It is pertinent to consider the results in relation to some information in the literature. Thus Stein, Kunkel, Cole, Spackman and Moore[15] have determined the amino acid composition of A_1 as isolated by starch block electrophoresis. Although this sample may well have been the most homogeneous sample of hemoglobin A yet analyzed, it clearly must have contained at least four components.

Recently, Rossi-Fanelli, de Marco, Benerecetti and Guacci[16] have published an amino acid analysis of A_2 that had been isolated by starch block electrophoresis. According to their analysis, there is a very considerable difference in the amino acid composition of A_2 and hemoglobin A as analyzed by Rossi-Fanelli, *et al.*[17] The present investigation has shown that A_2 may be contaminated with non-heme protein as Kunkel, *et al.*,[5] have also pointed out. It seems highly probable, therefore, that this analysis of A_2 is in reality the analysis of a mixture of A_2 and non-heme protein. The rather extreme differences that they report in amino acid composition of A and A_2 seem unlikely.

(15) W. H. Stein, H. G. Kunkel, R. D. Cole, D. H. Spackman and S. Moore, *Biochim. Biophys. Acta*, **24**, 640 (1957).

(16) A. Rossi-Fanelli, C. de Marco, A. S. Benerecetti and L. Guacci, *ibid.*, **38**, 380 (1960).

(17) A. Rossi-Fanelli, D. Cavallini and C. de Marco, *ibid.*, **17**, 377 (1955).

A_2 contains two α chains like those in hemoglobin A[18] and apparently has only a few changes in amino acid sequence.[19] Clearly, any reports of the properties of the components that may be electrophoretically isolated cannot ignore their heterogeneity.

The question may naturally be raised as to the extent of the heterogeneity of the minor components that may be chromatographically isolated. It is hoped that investigation now in progress[20] on the characterization of these components will throw some light on this subject. The main component, A_{II}, especially, may still hide other minor components. Component A_{IIIa}, no doubt, was observed by Clegg and Schroeder[1] but continues to be elusive and the conditions under which it may consistently be well separated from A_{II} have not yet been determined.

Acknowledgments.—It is a pleasure to acknowledge the benefit of discussions with Dr. Richard T. Jones during the course of this study. Mrs. Jean Cormick and Mrs. Kathleen McCalla assisted in some of the experiments.

(18) A. G. Schnek, R. T. Jones and W. A. Schroeder, to be published.

(19) A. O. W. Stretton and V. M. Ingram, *Fed. Proc.*, **19**, 343 (1960).

(20) R. T. Jones, unpublished.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE, RENSSELAER, N. Y.]

Steroidal[3,2-c]pyrazoles. II.[1] Androstanes, 19-Norandrostanes and their Unsaturated Analogs

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Utilizing a new approach to the concept of altering the structure-activity relationship in anabolic steroids, there have been synthesized several types of steroidal[3,2-c]pyrazoles. These were prepared from 3-ketoandrostanes, 3-ketoandrost-4-enes, 3-ketoandrosta-4,6-dienes, 3-keto-19-norandrostanes and 3-keto-19-norandrost-4-enes by formylation at the 2-position and reaction of the resulting 2-hydroxymethylene-3-ketosteroids with hydrazine or a substituted hydrazine. The derived steroidal[3,2-c]pyrazoles frequently possessed enhanced or unusual endocrinological activities. These included greatly increased anabolic/androgenic ratios, or the unexpected development of estrogenic activity.

Since the initial discovery by Kochakian and Murlin[2] that the administration of testosterone can reverse nitrogen loss in the castrate dog, much effect has been expended on the synthesis of compounds with the high anabolic potency but without the undesirable masculinizing effects of the male hormone.[3] That there still exists a need for an anabolic agent with few or no androgenic or progestational side-effects is amply demonstrated by the abundance of very recent publications in this field.[4] Without exception, these approaches to the problem have continued previous efforts to vary endocrine activity patterns by means of alterations within, or substitutions on, the steriod nucleus.

Several years ago, as a result of investigations of the known relationships between structure and anabolic activity in steroids, we began a program directed toward the synthesis of anabolic agents with a high specificity of action. We assumed, as have others, that the target receptors (enzyme systems, for example) at the sites of anabolic and androgenic

(1) Preceding communication. R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959).

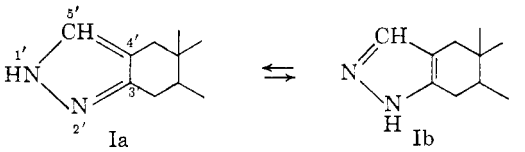
(2) C. D. Kochakian and J. R. Murlin, *J. Nutrition*, **10**, 437 (1935).

