hydroxide in 900 ml. of water was added 52 g. of carboxymethyl dithiobenzoate and 45 g. of N-amino-D-(+)-ephedrine. The mixture was stirred and heated at 50° for 3 hr. and then allowed to stand at room temperature overnight. The aqueous layer was decanted and the residual gummy solid was dissolved in 1000 ml. of chloroform. The chloroform solution was washed (water), dried (magnesium sulfate), and evaporated *in vacuo* to yield 66 g. of red oil. The red oil was cyclodehydrated without further purification as described in the following experiment.

Sulfuric Acid Cyclodehydration of *threo*-(+)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic Acid Hydrazide.—To 300 ml. of cold, stirred, concentrated sulfuric acid was added a solution of 66 g. of *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazide in 100 ml. of methylene chloride. The mixture was stirred at room temperature for 3 hr., poured onto 2 kg. of crushed ice, and extracted with four 500-ml. portions of chloroform. The chloroform solution was washed (sodium bicarbonate), dried (magnesium sulfate), and evaporated *in vacuo* leaving 37 g. of red oil. The 37 g. of red oil was chromatographed on a 40 × 5.5 cm. column of aluminum oxide powder (Baker 0537) using benzene as a solvent. Fractions 3–6 (130 ml. each) yielded 31.3 g. (49%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 67.5–69°.

Attempted Isomerization of *trans*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine. A. With Concentrated Sulfuric Acid.—*trans*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine (1.0 g.) was added, portionwise, to 10 ml. of concentrated sulfuric acid. The mixture was allowed to stand at room temperature for 18 hr. It was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*. The residual oil was crystallized with ethanol. Recrystallization from ethanol gave 0.88 g. (88%) of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 112–114°.

B. With Phosphorus Pentasulfide and Polyphosphoric Acid.—A mixture of 1.0 g. of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, 2.0 g. of phosphorus pentasulfide, 5.0 g. of polyphosphoric acid, and 100 ml. of chloroform was refluxed for 8 hr. and then allowed to stand at room temperature overnight. The cooled mixture was treated with 100 ml. of 2 *N* aqueous sodium hydroxide solution, and then stirred for 1 hr. The chloroform solution was separated, washed twice with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The pale yellow solid was recrystallized from ethanol to give 0.78 g. (78%) of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 111–113°.

Acknowledgment.—The authors are grateful to Dr. J. P. Heeschen for determining and interpreting the n.m.r. spectra and to Mr. R. A. Nyquist for determining and interpreting the infrared spectra.

The Reaction of 16-Hydroxymethylene-17-keto Steroids with Semicarbazide and Thiosemicarbazide to Give 17α-Hydroxy[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline Derivatives. 17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline, a Potential Nonfeminizing Hypocholesterolemic Agent

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16-Hydroxymethylene-17-keto steroids react with semicarbazide and various thiosemicarbazides to give 17α-hydroxy[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline derivatives. Similar results are obtained with the 16-ethoxalyl-17-keto system. With hydroxylamine the 17α-hydroxy[16β,17β-*d*]-$\Delta^{2'}$-isoxazolines are obtained. The structure of one of the pyrazolines was established by X-ray analysis. 17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline (III) shows good hypocholesterolemic action as well as a low uterotropic effect and therefore is of interest as a potential nonfeminizing hypocholesterolemic agent. The synthesis and structure of several open-chain analogs are reported.

The possibility of developing nonfeminizing, hypocholesterolemic estratriene derivatives has received considerable research attention in recent years.[1] We now wish to report the preparation of several 17α-hydroxyestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazolines and-[16β,17β-*d*]-$\Delta^{2'}$-isoxazolines, certain of which are of interest in this respect.

The pyrazolines III of this study were readily prepared in high yield by treating 16-hydroxymethylene-17-keto steroids (I) with semicarbazide, thiosemicarbazide, and certain N^4-substituted derivatives of the latter reagent. The formation of the pyrazoline derivative rather than the fully aromatic pyrazole II was not anticipated, inasmuch as hydrazine and certain substituted hydrazines were known to react with the 16-hydroxymethylene-17-keto system (I) to give the corresponding pyrazoles (II),[2] although we also were aware of the fact that reaction of this system (androstane series) with hydroxylamine gives isoxazolines (IV).[2c,3] Formation of the pyrazoline structures was indicated by combustion analyses, the infrared spectra (hydroxyl absorption, no band attributable to a 17-carbonyl group), and enhanced ultraviolet absorption corresponding to that anticipated for isolated semicarbazone or thiosemicarbazone chromophores.[4] Similarly, condensation of 16-hydroxymethylenestrone 3-methyl ether[5] with hydroxylamine afforded the 17-hydroxyisoxazoline XIX, which structure is supported by combustion analysis, infrared data, and ultraviolet evidence (no absorption attributable to an isoxazole chromophore).

In order to determine unequivocally all structural aspects of these interesting compounds, one of the pyrazolines, the 4-bromo derivative XVIII, was subjected to single-crystal X-ray analysis. For this purpose,

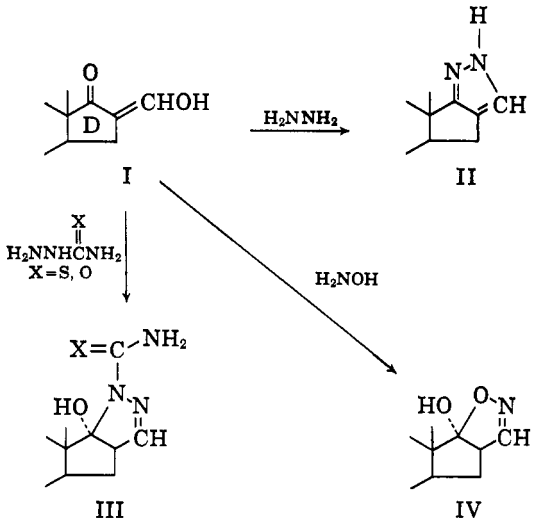
(1) See V. A. Drill and B. Riegel [*Recent Progr. Hormone Res.*, **14**, 50 (1958)] for a brief resume of the rationale to this approach.

(2) (a) P. de Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. chim. ital.*, **93**, 269 (1963); (b) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Med. Chem.*, **6**, 793 (1963); (c) R. E. Schaub and M. J. Weiss, unpublished observations.

(3) K. Brückner, K. Irmscher, F. v. Werder, K.-H. Bork, and H. Metz, *Chem. Ber.*, **94**, 2897 (1961).

(4) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954, p. 52.

