soc.*, **76**, 5597 (1954). See also R. B. Carlin and D. P. Carlson, *ibid.*, **81**, 4673 (1959), and references cited therein.

(15) For the procedures and appropriate references pertaining to these assays see C. H. Robinson, N. F. Bruce, E. P. Oliveto, S. Tolksdorf, M. Steinberg, and P. L. Perlman, *ibid.*, **82**, 5256 (1960).

(16) Melting points (corrected) were taken on a Koller block. Rotations were measured at 25° in dioxane solution, unless otherwise stated, at about 1% concentration. Ultraviolet spectra were recorded using methanol solutions, and infrared data refer to Nujol mulls. We thank the Physical Chemistry Department, Schering Corporation, for the measurement of rotations and ultraviolet and infrared spectra. Microanalyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., by Galbraith Laboratories, Knoxville, Tenn., and by Mr. E. Conner (Microanalytical Laboratory, Schering Corporation).

N-Alkylation and N-Acylation of 1,3,5(10)-Estratrieno[17,16-c]pyrazoles. (a) [17,16-c]N-Methylpyrazoles. 3-Methoxy-1,3,5(10)-estratrieno[17,16-c]N-methylpyrazole (IId) from 3-Hydroxy-1,3,5(10)-estratrieno[17,16-c]pyrazole (IIa).—To a stirred refluxing solution of 3-hydroxy-1,3,5(10)-estratrieno[17,-16-c]pyrazole (IIa, 1 g.) and potassium hydroxide (6 g.) in methanol (50 ml.) and water (10 ml.), was added dimethyl sulfate (1.0 ml.). After 30 min. another 1.0-ml. portion of dimethyl sulfate was added, and this operation was repeated twice more at 30 min. intervals (total volume of dimethyl sulfate used was 4 ml., total reaction time was 2 hr. under reflux). The reaction mixture was then concentrated to low volume, diluted with water, and left at room temperature overnight. The mixture was then extracted with methylene chloride, and the extract was washed with water and evaporated *in vacuo*. The solid residue was crystallized from aqueous methanol to give IId (740 mg.), identical in all respects with the compound obtained by the action of methylhydrazine on 16-hydroxymethylene estrone 3-methyl ether.

Similarly, 3-methoxy-1,3,5(10)-estratrieno[17,16-c]pyrazole (IIc) was N-methylated to IId, usingt he same procedure (dimethyl sulfate–potassium hydroxide).

(b) 1,3,5(10)-Estratrieno[17,16-c]N-acetylpyrazoles.—A solution of the steroidal [17,16-c]pyrazole (1.0 g.) in acetic anhydride (6 ml.) was heated at 95° for 3 hr. On cooling, the [17,16-c]-N-acetylpyrazole crystallized out, and was filtered off, dried, and recrystallized from acetone–hexane.

3β-Hydroxy-5-androsteno[17,16-c]pyrazole (IVa).—This compound was prepared from 16-hydroxymethylene-3β-hydroxy-5-androsten-17-one (10 g.) and hydrazine (10 g; 95%) in refluxing ethanol (300 ml.) for 3 hr. by the procedure outlined in b. The pure product (6.8 g.) had m.p. 256–259° dec.[9]; $[\alpha]_D$ −58, λ_{max}^{MeOH} 222 mμ (6,300); λ_{max}^{Nujol} 3.15, 6.00, 6.14, and 6.32 μ.

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.98; H, 9.17; N, 8.48.

3β-Acetoxy-5-androsteno[17,16-c]N-acetylpyrazole (IVb).—A solution of the foregoing pyrazole (IVa, 1 g.) in acetic anhydride (3.0 ml.) was heated at 95° for 1.5 hr. Evaporation to dryness gave a solid residue which was crystallized from aqueous methanol to furnish the pure N-acetylpyrazole (IVb, 880 mg.), m.p. 198–200°, $[\alpha]_D$ −60°, λ_{max}^{MeOH} 255 mμ (ε 20,500); λ_{max}^{Nujol} 5.75, 6.24, 6.62, and 8.00 μ.

Anal. Calcd. for $C_{24}H_{32}N_2O_3$: C, 72.69; H, 8.13; N, 7.07. Found: C, 72.93; H, 8.38; N, 7.35.

3β-Hydroxy-5-androsteno[17,16-c]pyrazolium Chloride (IVa·HCl). (a).—To a solution of 3β-hydroxy-5-androsteno[17,16-c]-pyrazole (IVa, 100 mg.) in methanol (15 ml.) was added concentrated hydrochloric acid (1.0 ml.), and the solution was left at room temperature overnight. Dilution with water and filtration gave the hydrochloride salt of IVa which was crystallized from aqueous methanol, to give material of m.p. 190–200° dec., λ_{max}^{Nujol} 3.05, 3.85, 5.3, 6.38, and 6.55 μ.

Anal. Calcd. for $C_{20}H_{29}ClH_2O$: C, 68.84; H, 8.38; N, 8.03; Cl, 10.16. Found: C, 68.37; H, 8.00; N, 7.81; Cl, 10.17.

(b) A solution of the [17,16-c]pyrazole (IVa, 200 mg.) in ether (15 ml.) and dioxane (30 ml.) was stirred while a brisk stream of hydrogen chloride gas was bubbled through the solution. The precipitated hydrochloride salt was filtered, washed with ether, and dried to give material identical (m.p., m.m.p., infrared), with the compound prepared in a.