(3) An excellent summation and critical review (through early 1957) has been made by V. A. Drill and B. Riegel, "Recent Progress in Hormone Research," Vol. XIV, Academic Press, Inc., New York, N. Y., 1958, Chapter 2.

(4) (a) Steroids substituted by alkyl groups: C. H. Robinson, O. Gnoj, W. Charney, M. L. Gilmore and E. P. Oliveto, *J. Am. Chem. Soc.*, **81**, 408 (1959); J. A. Zderic, H. C. Carpio and H. J. Ringold, *ibid.*, **81**, 432 (1959); J. A. Campbell and J. C. Babcock, *ibid.*, **81**, 4069 (1959); B. Camerino, D. Cattapan, U. Valcavi and B. Patelli, *Gazz. chim. ital.*, **89**, 674 (1959). (b) Steroids substituted by hydroxyl, halogen, cyano or nitro groups: A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hildago and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959); S. Nakanisha, K. Morita and E. V. Jensen, *ibid.*, **81**, 5259 (1959); J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959); A. H. Nathan, J. C. Babcock and J. A. Hogg, *J. Org. Chem.*, **24**, 1395 (1959). (c) 19-Nor derivatives: A. Bowers, H. J. Ringold and E. Denot, *J. Am. Chem. Soc.*, **80**, 6111 (1958) J. Iriarte, C. Djerassi and H. J. Ringold, *ibid.*, **81**, 436 (1959).

activities differed sufficiently to make at least theoretically feasible the synthesis of a compound which would "fit" only one of these cellular receptor systems. However, our investigations led us to believe that possibly this objective could best be accomplished by an entirely new approach to the problem; that is, by the alteration of one or both of the following relationships: (1) the relative distance between substituents at the 3-position and the 17-position of the steroid nucleus, as measured by receptor site bonding to these positions ("terminal bonding"); (2) the type and stability of receptor site bonding at either position. The first result might be achieved by an extension of the ring system, or by an increase in the projection of 3- or 17-bonding groups. The second effect would be observed if we were to substitute a more highly nucleophilic atom or group for, *e.g.*, oxygen at 3 or 17. As a matter of definition, the latter substitution must not change cellular absorption patterns (*i.e.*, compound with basic amino groups might not reach the receptor site), or fail to meet the steric requirements of the receptor system.

The present research was originally concerned with the above-mentioned second approach to the desired objective, wherein an attempt was made to alter the type or stability of receptor site bonding. The fusion of a (coplanar) pyrazole ring to the steroid nucleus at positions 2 and 3, in the manner shown by Ia-Ib, substitutes an "aromatic" nitrogen for oxygen at the 3-position, and thus changes the nucleophilic environment in this area. Models indicated no obvious increased steric



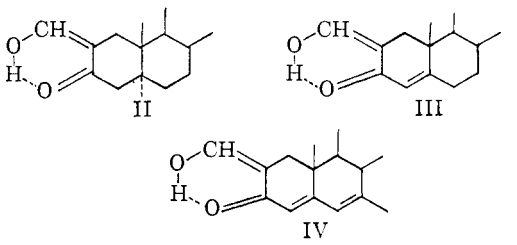
Ia Ib

interference (in a spacial connotation) with enzymatic bonding brought about by the fusion of the pyrazole ring to the steroid. On the other hand, the C–N bond distance between positions 2′ and 3′ is approximately 1.4 Å., whereas the C–O bond distance in a normal ketone is about 1.2 Å.; thus, there should also be a simultaneous effect on terminal bonding to the cellular receptors. Conceivably, the effect on terminal bonding could be even greater if the 1′-nitrogen were to become involved in hydrogen bonding to the enzyme.

The steroidal[3,2-c]pyrazoles constitute a novel class of compounds. Only a single derivative of this series is known: cholest-4-eno[3,2-c]pyrazole-5′-carboxylic acid, prepared by Ruzicka and Plattner[5] more than twenty years ago. In the present work the steroidal[3,2-c]pyrazoles were prepared from suitable 3-ketosteroids by the introduction of a 2-hydroxymethylene (2-formyl) group at C-2, followed by condensation of the resulting β-dicarbonyl compound with hydrazine or a substituted hydrazine. In the majority of cases these steps proceeded smoothly, and in good yield, but sometimes it proved necessary to explore a variety of methods for the introduction of a formyl group before an acceptable yield was obtained. Often, relatively minor changes in procedure gave considerable improvements in yields; similar effects have been noted by Robinson and Rydon.[6] Perhaps most of these observed experimental variations are ascribable to such factors as solubility phenomena, reaction rates, and, possibly in certain cases, to long-range "conformational transmission" effects.[7] Especially noteworthy is the very remarkable increase in the rate of reaction provided by the use of pyridine as a solvent in the formylation reaction.[6]

In general the 2-hydroxymethylene-3-ketosteroids[8] were obtained directly from the reaction mixture in a high state of purity, although frequently solvated by water. Often they were used for the preparation of the steroidal [3,2-c]pyrazoles without further treatment, since considerable losses were encountered during recrystallization. In these cases, the structures were confirmed, however, by their ultraviolet spectra (see below) and by the usual chelation tests with ferric chloride or cupric acetate.