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

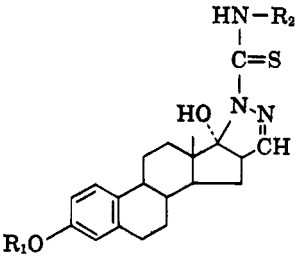


this compound was obtained as monoclinic needles containing 1 mole of acetone solvate. The analysis confirmed the postulated pyrazoline structure and established that the heterocyclic ring is fused to the steroid nucleus in the β-orientation. In addition it was found that the thiocarbamoyl group is coplanar with the pyrazoline system, with the sulfur atom equidistant from C-12, C-17, and C-18. It also was noted that the thiocarbamoylamino group and the carbonyl function of the acetone of solvation take part in an infinite chain of weak bifurcated hydrogen bonds in the direction of the needle axis, with N–O distances of 3.11 and 3.10 Å. Figure 1 shows a composite, three-dimensional electron density map for compound XVIII. On grounds of analogy, we have assumed that the other pyrazolines of this study as well as the oxazolines also have the configuration determined for XVIII.

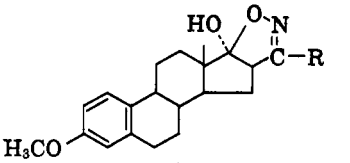
The isoxazoline derivative XIX proved to be a particularly potent estrogenic agent, having a uterotropic effect[6] in rats at the 3-γ oral dose level about six times that shown by estrone, and causing a decrease in serum cholesterol[6] to 7% of controls when administered to rats at a concentration of 0.005% in the diet. However, of greater interest was the significant separation of activities observed with the thiosemicarbazone-derived pyrazoline VI, which gave a good hypocholesterolemic effect in rats (0.005% in the diet) and was only 0.005–0.0009 times (depending on response level) as effective as estrone in the uterotropic assay. Since VI manifested a greater degree of separation of hypocholesterolemic from uterotropic activity than did the semicarbazide-derived product V, our follow-up efforts were concentrated on the thiocarbamoylpyrazoline type. Thus the N-methyl, ethyl, butyl, allyl, and phenyl analogs VII–XI were prepared by condensation of 16-hydroxymethylenestrone 3-methyl ether with the appropriate N⁴-substituted thiosemicarbazide (see Chart I). At the 3-position, the 3-O-ethyl (XII) and the 3-O-allyl (XIII) ethers as well as the free 3-hydroxy analogs XIV and XV were prepared. Several analogs with substitution in ring A also were synthesized; namely, the 2-diethylaminomethyl (XVI), the 4-nitro (XVII), and the aforementioned 4-bromo (XVIII) derivatives.

(6) The estrogenic and hypochlesterolemic assays were carried out by previously described procedures: S. Gordon, E. W. Cantrall, W. P. Ceklenlak, H. J. Albers, S. Mauer, S. M. Stolar, and S. Bernstein, *Steroids*, **4**, 267 (1964).

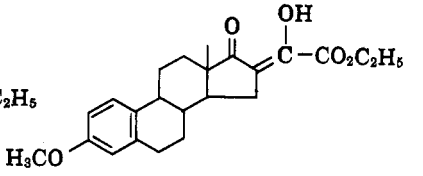
CHART I



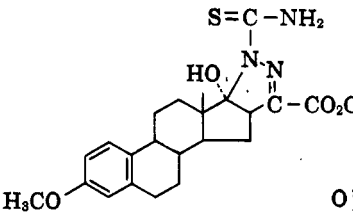
V, $R_1 = CH_3$; $R_2 = H(C(=O)-NHR_2)$
VI, $R_1 = CH_3$; $R_2 = H$
VII, $R_1 = R_2 = CH_3$
VIII, $R_1 = CH_3$; $R_2 = C_2H_5$
IX, $R_1 = CH_3$; $R_2 = n\text{-}C_4H_9$
X, $R_1 = CH_3$; R_2 = allyl
XI, $R_1 = CH_3$; $R_2 = C_6H_5$
XII, $R_1 = C_2H_5$; $R_2 = H$
XIII, R_1 = allyl; $R_2 = H$
XIV, $R_1 = R_2 = H$
XV, $R_1 = H$; $R_2 = CH_3$
XVI, $R_1 = H$; $R_2 = H, 2\text{-}CH_2N(C_2H_5)_2$
XVII, $R_1 = CH_3$; $R_2 = H$, 4-nitro
XVIII, $R_1 = CH_3$; $R_2 = H$, 4-bromo



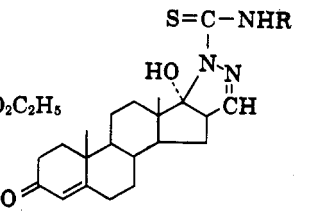
XIX, R=H
XX, $R=CO_2C_2H_5$



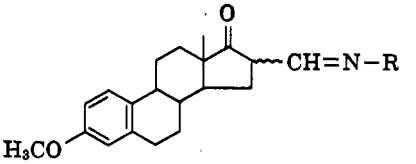
XXI

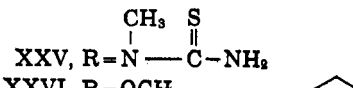


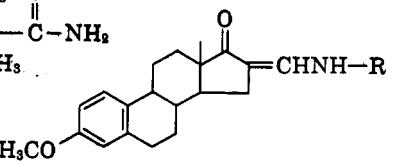
XXII

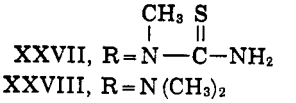


XXIII, R=H
XXIV, $R=CH_3$









XXV, $R=N-C-NH_2$
XXVI, $R=OCH_3$
XXVII, $R=N-C-NH_2$
XXVIII, $R=N(CH_3)_2$

All the analogs were obtained by formylation of the appropriate estrone derivative followed by reaction with thiosemicarbazide. The various pyrazolines are listed in Table I.

Condensation of hydroxylamine and thiosemicarbazide with the 16-ethoxalyl-17-ketone XXI[7] gave products to which we assign formulas XX and XXII, respectively. The assignment of a cyclic imino structure

(7) H. M. Kissman, R. E. Schaub, and M. J. Weiss, paper in preparation.