3-Methoxy 1,3,5(10)-Estratrieno[17,16-c]pyrazolium Chloride.—Dry HCl gas was bubbled through an ethereal solution (150 ml.) of 3-methoxy 1,3,5(10)-estratrieno[17,16-c]pyrazole (IIc, 1 g.) until a white precipitate formed. The mixture was filtered, and the solid was washed with ether and then crystallized twice from methanol to give the pyrazolium chloride (IIc·HCl, 200 mg.), m.p. 232–235°, λ_{max}^{Nujol} 3.88, 6.22, 6.38, and 6.7 μ.

Anal. Calcd. for $C_{20}H_{33}ClN_2O$: C, 69.65; H, 7.31; N, 8.12; Cl, 10.28. Found: C, 69.43; H, 7.34; N, 8.38; Cl, 10.48.

3-Hydroxy 1,3,5(10)-Estratrieno[17,16-c]pyrazolium Chloride.—A solution of 3-hydroxy 1,3,5(10)-estratrieno[17,16-c]-pyrazole (IIa, 600 mg.) in methanol (90 ml.) containing concentrated HCl (6 ml.) was left at room temperature for 48 hr. Dilution with water gave a precipitate which was filtered, washed with water, and dried. Crystallization from methanol–water gave the pyrazolium chloride (IIa·HCl, 400 mg.), m.p. 303–309° dec.; λ_{max}^{Nujol} 2.95, 3.18, 3.7, 5.3, 6.2, 6.35, 6.45, and 6.7 μ.

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.01; N, 8.47; Cl, 10.72. Found: C, 68.64; H, 7.38; N, 8.31; Cl, 10.99.

Anesthetic Steroid Derivatives

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Received June 24, 1963

In connection with a study of water soluble derivatives of the anesthetic steroids, pregnan-3α-ol-20-one and pregnan-3α-ol-3,20-dione,[1] a number of functional derivatives were prepared which could revert to the parent compound *in vivo*. Two of the more interesting compounds in this series are described. The 3-phosphate ester of pregnan-3α-ol-20-one could conceivably be hydrolyzed to the parent sterol *in vivo*, since phosphate esters of 21-oxy steroids are known to possess the antiinflammatory activity of the parent steroid.[2] Likewise, 21-carboxypregnan-3α-ol-3,20-dione was prepared in the hope that the solubilizing carboxy group would be removed *in vivo* following intravenous administration of the sodium salt.

The phosphate ester of pregnanolone was prepared by addition of pregnanolone to phosphorus oxychloride to produce the dichlorophosphate. This in turn was hydrolyzed in dilute acid to the dihydrogen phosphate ester which fortunately could be separated by extraction from phosphoric acid.

The 21-carboxy derivative of 11-ketopregnanolone was obtained *via* the oxalyl derivative, isolated as the enolate following condensation of dimethyl oxalate with the steroid in the presence of dry sodium methoxide. Hydrogen peroxide cleavage of the keto ester gave the desired 21-carboxylic acid. The acid slowly lost carbon dioxide at room temperature and at the melting point was completely converted into 11-ketopregnanolone.

Intravenous administration of the 3-phosphate ester of pregnanolone to dogs at a dose of 10 mg./kg. produced no anesthesia. Similarly, administration of the freshly prepared sodium salt of 21-carboxy-11-keto pregnanolone at a dose of 10 mg./kg. (11-ketopregnanolone equivalent) resulted only in a transient sedation with no measurable anesthesia.[3]

Experimental[4]

21-Oxalylpregnan-3α-ol-11,20-dione.—Sodium methoxide (2 *N*, 11 ml.) in methanol was added to 25 ml. of dry benzene and the solvent was removed *in vacuo*. Additional solvent was added followed by a second concentration and, finally, baking on a steam bath under vacuum. To the dry fluffy powder, 2.36 g. (0.02 mole) of freshly distilled dimethyl oxalate was added at room temperature. The mixture was heated with stirring to reflux and cooled, and then 3.32 g. (0.01 mole) of 11-ketopregnanolone in about 25 ml. of benzene was added portionwise at room temperature. Almost immediately a yellow gum precipitated. The reaction mixture was stirred for 2 hr. and then decanted, and the gum was washed with ether by decantation. Following drying *in vacuo*,

(1) For selected references on steroid anesthetics see: (a) H. Selye, *Proc. Soc. Exptl. Biol. Med.*, **46**, 116 (1941); (b) S. K. Figdor, M. J. Kodet, B. M. Bloom, E. G. Agnello, S. K. P'an, and G. D. Laubach, *J. Pharmacol. Exptl. Therap.*, **119**, 229 (1957).

(2) (a) G. I. Poos, R. Hirschmann, G. A. Bailey, F. Cutler, Jr., L. H. Sarett, and J. M. Chemerda, *Chem. Ind.* (London), 1260 (1958); (b) J. C. Melby and R. H. Silber, *Am. Practitioner Dig. Treat.*, **12**, 156 (1961).

(3) The authors are indebted to Dr. L. S. Watson of our Biological Research Laboratories for these results.

(4) Melting points were taken on a Kofler micro hot stage. The authors are indebted to Dr. N. R. Trenner and Mr. R. Walker for the infrared spectra and to Mr. R. Boos for the microanalyses.