The 2-hydroxymethyleneandrostan-3-ones (II) possess a single, rather broad absorption maximum in the ultraviolet at about 282 mμ (ε∼9000), comparable in position and intensity to the similar



II III IV

(λ_{max} 272 mμ, ε ∼10,000) maxima found for simple aliphatic β-diketones. The maximum observed for II in 0.01 *N* sodium hydroxide solution was shifted to 315 mμ (ε ∼ 17,300), analogous to the similar shift (272 mμ → 294 mμ) found in the aliphatic series.[9]

With the 2-hydroxymethyleneandrost-4-en-3-ones (III) there were observed characteristic maxima at 252 mμ (ε ∼ 11,500) and 307 mμ (ε ∼ 5,000), which are attributable to the α,β-unsaturated chelate system.[10] In 0.01 *N* sodium hydroxide the lower band underwent a hypsochromic shift to 248 mμ (ε ∼ 16,000) and the upper band a bathochromic shift to 355 mμ (ε ∼ 10,000).

Further extension of the system, as in the 2-hydroxymethyleneandrosta-4,6-dien-3-ones (IV), produced an additional bathochromic effect, with the observed maxima at 291 mμ (ε ∼ 17,000) and

(5) L. Ruzicka and P. A. Plattner, *Helv. Chim. Acta*, **21**, 1717 (1938).

(6) R. Robinson and H. N. Rydon, *J. Chem. Soc.*, 1394 (1939).

(7) D. H. R. Barton and A. J. Head, *ibid.*, 932 (1956); D. H. R. Barton, A. J. Head and P. J. May, *ibid.*, 935 (1957).

(8) Very recently a number of 2-hydroxymethylene-3-ketosteroids have appeared in the literature: (a) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 424 (1959); (b) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959); (c) F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959); (d) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959).

(9) G. S. Hammond, W. G. Borduin and G. A. Guter, *ibid.*, **81**, 4682 (1959).

(10) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952); S. Läufer, *Z. Naturforsch.*, (B) **12**, 359 (1957).

327 mμ (ε ~ 8,000). Our values are in good agreement with those recently reported for 2-hydroxymethylene ergosta-4,6,22-trien-3-one by Tsuda and Nozoe.[11] In 0.01 *N* sodium hydroxide solution IV gave rise to three bands, at 255 mμ (ε ~ 12,000) 292 mμ (ε ~ 16,000) and 382 mμ (ε ~ 10,000).

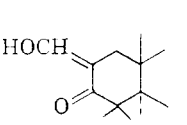
The resonance energy in the cyclic chelate ring,[12] *e.g.*, II, is increased and the structure is stabilized by the energy contribution of the hydrogen bond and by the existence of several ionic resonance structures derived from the enolic form.[13]

The observed 10 mμ difference between the ultraviolet maximum of acetylacetone and that of II is related to the effect of hyperconjugation produced by the substitution of an alkyl or methylene group for hydrogen in the α-position of an α,β-unsaturated ketone.

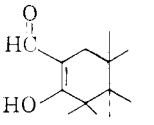
Of interest in this connection is the observation that the compound 2-hydroxymethylene-4,4,17α-trimethylandrostan-17β-ol-3-one has λ_{max} 294 mμ (ε 7500). It can be clearly shown by models of this system that considerable ring deformation is brought about by the 1,3-diaxial methyl–hydrogen (C_4–C_6) and 1,3-diaxial methyl–methyl (C_4–C_{10}) interactions. The bathochromic shift of 12 mμ relative to II is therefore probably due to p-orbital overlap caused by strain-induced rehybridization in the orbitals of C_3. A similar effect is noted with the parent ketone 4,4,17α-trimethylandrostan-17β-ol-3-one, which has λ_{max}) 290 mμ (ε 30) whereas 17α-methylandrostan-17β-ol-3-one has λ_{max} 282 mμ (ε 31).