TABLE I

Product	Reactants: Steroid	Reactants: Reagent	Yield, %	M.p., °C.[a]	[α]D, deg.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
2′-Carbamoyl-17α-hydroxy-3-methoxyestra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (V)	16-Hydroxymethylenestrone methyl ether	Semicarbazide·HCl	87	219–220 (D–C)	+100 (dioxane)	$C_{21}H_{27}N_3O_3$	68.27	68.11	7.37	7.31	11.37	11.36		
17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno-[17β,16β-c]-Δ1′(5′)-pyrazoline (VI)	16-Hydroxymethylenestrone 3-methyl ether	Thiosemicarbazide	94	223 (A)	−197 (dioxane)	$C_{21}H_{27}N_3O_2S$[c]	65.43	65.66	7.06	7.01	10.91	11.02	8.32	8.98
17α-Hydroxy-3-methoxy-2′-(methylthiocarbamoyl)estra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (VII)	16-Hydroxymethylenestrone 3-methyl ether	4-Methylthiosemicarbazide	66	198–199 (D–C)	−214	$C_{22}H_{29}N_3O_2S$	66.14	66.22	7.32	7.00	10.52	10.16	8.03	8.09
17α-Hydroxy-3-methoxy-2′-(ethylthiocarbamoyl)-estra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (VIII)	16-Hydroxymethylenestrone 3-methyl ether	4-Ethylthiosemicarbazide	88	198–200 (D–C)	−200	$C_{23}H_{31}N_3O_2S$	66.78	66.80	7.56	7.73	10.16	10.17	7.75	7.82
17α-Hydroxy-3-methoxy-2′-(butylthiocarbamoyl)-estra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (IX)	16-Hydroxymethylenestrone 3-methyl ether	4-Butylthiosemicarbazide	80	167–169 (D–C)	−179	$C_{25}H_{35}N_3O_2S$	67.99	67.89	7.99	7.69	9.52	9.21	7.26	7.11
17α-Hydroxy-3-methoxy-2′-(allylthiocarbamoyl)-estra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (X)	16-Hydroxymethylenestrone 3-methyl ether	4-Allylthiosemicarbazide	86	179–181 (D–C)	−184	$C_{24}H_{31}N_3O_2S$	67.72	68.00	7.34	6.78	9.87	9.51	7.53	7.57
17α-Hydroxy-3-methoxy-2′-(phenylthiocarbamoyl)estra-1,3,5-(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XI)	16-Hydroxymethylenestrone 3-methyl ether	4-Phenylthiosemicarbazide	43	160–161 (D–C)	−209	$C_{27}H_{31}N_3O_2S$	70.25	70.05	6.77	7.07	9.11	9.14	6.95	6.99
3-Ethoxy-17α-hydroxy-2′-thiocarbamoylestra-1,3,5-(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XII)	16-Hydroxymethylenestrone 3-ethyl ether	Thiosemicarbazide	76	169–171 (D–C)	+61	$C_{23}H_{33}N_3O_2S$	66.14	66.26	7.32	6.79	10.52	10.55	8.03	7.99
3-Allyloxy-17α-hydroxy-2′-thiocarbamoylestra-1,3,5-(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XIII)	16-Hydroxymethylenestrone 3-allyl ether	Thiosemicarbazide	60	147–149 (D–C)	+111	$C_{23}H_{29}N_3O_2S$	67.27	66.89	7.12	7.49	10.23	10.27	7.81	7.85
3,17α-Dihydroxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XIV)	16-Hydroxymethylenestrone[d]	Thiosemicarbazide	52	173–175 (D–C)	−218 (dioxane)	$C_{20}H_{25}N_3O_2S$	64.66	64.24	6.78	7.20	11.32	10.84	8.63	8.37
3,17α-Dihydroxy-2′-(methylthiocarbamoyl)estra-1,3,5-(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XV)	16-Hydroxymethylenestrone[d]	4-Methylthiosemicarbazide	86	221 (D)	−175 (dioxane)	$C_{21}H_{27}N_3O_2S$	65.43	65.51	7.06	7.06	10.91	10.57	8.32	8.42
2-Diethylaminomethyl-3,17α-dihydroxy-2′-thiocarbamoylestra-1,3,5(10)-trieno-[17β,16β-c]-Δ1′(5′)-pyrazoline (XVI)	2-Diethylamino methyl-16-hydroxymethylenestrone	Thiosemicarbazide	86	Amorphous	+63	$C_{24}H_{38}N_4O_2S$	64.83	64.65	8.16	8.17	12.60	11.75	7.21	6.61
17α-Hydroxy-3-methoxy-4-nitro-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XVII)	16-Hydroxymethylene-4-nitroestrone 3-methyl ether	Thiosemicarbazide	90	223 (D–C)	−68	$C_{21}H_{26}N_4O_4S$	58.59	58.60	6.08	6.15	13.02	12.61	7.45	7.43

TABLE I (*continued*)

Product	Reactants: Steroid	Reactants: Reagent	Yield, %	M.p., °C.[a]	[α]D, deg.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-Bromo-17α-hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-c]-Δ1′(5′)-pyrazoline (XVIII)	4-Bromo-16-hydroxymethylenestrone 3-methyl ether	Thiosemicarbazide	78	210 (A)	−204	$C_{21}H_{28}BrN_3O_2S$[d]	54.31	54.56	5.65	5.67	9.06	8.54	6.91	6.78
17α-Hydroxy-3-methoxyestra-1,3,5(10)-trieno-[16β,17β-d]-Δ2′-isoxazoline (XIX)	16-Hydroxymethylenestrone 3-methyl ether	Hydroxylamine·HCl	96	221–223 (A–B)	+105	$C_{20}H_{25}NO_4$[c]	73.36	73.42	7.70	7.96	4.28	4.60		
3′-Carbethoxy-17α-hydroxy-3-methoxyestra-1,3,5(10)-trieno[16β,17β-d]-Δ2′-isoxazoline (XX)	16-Ethoxyalylestrone 3-methyl ether (XXI)[f]	Hydroxylamine·HCl	34	175–176 (A–B)	−1.9	$C_{23}H_{29}NO_6$	69.15	69.19	7.32	7.51	3.51	3.87		
4′-Carbethoxy-17α-hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno-[17β,16β-c]-Δ1′(5′)-pyrazoline (XXII)	16-Ethoxalylestrone 3-methyl ether (XXI)[f]	Thiosemicarbazide	67	225–226 (D–C)	−150	$C_{24}H_{31}N_3O_4S$	62.99	63.29	6.83	7.03	9.19	9.14	7.01	6.88
Ethylene ketal of 17α-hydroxy-3-oxo-2′-thiocarbamoylandrost-4-eno[17β,16β-c]-Δ1′(5′)-pyrazoline (XXIII)	3-Ethylenedioxy-16-hydroxymethylene-5-androsten-17-one[g]	Thiosemicarbazide	92	>220 dec. (D–C)	−208	$C_{23}H_{33}N_3O_3S$	64.00	64.50	7.71	7.64	9.74	9.49	7.43	7.60
Ethylene ketal of 17α-hydroxy-3-oxo-2′-(methylthiocarbamoyl)-androst-4-eno-[17β,16β-c]-Δ1′(5′)-pyrazoline (XXIV)	3-Ethylenedioxy-16-hydroxymethylene-5-androsten-17-one[g]	4-Methylthiosemicarbazide	85	206–207 (E)	−97	$C_{24}H_{35}N_3O_3S$	64.69	64.89	7.92	8.01	9.43	9.46	7.20	7.20

[a] Analytical melting point. Recrystallization solvents: A, acetone; B, petroleum ether (b.p. 60–70°); C, ether; D, methylene chloride; and E, methanol. [b] Unless otherwise noted, rotations were measured in chloroform at a concentration of 0.5–1.2%. Pertinent ultraviolet and infrared data follow. For the hydroxymethylenestrone–thiosemicarbazide-derived pyrazolines: λ_{max} 221–225, 230, 272–288 mμ [ε 10,200–14,000 (18,000 for N-phenyl derivative XI and 16,000 for 4-NO_2 derivative XVII), 9700–13,100, 17,200–23,000]; in the infrared the 17-C=O band was absent. For acetone thiosemicarbazone: λ_{max} 268 mμ (ε 24,700). For estrone methyl ether: λ_{max} 222, 277, 285 mμ (ε 8850, 2270, 2130). For the semicarbazide derivative V: λ_{max} 226, 278, 288 mμ (ε 14,700, 1850, 1850); 17-C=O band absent in the infrared. For acetone semicarbazone[4]: λ_{max} 226 mμ (ε 11,000). For the hydroxymethylenehydroxylamine product XIX: λ_{max} 224, 280, 288 mμ (ε 9800, 1960, 1960); no 17-C=O band in the infrared. For the ethoxalylhydroxylamine derivative XX: λ_{max} 225, 279, 288 mμ (ε 13,400, 2400, 2200); $\lambda_{max}^{CCl_4}$ 5.78, 7.85, 7.92, 8.04 μ. For ethyl pyruvate oxime[8]: λ_{max} 215 mμ (ε 9700); λ_{max}^{KBr} 5.78, 7.61, 8.47 μ; n.m.r. triplet centered at 80 (J = 7 c.p.s., 3 protons –O–C–CH_3), 125.5 (3 protons, unsplit, CH_3–C⩽), quartet centered at 257 (J = 7 c.p.s., 2 protons, –O–CH_2–), 620 c.p.s. (1 proton, N–O–H). For the ethoxalylthiosemicarbazide product XXII: λ_{max} 225, 230, 282, 287, 313 mμ (ε 11,900, 10,500, 9600, 10,700, 17,500); λ_{max} 5.78, 7.62, 7.80, 8.07 μ. For ethyl pyruvate thiosemicarbazone[9]: λ_{max} 235, 299 mμ (ε 6400, 19,600); λ_{max} 5.77, 7.73, 8.53 μ; n.m.r. [4:1 $CDCl_3$–$(CD_3)_2SO$] triplet centered at 80 (J = 7 c.p.s., 3 protons, –O–C–CH_3), 130 (3 protons unsplit, CH_3–C(=N)–), quartet centered at 256 (J = 7–8 c.p.s., 2 protons, –O–CH_2–), 481 and 457 (each 1 proton, NH_2), 592 c.p.s. [1 proton, –N–N(H)–C(=S)–]. For the 3-ethylenedioxyandrost-5-enepyrazolines (ketals of XXIII and XXIV): λ_{max} 272–274 mμ (ε 19,250), no 17-C=O infrared band. [c] No water by Karl–Fischer analysis. [d] Ref. 2a. [e] Calcd.: Br, 17.21. Found: Br, 16.89. [f] Ref. 7. [g] Ref. 10.

to these compounds rather than the corresponding cyclic α,β-unsaturated ester structure is supported by a satisfactory comparison of infrared and ultraviolet data with the oxime[8] and thiosemicarbazone[9] of ethyl pyruvate, the imino ester structures of which are clearly established by n.m.r. data.

Extension of the pyrazoline synthesis to the androstane field gave the Δ4-3-keto derivatives XXIII and XXIV, obtained on reaction of 3-ethylenedioxy-16-hydroxymethylenandrost-5-en-17-one[10] with thiosemicarbazide and 4-methylthiosemicarbazide, respectively, followed by acid hydrolysis of the intermediate pyrazoline 3-ketals. The latter derivatives are listed in Table I.

It also was of interest to prepare several related noncyclized derivatives. Treatment of the 16-hydroxymethylene derivative of estrone methyl ether (see I) with 2-methylthiosemicarbazide gave a product which in methanolic solution appears to be a mixture of the nonconjugated thiosemicarbazone and conjugated aminomethylene-17-keto forms XXV and XXVII, respectively. Thus, the ultraviolet absorption spectrum of this solution shows a major peak at 281 mμ (ε 21,100) indicative of XXV[11] and a shoulder at about 300 mμ

(8) E. Sharratt and W. Wardlaw, *J. Chem. Soc.*, 563 (1936).

(9) J. Gut, *Chem. Listy*, **51**, 1947 (1957); *Chem. Abstr.*, **52**, 4662 (1958).

(10) H. M. Kissman, A. S. Hoffman, and M. J. Weiss *J. Org., Chem.*, **27**, 3168 (1962).

(11) For acetaldehyde 2′-methylthiosemicarbazone: $\lambda_{max}^{CH_3OH}$ 211, 239, and 270 mμ (ε 7900, 6600, and 25,000). In passing, it is of interest to note an example of the effect of steric crowding on ultraviolet absorption. Thus, the long-wave-length absorption maximum observed for acetone 2′-methylthiosemicarbazone [$\lambda_{max}^{CH_3OH}$ 243 mμ (ε 12,500)] represents a significant hypsochromic shift and a decrease in intensity from that observed for acetaldehyde 2′-methylthiosemicarbazone and for acetone thiosemicarbazone [$\lambda_{max}^{CH_3OH}$ 268 mμ (ε 24,700)]. Dreiding models clearly show a strong steric interaction between the N-methyl group and either of the C-methyl groups of acetone 2′-methylthiosemicarbazone.

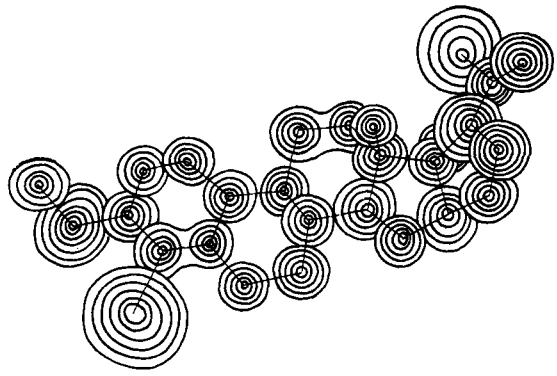


Figure 1.—Composite electron density map. Contours for 4-bromo-17α-hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-c]-$\Delta^{1'(5')}$-pyrazoline (XVIII) shown at intervals of 1 e/Å.^{3} (zero contour omitted). Intervals for bromine are 5 e/Å.^{3}, for sulfur 3 e/Å.^{3}.