A part of the steric interaction in the 4,4-dimethylandrostanes is relieved by the insertion of a 5,6-double bond. This is confirmed by the hypsochromic shifts in ultraviolet maxima toward those observed for the unmethylated steroids: for 4,4,-17α-trimethylandrost-5-en-17β-ol-3-one, λ_{max} is at 288 mμ and for 2-hydroxymethylene-4,4,17α-trimethylandrost-5-en-17β-ol-3-one λ_{max} is at 282 mμ.

We cannot at present discuss individual ultraviolet absorption bands in connection with such systems as II-IV, which may contain both the cyclic chelate and extended conjugation, due to the difficulty of dealing with the very numerous excited states.[14] However, it is pertinent to mention several examples wherein there appears to be related empirical evidence. Holker, *et al.*,[15] formylated methyl ketoeburic-8-enoate and obtained a 2-hydroxymethylene derivative with m.p. 121–123° and λ_{max} 290 mμ. This compound, when treated with a trace of acid, was converted to an isomer with m.p. 153° and λ_{max} 275 mμ, and the latter compound in turn was reconverted to the low-melting isomer when treated with base. Holker, *et al.*,[15] tentatively assigned to these two compounds the enolic structures indicated by V and



V



VI

VI. It can be assumed in this case that the 4,4-dimethyl grouping is responsible for stabilization of the tautomers V and VI because of the 1,3-diaxial interactions discussed above; as would be expected, we were unable to demonstrate the existence of comparable tautomers in simple systems such as II.

Recently Tsuda and Nozoe[11] have disclosed two other examples. The formylation of ergosta-4,6,-22-trien-3-one gave a 2-hydroxymethylene derivative having λ_{max}) 292 and 331 mμ, which was changed by treatment with a trace of acid into an isomer with λ_{max}) 294 and 323 mμ. Both isomers showed the characteristic hydroxyl and carbonyl chelate bonding (see below) in their infrared spectra. Two analogous enolic tautomers were also prepared from stigmasta-4,22-dien-3-one. It thus seems to be possible to isolate the two enolic tautomers if these structures are stabilized by conjugation with one or more double bonds.[16]

The spectrum of an enolizable β-dicarbonyl compound in basic solution is a function of the sum of the resonating *ionic* species. In the acyclic saturated β-dicarbonyl compounds, the ionic pentad system $^{\ominus}OC^{-}{=}CHC^{-}{=}O$ attains a maximum of resonance energy because the two extreme ionic species are essentially equivalent; there is therefore a bathochromic shift of the long wave length maximum. In ionic structures derived from the alicyclic structure II, there is an even greater bathochromic shift of this maximum.[17] The analogous shifts in the long wave length maxima for the structures III and IV, in basic solution, follow the expected pattern.

The 2-hydroxymethylene-3-ketosteroids show the characteristic[12] infrared bands at 3.7–3.8μ (chelated hydroxyl group) and at 6.1–6.25μ (chelated carbonyl group), as well as the expected normal bands. In addition they all possess medium to strong bands at 6.38–6.42 and at 6.88–6.92 μ.

The effect upon optical activity of the conversion of a 3-ketosteroid to its 2-hydroxymethylene derivative is of some interest, since the Δ[M]D values will reflect the influence of the chelate ring in creating spatial distortion of the molecule. In Table I there are listed Δ[M]D values derived from the conversion of a 3-ketosteroid to its 2-hydroxymethylene derivative. Noteworthy in this series are the negative Δ[M]D values found for the unsaturated compounds, especially the very large negative increment observed when a 2-hydroxymethylene group is attached to 17α-methylandrosta-4,6-dien-17β-ol-3-one.

The androstano[3,2-c]pyrazoles (I) all possess a maximum at 223 mμ (ε ~ 5000), which is shifted

(11) K. Tsuda and S. Nozoe, *Chem. Pharm. Bull (Tokyo)*, **7**, 232 (1959).

(12) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(13) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York N. Y., 1955, p. 47.

(14) Reference 13, p. 278.

(15) J. S. E. Holker, A. D. G. Powell, A. Robertson, J. J. H. Simes and R. S. Wright, *J. Chem. Soc.*, 2414 (1953).

(16) We have been unable to confirm these observations with related compounds; see experimental.

(17) 2-Hydroxymethylene-1-methone (W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.*, **67**, 1750 (1945)) has λ_{max} 290 mμ, shifted to λ_{max} 317 mμ in 0.01 *M* sodium hydroxide–ethanol.