(ϵ 14,200) indicative of XXVII.[12] However, absorption ascribable to the latter chromophore was not observed in chloroform or acetonitrile solution and in the infrared (KBr disks) only a nonconjugated ketonic band at 5.74 μ was present. In these latter circumstances we therefore assume this substance to be essentially in the thiosemicarbazone form XXV, probably, at least in solution, as an epimeric mixture in view of our observations with the methoxyamine derivative XXVI (see below) and those already noted for 17-ketones substituted at C-16 with proton-labilizing groups.[13]

Treatment of 16-hydroxymethylenestrone 3-methyl ether with methoxyamine gave the nonconjugated oximino ketone XXVI (λ_{max}^{KBr} 5.73 μ); no ultraviolet evidence of appreciable methoxyaminomethylene-17-keto content was noted either in chloroform solution or even in methanol solution. N.m.r. determinations in deuteriochloroform indicated, by the presence of two unequal signals for C-18–CH_3 and also for N–OCH_3, that this substance was a mixture of C-16 epimers in a rough ratio of 3:1. After standing for 2 weeks the epimeric ratio appeared to approximate 2:1.[16]

In contrast to the results obtained with 2-methylthiosemicarbazide and methoxyamine, the reaction of 16-hydroxymethylenestrone 3-methyl ether with 1,1-dimethylhydrazine gave only the conjugated hydrazinomethylene 17-ketone XXVIII [λ_{max}^{KBr} 5.97 μ, $\lambda_{max}^{CH_3OH}$ 309 mμ (ϵ 21,600)[12]].

Biological Evaluation.—None of the analogs prepared in this study were found to have as much promise as potential nonfeminizing hypocholesterolemic agents as the lead pyrazoline VI. We also would note that, according to the assays available to us, VI is of considerably greater interest in this regard than is the related 3-methoxy-1,3,5-(10)-estratrieno[17,16-c]pyrazole for which activity has been reported.[2b] We have found that not only is the hypocholesterolemic effect induced by the latter compound somewhat weaker than that which we attribute to VI, but also that the uterotropic effect is significantly greater. Thus, the potency (single-dose estimate[6]) of the pyrazole derivative is about 0.08 times estrone, whereas, as noted above, the pyrazoline VI has a potency relative to estrone of 0.005 to 0.0009.

The testosterone-derived pyrazolines XXIII and XXIV showed no androgenic or anabolic action when assayed at a 1000-γ subcutaneous dose by the ventral prostate–levator ani procedure.[17]

Experimental

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are corrected. Unless otherwise noted, optical rotations were measured at 25° in chloroform solution at concentrations of 0.5–1.2%. Ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer, and infrared spectra (pressed potassium bromide disks) were carried out with a Perkin-Elmer spectrophotometer (Model 21). N.m.r. spectra were determined with tetramethylsilane as an internal standard in deuteriochloroform solution, unless otherwise noted, with a Varian Model A-60 spectrometer. All evaporations were carried out under reduced pressure, and the petroleum ether used was that fraction boiling at 60–70°. Nitrogen analyses were carried out by the Dumas method.

Procedure for the Condensation of 16-Hydroxymethylene or 16-Ethoxalyl 17-Ketones with Various Thiosemicarbazides, Semicarbazide, and Hydroxylamine to Give [17β,16β-c]-$\Delta^{1'(5')}$-Pyrazolines (from Thiosemicarbazides and Semicarbazide) or [16β,17β-d]-$\Delta^{2'}$-Isoxazolines (from Hydroxylamine). Formation of 17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,-16β-c]-$\Delta^{1'(5')}$-pyrazoline (VI).—The following preparation of VI serves to illustrate this procedure. The various products so prepared are listed in Table I.

A suspension of 1 g. of 16-hydroxymethylenestrone 3-methyl ether (see I)[5] and 320 mg. of thiosemicarbazide (with hydroxylamine hydrochloride or semicarbazide hydrochloride a twofold excess of sodium acetate was added) in 30 ml. of absolute alcohol was heated at the reflux temperature for 1 hr. Solution was complete as the temperature approached the boiling point, and shortly thereafter solid material began to precipitate. After the heating period, the solution did not react to ferric chloride. The solid was collected and washed several times with absolute alcohol to give 1.16 g. (94%) of product (VI), m.p. 223° dec. For further characterization of this substance, see Table I.

X-Ray Structure Analysis.—Crystals of 4-bromo-17α-hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-c]-$\Delta^{1'(5')}$-pyrazoline (XVIII) were obtained by recrystallization from acetone. A needle with approximate dimensions 10 × 40 × 300 μ, which was selected for single-crystal X-ray analysis, was found to be monoclinic with the space group C2, with the dimensions of the unit cell a = 21.14 Å., b = 7.54 Å., c = 15.52 Å., β = 104.7°. The density, ρ_{obsd}, of 1.44 g./cc., obtained *via* the flotation method indicated solvation with 1 mole of acetone (ρ_{calcd} = 1.42 for Z = 4).

Three-dimensional intensity data were obtained with copper Kα radiation (λ 1.5418 Å.) on a General Electric XRD-6 diffractometer equipped with an Eulerian cradle by means of the stationary crystal–stationary counter method. The reflections were monitored using a scintillation counter with wide-open aperture, pulse-height discrimination, and balanced filters. Of the 1524 reflections accessible within a sphere of 1 Å. resolution ($2\theta_{max}$ = 105°), 1301 (85.4%) were considered to be observable.

A three-dimensional Patterson function was computed using as amplitudes the observed $|F|^2$ values modified by a sharpening

(12) 16-Aminomethylene-17-ketones in general show 17-carbonyl absorption above 5.90 μ and ultraviolet absorption maxima at 302–306 mμ (ϵ 21,000–30,000): R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clarke, K. F. Jennings, and P. E. Shaw, *J. Org. Chem.*, **27**, 1148 (1962); R. E. Schaub and M. J. Weiss, unpublished work; U. S. Patent 3,091,609 (May 28, 1963).

(13) At least in chloroform solution, 16-cyano 17-ketones exist as an epimeric mixture with no significant enolic content.[14] 16-Nitro 17-ketones behave similarly and in addition show considerable enolic character in methanol solution.[15]

(14) R. E. Schaub, H. M. Kissman, and M. J. Weiss, *J. Org. Chem.*, **29**, 2775 (1964).

(15) R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, **20**, 373 (1964); A. Hassner and J. Larkin, *J. Am. Chem. Soc.*, **85**, 2181 (1963).

(16) 16-Substituted 17-ketones usually give epimeric mixtures with the β-substituent predominating (see ref. 14 for leading references). In the instance of the 16-cyano-17-keto system the epimer present in major amount caused the greater degree of C-18–CH_3 deshielding; the reverse situation obtains with XXVI.

(17) This assay is a modification of that reported by L. G. Hershberger, E. G. Shipley, and R. K. Meyer [*Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953)].

function based on the bromine-scattering curve. This calculation confirmed the choice of C2 as the space group, which had been adopted since the alternatives Cm or C2/m are not allowed in the case of optically active compounds. The positions of the bromine and sulfur atoms were readily obtained from the vector map, and a subsequent density calculation, which was phased with these two atoms only, yielded most of the remaining atoms. The steroid skeleton could be distinguished without doubt, along with an added five-membered ring. Even though more detail was present, only these atoms were included in the subsequent structure-factor calculations, with all the lighter atoms weighted as carbons. The phases thus obtained were applied to a second density map $\rho(2)$, which confirmed the positions of the previously recognized atoms, and also yielded those of the remaining substituents. In a third density map, which revealed the acetone of solvation, the identity of the noncarbon atoms could be established from the observed peak heights, which in essence confirmed the chemical structure. Figure 1 shows a composite of the three-dimensional electron-density map obtained after three cycles of isotropic least-squares refinement had improved the positional parameters sufficiently to yield an over-all R value of 0.13. Deductions concerning the structure of XVIII are described in the discussion section.

Estrone Ethyl Ether [3-Ethoxyestra-1,3,5(10)-trien-17-one].—A suspension of 10 g. of estrone, 21 g. of anhydrous potassium acetate, and 61 ml. of ethyl iodide in 300 ml. of absolute alcohol was stirred at the reflux temperature for 20 hr. After concentration to a small volume the solution was diluted with methylene chloride. The solution was washed with water, dried, and evaporated to dryness. The residue was triturated with ether and collected to give 9.9 g. (90%) of product, m.p. 123–126°. Recrystallization from methylene chloride–ether gave white crystals: m.p. 124–125°; $[\alpha]D$ +140° [lit.[18] m.p. 126°; $[\alpha]D$ +150° (1% in dioxane)]; λ_{max} 222 mμ (ε 9000), 230 (7500), 278 (2100), 288 (1800); λ_{max} 5.75, 6.22, 6.35, 6.66, 9.50 μ.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 79.83; H, 8.60.

4-Bromoestrone Methyl Ether [4-Bromo-3-methoxyestra-1,3,5(10)-trien-17-one].—A suspension of 2 g. of 4-bromoestrone[19] and 4 g. of anhydrous potassium carbonate in 100 ml. of absolute alcohol containing 7.4 ml. of methyl iodide was stirred at the reflux temperature for 18 hr. After filtration, the solution was cooled, whereupon crystals were deposited to give 1.7 g. (81%) of product: m.p. 187–189° dec. (Schwenk, *et al.*,[1] report m.p. 289°; no procedural details were given); $[\alpha]D$ +113°; λ_{max} 222 mμ (ε 10,200), 278 (2020), 288 (2020); λ_{max} 5.76, 6.28, 6.42, 6.77, 7.83, 9.32 μ; n.m.r. 53 (C-18–CH_3), 232 (–OCH_3), 406 (doublet, J = 8 c.p.s., C-2–H), 433 c.p.s. (doublet, J = 7 c.p.s., C-1–H).

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.39; Br, 22.00. Found: C, 62.46; H, 6.47; Br, 21.91.

16-Hydroxymethylenestrone 3-Ethyl Ether [3-Ethoxy-16-hydroxymethylenestra-1,3,5(10)-trien-17-one].—Treatment of 7 g. of estrone ethyl ether in 210 ml. of dry benzene with 3.7 g. of sodium hydride oil dispersion and 7.1 ml. of ethyl formate, according to the procedure described below for the preparation of 4-bromo-16-hydroxymethylenestrone 3-methyl ether, gave 4.71 g. (62%) of product, m.p. 133–136° (gas). Two recrystallizations from methylene chloride–ether furnished white crystals: m.p. 132–135°; $[\alpha]D$ +140°; λ_{max} 222 mμ (ε 9500), 265 (11,400), 302 (1700); $\lambda_{max}^{0.1\ N\ NaOH}$ 222 mμ (ε 9000), 302 (22,800); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 12,600), 265 (14,800); λ_{max} 5.88, 5.91, 6.22, 6.36, 6.67, 8.05, 9.55 μ.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.11; H, 8.30.

16-Hydroxymethylenestrone 3-Allyl Ether [3-Allyloxy-16-hydroxymethylenestra-1,3,5(10)-trien-17-one].—Treatment of 2 g. of estrone allyl ether[20] in 85 ml. of anhydrous benzene with 3 g. of sodium hydride oil dispersion and 3.4 ml. of ethyl formate, according to the procedure described below for the preparation of 4-bromo-16-hydroxymethylenestrone 3-methyl ether, furnished, after recrystallization from ethanol–petroleum ether, 1.66 g. (76%) of product: m.p. 84–87°; $[\alpha]D$ +104°; λ_{max} 222 mμ (ε 8500), 265 (8100), 305 (2500); $\lambda_{max}^{0.1\ N\ NaOH}$ 222 mμ (ε 8500), 305 (19,600); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 19,000), 268 (10,500); λ_{max} 5.87, 5.95, 6.22, 6.35 (sh), 6.66 μ.

A satisfactory analysis could not be obtained.

2-Diethylaminomethyl-16-hydroxymethylenestrone [2-Diethylaminomethyl-3-hydroxy-16-hydroxymethylenestra-1,3,5(10)-trien-17-one].—Treatment of 3 g. of 2-diethylaminomethylestrone[21] in 120 ml. of dry benzene with 4 g. of 55% sodium hydride oil dispersion and 4.3 ml. of ethyl formate, according to the procedure described below for the preparation of 4-bromo-16-hydroxymethylenestrone 3-methyl ether, gave 2.27 g. (70%) of product as an amorphous powder: $[\alpha]D$ +110°; λ_{max} 222 mμ (ε 9600), 292 (9800); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 9600), 272 (7700); $\lambda_{max}^{0.1\ N\ NaOH}$ 303 mμ (ε 24,000); λ_{max} 2.95, 5.97, 5.95, 6.18, 6.68 μ. A completely satisfactory analysis for this amorphous product could not be obtained.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.05; H, 8.67; N, 3.45.

16-Hydroxymethylene-4-nitroestrone 3-Methyl Ether [16-Hydroxymethylene-3-methoxy-4-nitroestra-1,3,5(10)-trien-17-one].—A solution of 1.22 g. of 4-nitroestrone methyl ether[22] in 70 ml. of anhydrous benzene was treated with 1.9 g. of sodium hydride oil dispersion and 2.2 ml. of ethyl formate, according to the procedure described below for the preparation of 4-bromo-16-hydroxymethylenestrone 3-methyl ether, except that the reaction time was 5 hr., to give 1.29 g. (97%) of product: m.p. 204–207° dec. (Two recrystallizations from methylene chloride–ether raised the melting point to 211–213° dec.); $[\alpha]D$ +189°; λ_{max} 222 mμ (ε 12,000), 265 (9100); $\lambda_{max}^{0.1\ N\ NaOH}$ 222 mμ (ε 11,000), 302 (21,500); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 12,000), 268 (6000); λ_{max} 5.73, 5.85, 5.96, 6.23, 6.37, 6.55, 670, 7.30, 7.79, 9.28 μ.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.41; H, 6.59; N, 3.92.