TABLE I

MOLECULAR ROTATION DIFFERENCES FOR 2-HYDROXYMETHYLENE-3-KETOSTEROIDS

3-Ketosteroid	[M]D, $CHCl_3$ 3-Keto-steroid	[M]D, $CHCl_3$ 2-Formyl-deriv.	Δ[M]D[a]
Androstan-17β-ol-3-one	87	191	104
17α-Methylandrostan-17β-ol-3-one	35	120	85
6α,17α-Dimethylandrostan-17β-ol-3-one	33	187	154
17α-Methyl-19-norandrostan-17β-ol-3-one	102	305	203
Androst-4-en-17β-ol-3-one	314[b]	166[b]	−148
17α-Methylandrost-4-en-17β-ol-3-one	254	46	−208
17α-Methyl-19-norandrost-4-en-17β-ol-3-one	89	−234	−323
17α-Methylandrosta-4,6-dien-17α-ol-3-one	108	−684	−792

[a] [M]D 2-hydroxymethylene-3-ketosteroid minus [M]D 3-ketosteroid. [b] In 95% ethanol.

to 229 mμ (ε ~ 6200) in 0.01 *N* ethanolic hydrochloric acid. These bands agree well with those reported by Casoni, Mangini and Passerini[18] for the simple 3,4-dialkylsubstituted pyrazoles. Conjugation of the pyrazole ring with a double bond, as in the androst-4-eno[3,2-c]pyrazoles, moved the maximum to 261 mμ (ε ~ 10,000), which in turn underwent a bathochromic shift to 273 mμ (ε ~ 12,000) in 0.01 *N* ethanolic hydrochloric acid. A much more complex ultraviolet spectrum was observed for the androsta-4,6-dieno[3,2-c]pyrazoles, with maxima at about 220, 225, 232, 296 and 308 mμ. These bands were altered only slightly (219, 225, 231, 300 and 309 mμ) when the spectrum was taken in 0.01 *N* ethanolic hydrochloric acid, but two additional bands appeared at 251 and 259 mμ.

The bathochromic shift of maxima in acidic solution, observed with the androstano- and androst-4-eno[3,2-c]pyrazoles, as well as the appearance of two new bands in the acid spectra of androsta-4,6-dieno[3,2-c]pyrazoles, occurs because of protonation of the pyrazole ring. The result is an increase in resonance energy produced by the new ionic species[19]; as would be expected, no shift of maxima occurred with any of the pyrazoles in 0.01 *N* ethanolic sodium hydroxide solution. The infrared spectra of all of the steroidal[3,2-c]-pyrazoles show bands at 6.03–6.17, 6.25–6.28, 6.36–6.44, 6.60–6.80 and 6.89–6.92 μ, which appear to be quite characteristic of the pyrazole ring, regardless of external conjugation.[20]

Using the relationship Δ[M]D = [M]D steroidal-[3,2-c]pyrazole − [M]D parent 3-ketosteroid, we have calculated the molecular rotation increment due to the attachment of a pyrazole ring to a steroid in the 2,3-positions. These data are listed in Table II. Here again we note very large negative Δ[M]D values for the 4,6-diene derivatives.

TABLE II

MOLECULAR ROTATION DIFFERENCES FOR STEROIDAL[3,2-c]PYRAZOLES

3-Ketosteroid	[M]D, $CHCl_3$ 3-Keto-steroid	[M]D, $CHCl_3$ [3,2-c]-pyrazole	Δ[M]D[a]
Androstan-17β-ol-3-one	87	199	112
17α-Methylandrostan-17β-ol-3-one	35	117	82
17α-Ethylandrostan-17β-ol-3-one	44	112	68
17α-Propylandrostan-17β-ol-3-one	51	125	74
17α-Vinylandrostan-17β-ol-3-one	28	83	55
17α-Ethinylandrostan-17β-ol-3-one	−80[b]	34[b]	114
17β-Propinylandrostan-17β-ol-3-one	−93[b]	−104[b]	−11
6α,17β-Dimethylandrostan-17β-ol-3-one	33	154	121
4,4,17α-Trimethylandrostan-17β-ol-3-one	−116[c]	17[c]	133
17α-Methyl-19-norandrostan-17β-ol-3-one	102	283	181
17α-Ethyl-19-nonandrostan-17β-ol-3-one	100	300[b]	200
Androst-4-en-17β-ol-3-one	288[b]	458[b]	170
17α-Methylandrost-4-en-17β-ol-3-one	308[b]	434[b]	126
17α-Ethylandrost-4-en-17β-ol-3-one	246	347	101
17α-Propylandrost-4-en-17β-ol-3-one	249	317	68
17α-Vinylandrost-4-en-17β-ol-3-one	239[d]	317[d]	78
17α-Allylandrost-4-en-17β-ol-3-one	261	330	69
17α-Ethinylandrost-4-en-17β-ol-3-one	69[d]	184[d]	115
17α-Propargylandrost-4-en-17β-ol-3-one	212	264	52
6α-Methyl-17α-propinylandrost-4-en-17β-ol-3-one	41	28	−13
4,4-Dimethylandrost-5-en-17β-ol-3-one	−42	−68	−26
4,4,17α-Trimethylandrost-5-en-17β-ol-3-one	−106[c]	−195[c]	−89
17α-Methyl-19-norandrost-4-en-17β-ol-3-one	89	1	−88
17α-Ethyl-19-norandrost-4-en-17β-ol-3-one	75	192[b]	117
9β,11β-Epoxy-17α-methylandrost-4-en-17β-ol-3-one	−126	−483	−357
9α-Fluoro-17α-methylandrost-4-ene-11β,17β-diol-3-one	367[c]	364[c]	−3
9α-Fluoro-17α-methylandrost-4-en-17β-ol-3,11-dione	482	428	−54
Androsta-4,6-dien-17β-ol-3-one	45[c]	−425[c]	−470
17α-Methylandrosta-4,6-dien-17β-ol-3-one	228[b]	−408[b]	−636
17α-Ethylandrosta-4,6-dien-17β-ol-3-one	229[b]	−186[b]	−415

[a] [M]D steroidal[3,2-c]pyrazole minus [M]D parent 3-ketosteroid. [b] In pyridine. [c] In 95% ethanol. [d] In dioxane.

(18) D. D. Casoni, A. Mangini and R. Passerini, *Boll. sci. fac. chim. ind. Bologna*, **12**, 147 (1954), *C. A.*, **49**, 8700 (1955).

(19) *Cf.* D. DalMonte: A. Mangini and R. Passerini, *Gazz. chim. ital.* **86**, 797 (1956).

(20) P. Mirone and M. Vampiri, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat. e not.*, **12**, 583 (1952) (*C. A.*, **46**, 9423 (1952); C. S. Rondestvedt, Jr., and P. K. Chang, *J. Am. Chem. Soc.*, **77**, 6532 (1955)).

TABLE III

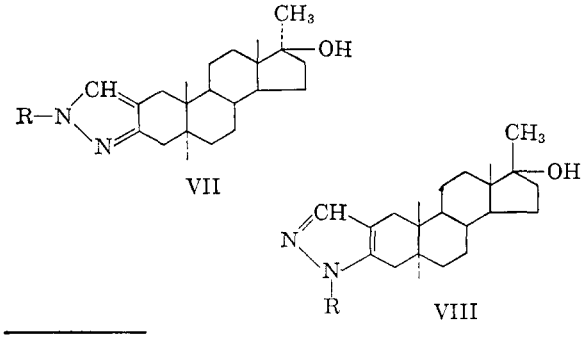
MOLECULAR ROTATION DIFFERENCES DUE TO SUBSTITUTION IN THE PYRAZOLE RING

-[3,2-c]pyrazole	Derivative	$[M]_D$, $CHCl_3$ Parent	$[M]_D$, $CHCl_3$ Derivative	$\Delta[M]_D$[a]
17β-Propionoxyandrostano-	N-Propionyl	149	202	53
17β-Cyclohexylpropionoxyandrostano-	N-Cyclohexylpropionyl	190	244	54
17β-Hydroxy-17α-methylandrostano-	1'-Methyl	117[b]	134[b]	17
	2'-Methyl	117	131	14
	1'-Phenyl	117	240	123
	1',2'-Dimethyl, iodide	159[c]	173[c]	14
	N-Acetyl	117	179	62
	N-Propionyl	117	167	50
	N-(4-Chlorophenoxyacetyl)	117	174	57
17β-Acetoxy-17α-methylandrostano-	N-Acetyl	164	226	62
17β-Hydroxyandrost-4-eno-	N-Carbamyl	458[d]	296[d]	−162
17β-Propionoxyandrost-4-eno-	N-Propionyl	366	222	−144
17-Ketoandrost-4-eno-	N-Carbamyl	657[d]	502[d]	−155
17β-Hydroxy-17α-methylandrost-4-eno-	1'-Methyl	434[d]	452[d]	18
	1',2'-Dimethyl, iodide	338[c]	64[c]	−274
	N-Acetyl	434[d]	321[d]	−113
17β-Hydroxy-17α-methyl-19-norandrost-4-eno-	N-Propionyl	1	24	23
17β-Hydroxy-17α-methylandrosta-4,6-dieno-	N-Acetyl	−408[d]	−703[d]	−295

[a] $[M]_D$ steroidal[3,2-c]pyrazole (column one) minus $[M]_D$ steroidal[3,2-c]substituted pyrazole (column two). [b] In 95% ethanol. [c] In methanol. [d] In pyridine.