4-Bromo-16-hydroxymethylenestrone 3-Methyl Ether [4-Bromo-3-methoxy-16-hydroxymethylenestra-1,3,5(10)-trien-17-one].—A mixture of 2 g. of 4-bromoestrone methyl ether, 2.8 g. of sodium hydride oil dispersion (55%, Metal Hydride product), 3.28 ml. of ethyl formate, and 115 ml. of anhydrous benzene was stirred under nitrogen. The reaction was initiated by the addition of a few drops of absolute alcohol and stirring was continued for 18 hr. Excess sodium hydride was destroyed by the addition of methanol. The mixture was extracted three times with water. The combined extracts were acidified with 4 N hydrochloric acid. The solid was collected and recrystallized from methylene chloride–ether to give 1.76 g. (82%) of product in two crops, m.p. 192–196° dec. The material gave a positive enol test with alcoholic ferric chloride solution. A sample of this compound obtained in a similar experiment was recrystallized from methylene chloride–ether: m.p. 191–194° dec.; $[\alpha]D$ +109°; λ_{max} 222 mμ (ε 10,700), 268 (9800), 308 (1950); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 10,700), 268 (12,300); $\lambda_{max}^{0.1\ N\ NaOH}$ 222 mμ (ε 10,700), 303 (21,900); λ_{max} 2.95, 5.95, 6.15, 6.28, 6.77, 7.82, 9.32 μ.

Anal. Calcd. for $C_{20}H_{23}BrO_3$: C, 61.39; N, 5.93; Br, 20.32. Found: C, 60.68; H, 5.94; Br, 20.65.

17α-Hydroxy-3-oxo-2′-thiocarbamoylandrost-4-eno[17β,16β-c]-Δ1′(5′)-pyrazoline (XXIII).—A suspension of 500 mg. of 3-ethylenedioxy-17α-hydroxy-2′-thiocarbamoylandrost-5-eno[17β,-16β-c]Δ1′(5′)-pyrazoline (Table I) in 100 ml. of methanol containing 4 ml. of 8% (v./v.) sulfuric acid was heated at the reflux temperature for 30 min., solution being complete in approximately 5 min. The solution was concentrated to a small volume, water was added, and the solution was extracted thrice with methylene chloride. The combined extracts were washed with water, dried, and evaporated to dryness. Recrystallization of the amorphous residue from absolute alcohol furnished 133 mg. (30%) of product, m.p. 198° dec. Recrystallization from acetone–petroleum ether afforded white crystals: m.p. 200° dec.; $[\alpha]D$ −52° (0.9% in dioxane); λ_{max} 240 mμ (ε 23,000), 275 (18,400); $\lambda_{max}^{0.1\ N\ HCl}$ 243 mμ (ε 22,800), 265 (20,000); $\lambda_{max}^{0.1\ N\ NaOH}$ 248 mμ (ε 19,400), 362 (27,700); λ_{max} 2.94, 3.06, 6.02, 6.31, 6.83 μ.

Anal. Calcd. for $C_{21}H_{29}N_3O_2S$: C, 65.09; H, 7.54; N, 10.85; S, 8.27. Found: C, 64.80; H, 7.75; N, 11.03; S, 8.45.

17α-Hydroxy-3-oxo-2′-(methylthiocarbamoyl)-androst-4-eno-[17β,16β-c]-Δ1′(5′)-pyrazoline (XXIV).—A suspension of 500 mg. of 3-ethylenedioxy-17α-hydroxy-2′-(methylthiocarbamoyl) androst-4-eno[17β,16β-c]-Δ1′(5′)-pyrazoline (Table I) and 50 mg.

(18) R. Courrier, L. Velluz, J. J. Alloiteau, and G. Rousseau, *Compt Rend. Soc. Biol.*, **139**, 128 (1945).

(19) E. Schwenk, C. G. Castle, and E. Joachim, *J. Org. Chem.*, **28**, 136 (1963).

(20) R. Miescher and C. Scholz, *Helv. Chim. Acta*, **20**, 1237 (1937).

(21) T. L. Patton, *J. Org. Chem.*, **25**, 2148 (1960).

(22) A. J. Tomson and J. P. Horwitz, *ibid.*, **24**, 2056 (1959).

of *p*-toluenesulfonic acid in 30 ml. of acetone was stirred at room temperature for 34 hr. The resulting solution was diluted with water, excess saturated sodium bicarbonate solution was added, and the solution was extracted twice with methylene chloride. The combined extracts were washed with water, dried, and evaporated. The residue was triturated with acetone and filtered to furnish 118 mg. of product, m.p. 199–200° dec. Recrystallization from acetone–petroleum ether afforded white crystals: m.p. 205–207° dec.; $[\alpha]D$ −97°; λ_{max} 243 mμ (ε 23,000), 271 (16,500); $\lambda_{max}^{0.1\ N\ HCl}$ 242 mμ (ε 22,400), 271 (14,000); $\lambda_{max}^{0.1\ N\ NaOH}$ 240 mμ (ε 19,600), 366 (28,200); λ_{max} 3.02, 6.00, 6.20, 6.53 μ.

Anal. Calcd. for $C_{22}H_{31}N_3O_2S$: C, 65.79; H, 7.78; N, 10.47; S, 7.99. Found: C, 65.43; H, 7.67; N, 10.67; S, 8.01.

Reaction of 16-Hydroxymethylenestrone 3-Methyl Ether with 2-Methylthiosemicarbazide. Formation of 16ξ-[(2-Methyl-3-thiosemicarbazono)methyl]estrone Methyl Ether (XXV) and 16-[(2-Methyl-3-thiosemicarbazido)methylene]estrone Methyl Ether (XXVII).—A solution of 500 mg. of 16-hydroxymethylenestrone 3-methyl ether and 185 mg. of 2-methylthiosemicarbazide in 25 ml. of absolute alcohol was heated at the reflux temperature for 18 hr. After cooling, the solution was filtered to give 415 mg. (65%) of product, m.p. 207° dec. Recrystallization from methylene chloride–ether furnished white needles: m.p. 208° dec.; $[\alpha]D$ +145°; λ_{max} 230 mμ (ε 11,300), 242 (9500), 281 (21,100), 300 (sh) (14,200); $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ε 12,000), 280 (5600), 288 (5100); $\lambda_{max}^{0.1\ N\ NaOH}$ 222 mμ (ε 13,000), 280 (4800), 288 (4800); $\lambda_{max}^{CH_3CN}$ 280 mμ (ε 31,600); $\lambda_{max}^{CHCl_3}$ 284 mμ (ε 33,000) initially and unchanged on standing 5 days; λ_{max} 2.92, 3.05, 5.74, 6.21, 6.32, 6.65, 6.73, 6.98 μ. [Compare data with that of acetaldehyde 2′-methylthiosemicarbazone (below).]

Anal. Calcd. for $C_{22}H_{29}N_3O_2S$: C, 66.14; H, 7.32; N, 10.32; S, 8.03. Found: C, 65.83; H, 7.28; N, 10.55; S, 8.17.

3-Methoxy-16α- and -16β-methoxyiminomethylestra-1,3,5(10)-trien-17-one (XXVI).—A suspension of 1 g. of 16-hydroxymethylenestrone 3-methyl ether (see I), 750 mg. of anhydrous sodium acetate, and 294 mg. of methoxyamine hydrochloride in 30 ml. of absolute alcohol was stirred at the reflux temperature for 1 hr. The cooled solution was diluted with water, concentrated to remove the alcohol, and filtered to furnish 758 mg. (70%) of product, m.p. 133–136°. Recrystallization from acetone–petroleum ether gave white crystals: m.p. 145–147°; $[\alpha]D$ +145°; λ_{max} 220 mμ (ε 13,100), 278 (2200), 288 (2200); $\lambda_{max}^{CHCl_3}$ 280 mμ (ε 2300), 288 (2300) initially and unchanged on standing 5 days; $\lambda_{max}^{0.1\ N\ HCl}$ 220 mμ (ε 13,800), 282 (6300), 290 (5960); $\lambda_{max}^{0.1\ N\ NaOH}$ 319 mμ (ε 11,700); λ_{max} 5.73, 6.19, 6.34, 6.66, 7.96, 9.62 μ; n.m.r. C-18–CH_3 signals at 55 and 61 c.p.s. (intensity ratio about 3.5:1), 232 c.p.s. (3-OCH_3), N–OCH_3 signals at 237 and 240 c.p.s. (intensity ratio about 3:1.2), 1-proton doublet centered at 456.5 c.p.s. (J = 5 c.p.s., >CH—CH=N—), no active hydrogen observed on exchange experiments with D_2O; on standing 2 weeks the relative intensity of the C-18–CH_3 signal pair and of the N–OCH_3 pair approached a ratio of about 2:1 and the 456.5-c.p.s. doublet broadened.

16-(2,2-Dimethylhydrazinomethylene)estrone Methyl Ether [16-(2,2-Dimethylhydrazinomethylene)-3-methoxyestra-1,3,5-(10)-trien-17-one, XXVIII].—A solution of 1 g. of 16-hydroxymethylenestrone 3-methyl ether and 0.3 ml. of 1,1-dimethylhydrazine in 30 ml. of absolute alcohol was heated at the reflux temperature for 30 min. A ferric chloride enol test was then negative. Concentration to a small volume, dilution with water, and filtration afforded 754 mg. (67%) of product: m.p. 135–137° dec.; $[\alpha]D$ +82.5°; λ_{max} 220 mμ (ε 9400), 309 (21,600); $\lambda_{max}^{0.1\ N\ NaOH}$ 220 mμ (ε 9400), 309 (20,500); $\lambda_{max}^{0.1\ N\ HCl}$ 220 mμ (ε 9400), 278 (9200), 287 (9200); λ_{max} 3.16, 5.97, 6.24–6.37 (broad), 6.68, 8.00 μ.

Anal. Calcd. for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.56; H, 8.58; N, 7.89.

Acetaldehyde 2′-Methylthiosemicarbazone.—To a stirred mixture of 720 mg. of 2-methylthiosemicarbazide in 15 ml. of absolute ethanol was added 3 ml. of acetaldehyde, solution being complete in a few minutes. After an additional 15 min. the solution was concentrated to a small volume. The resulting mixture was filtered to furnish 644 mg. (71%) of product, m.p. 135–137°. Recrystallization from methylene chloride–ether afforded white plates: m.p. 138–140°; $[\alpha]D$ 0°; λ_{max} 2.98, 3.09, 3.20, 6.10, 6.30, 6.68, 9.90, 11.50, 13.88 μ; n.m.r. C–CH_3, doublet centered at 123 c.p.s. (J = 5 c.p.s., CH_3—CH=N—), N–CH_3 unsplit at 220 c.p.s., 1-proton quartet centered at 424 c.p.s. (J = 5 c.p.s., CH_3—CH=N—); λ_{max} 211 (ε 7900), 239 (6600), 271 (25,000); $\lambda_{max}^{0.1\ N\ HCl}$ 211 mμ (ε 8900); $\lambda_{max}^{0.1\ N\ NaOH}$ 211 mμ (ε 8300), 239 (7200), 265 (20,000).

Anal. Calcd. for $C_4H_9N_3S$: C, 36.61; H, 6.92; N, 32.03; S, 24.44. Found: C, 37.05; H, 7.10; N, 31.78; S, 24.40.

Acetone 2′-Methylthiosemicarbazone.—A suspension of 1 g. of 2-methylthiosemicarbazone in 1 ml. of acetone and 15 ml. of absolute ethanol was stirred at the reflux temperature for 2 hr., solution being complete in approximately 30 min. Upon concentration to a small volume a solid separated which was collected to give 725 mg. (53%) of product, m.p. 118–121° (gas). Recrystallization from methylene chloride–ether gave white crystals: m.p. 133–135°; λ_{max} 243 mμ (ε 12,500); $\lambda_{max}^{0.1\ N\ HCl}$ 237 mμ (ε 8400); $\lambda_{max}^{0.1\ N\ NaOH}$ 220 mμ (ε 9400), 239 (11,600); $\lambda_{max}^{CHCl_3}$ 254 mμ (ε 13,400), 275 (9300); λ_{max} 3.07, 3.19, 6.20, 6.39, 6.66, 7.45 μ; n.m.r. 119 and 128 [2 unsplit CH_3, =C(CH_3)$_2$], 207 (3 protons, unsplit, –N–CH_3), 371 c.p.s. (–NH_2); for acetone thiosemicarbazone: λ_{max} 228 mμ (ε 8800), 268 (24,700); $\lambda_{max}^{0.1\ N\ HCl}$ 239 mμ (ε 11,000), 268 (4500); $\lambda_{max}^{0.1\ N\ NaOH}$ 230 mμ (ε 11,300), 265 (11,500); $\lambda_{max}^{CHCl_3}$ 275 mμ (ε 24,800); λ_{max} 2.97, 3.10, 3.18, 6.26, 6.61, 6.82, 6.98 μ; n.m.r. 114 and 120 [2 unsplit CH_3, =C(CH_3)$_2$], 432 (–NH_2), 517 c.p.s. (–N–H).

Anal. Calcd. for $C_5H_{11}N_3S$: C, 41.35; H, 7.64; N, 28.94; S, 22.08. Found: C, 41.12; H, 7.53; N, 29.25; S, 22.07.

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