The molecular rotations of the steroidal[3,2-c]-pyrazoles are in turn affected by substituents on the pyrazole ring, as may be seen in Table III. Herein are summarized the changes produced by, *e.g.*, acylation or alkylation of the pyrazole ring. The substitution of an alkyl group at the 1'- or 2'-positions has a small or negligible effect on the molecular rotation in the androstane series but the effect is quite pronounced in the androst-4-ene series. N-Acetylation of the androstano- or 19-norandrost-4-eno[3,2-c]pyrazoles produced a moderate positive increment in $\Delta[M]_D$ values, whereas N-acylation (or formation of the N-carbamyl derivative) of the androst-4-eno[3,2-c]-pyrazoles gives a large negative increment. The similarity of the $\Delta[M]_D$ values for the formation of an N-acyl or N-carbamyl derivative is confirmatory evidence that these groups occupy the same position on the pyrazole ring; *cf.* the ultraviolet absorption spectral data below.

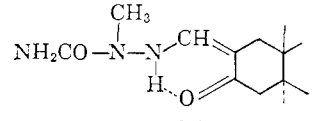
The reaction between a 2-hydroxymethylene-3-ketosteroid and an alkyl- or aryl-monosubstituted hydrazine could conceivably give a mixture[21] of 1'- and 2'-alkyl(aryl)substituted steroidal-[3,2-c]-pyrazoles, as illustrated by VII and VIII. Since the substituted nitrogen in an alkyl monosubstituted hydrazine is the more nucleophilic of the two,[22] we expected to obtain at least a preponderance of the compound corresponding to VII (R = CH_3) when methylhydrazine was condensed with 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one. Actually, we were able to isolate only a single crystalline steroidal[3,2-c]-N-methylpyrazole, in about 72% yield, with λ_{max} 231 mμ, although traces of an isomer may have been present.



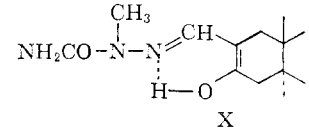
VII

VIII

In order to substantiate the tentatively assigned structure (VII, R = CH_3) of the above compound, we prepared the isomeric compound VIII (R = CH_3) by an alternative route. The reaction between 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one and 2-methylsemicarbazide (which undoubtedly involves the hydroxymethylene group), gave an N-methylsemicarbazone. To this compound we assigned a hydrogen-bonded structure, IX or X, on the basis of its positive ferric chloride test and absorption maxima at 234 and 290 mμ. Pyrolysis of the N-methylsemicarbazone, IX or X, eliminated the carbamyl group with simultaneous ring closure[23] to yield 17β-hydroxy-17α-methylandrostano[3,2-c]2'-methylpyrazole (VIII, R = CH_3), with λ_{max} 229 mμ. The small but significant difference in the ultraviolet absorption maxima between VII and VIII is in agreement with the assigned structure, since a similar effect has been noted[13] with the compounds 1,3,4-tri-



IX



X

(21) *Cf.* K. v. Auwers and W. Schmidt, *Ber.*, **58**, 528 (1925); K. v. Auwers and H. Stuhlmann, *ibid.*, **59**, 1043 (1926).

(22) G. von Brüning, *Ann.*, **253**, 5 (1889); G. Young and W. H. Oates, *J. Chem. Soc.*, **79**, 659 (1901); A. Michaelis and E. Hadack, *Ber.*, **41**, 3285 (1908).

(23) *Cf.* K. v. Auwers and H. Mauss, *Ann.*, **452**, 182 (1927).

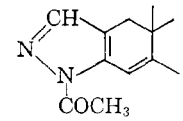
methylpyrazole and 1,4,5-trimethylpyrazole, in which the former compound absorbs at the longer wave length.

When 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one was condensed with phenylhydrazine, a single pyrazole was obtained. Since phenylhydrazine has its more nucleophilic nitrogen β to the phenyl group, we would expect the product to possess the structure VIII (R = (C_6H_5)). Experimental verification of this mechanism with simple β-dicarbonyl compounds is found in the literature.[24]

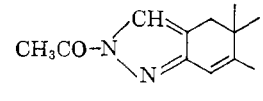
Methylation of the steroidal[3,2-c]-N-alkylpyrazoles (*e.g.*, VII, R = CH_3) by means of methyl iodide[25] required heating of the components in a bomb tube, since the reaction rate at normal temperatures was extremely slow. The derived steroidal[3,2-c]-1′,2′-dimethylpyrazolium iodides were stable, high-melting salts, which were relatively insoluble in water. With the androstano[3,2-c]-1′-methylpyrazoles, quaternization shifted the ultraviolet maximum hypsochromically by 9 mμ, with a simultaneous marked increase in the intensity of absorption. In the analogous androst-4-eno system, quaternization of the 1′-methylpyrazole derivative produced a bathochromic shift of 15 mμ in the long wave length maximum and an increase in the intensity of absorption.

The preparation of steroidal[3,2-c]-N-acylpyrazoles was readily carried out by treatment of the steroidal[3,2-c]pyrazole with an acid anhydride in the presence of pyridine. However, because of this relative ease of N-acylation we were unable to effect O-acylation selectively with steroidal[3,2-c]pyrazoles containing secondary hydroxyl groups. Initially the O-acyl substituted esters were prepared by carrying out the reaction between, *e.g.*, 2-hydroxymethyleneandrostan-17β-ol-3-one and hydrazine in an organic acid in the presence of a strong acid catalyst. The yield of O-acyl ester obtained by this method was quite low. Later it was found that the N-acyl groups in O,N-diacyl steroidal-[3,2-c]pyrazoles were sufficiently labile to be quite easily and selectively removed by refluxing aqueous acetic acid. Thus, by means of this sequence we were able to obtain excellent over-all yields of esters.

In general the acylation of a pyrazole gives the more "stable" isomer[26] but we cannot at the present time definitely assign the position of the N-acyl group in our compounds (*i.e.*, VII and VIII, R = acyl). We attempted to methylate the unsubstituted nitrogen in a steroidal[3,2-c]-N-acylpyrazole under a variety of conditions, but in all cases the reaction resulted only in cleavage of the N-acyl group and subsequent formation of the 1,2-dimethylpyrazolium iodide. The ultraviolet spectral data were also inconclusive, since we did not possess both N-acyl isomers. However, in the androst-4-eno[3,2-c]-N-acylpyrazoles the multiplicity of maxima at long wave lengths would seem to favor the extended system XI rather than the cross-conjugated system XII.



XI



XII

Due to the fact that the pyrazole ring readily forms complex salts with heavy metals the N-carbamyl group was used to protect the pyrazole ring in syntheses involving, for example, oxidations at C-17. The steroidal[3,2-c]-N-carbamylpyrazoles[27] were prepared in excellent yield by treatment of the parent pyrazoles with potassium cyanate in dilute alcoholic hydrochloric acid in the usual manner. The protective carbamyl group was readily removed by heating the derivative with an excess of hydrogen chloride in aqueous alcoholic solution, or by prolonged refluxing in aqueous tertiary butanol solution.

There was a strong tendency for most of the steroidal[3,2-c]pyrazoles to crystallize as reproducible solvates, from such diverse solvents as benzene, ethyl acetate, alcohols and ethers. The pronounced stability of these solvates (often to 50° above the boiling point of the bound solvent) may indicate the possibility of representing them as inclusion compounds (clathrates).[28]

The pK_b values were determined[29] for several of the steroidal[3,2-c]pyrazoles by titration in a non-aqueous system (acetonitrile–methyl Cellosolve) with 0.1 *M* perchloric acid in dioxane, using pyrazole (pK_b 11.5) as a reference standard. The pK_b values found for all of the steroidal[3,2-c]-pyrazoles checked were in the range 9.4–10.0, with no differences ascribable to structural variations. Within the limitations of the experimental method the pK_b values are substantially alike, and agree well with the data reported by Dedichen[30] for comparable disubstituted pyrazoles.

Structure–Activity Relationships.—The fusion of a [3,2-c]pyrazole ring onto a steroid in the manner of formula I usually produced quite pronounced changes in endocrinological activity.[31] The most noteworthy effects were apparent in the altered anabolic/androgenic ratios and in the development of new types of activity. For example, androstan-17β-ol-3-one and 17α-methylandrostan-17β-ol-3-one are both highly anabolic and androgenic; the latter activity is so high, however, that neither compound has found clinical acceptance for more than short-term usage as an anabolic drug. The corresponding 17β-hydroxyandrostano[3,2-c]-pyrazole and 17β-hydroxy-17α-methylandrostano-[3,2-c]pyrazole, on the other hand, afforded a much greater separation of activities. The relative

(24) K. v. Auwers and H. Mauss, *Ber.*, **59**, 611 (1926); P. J. Drumm, *Proc. Roy. Irish Acad.*, **40B**, 106 (1931).

(25) Compare K. v. Auwers and H. Hollmann, *Ber.*, **59**, 1282 (1926).

(26) T. L. Jacobs in "Heterocyclic Compounds," R. C. Elderfield, Editor, Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1597, Chapter 2, p. 95.

(27) Comparison of the ultraviolet spectral data (see Experimental) indicates that the N-carbamyl group occupies the same (stable) position as the N-acyl group on the pyrazole ring. The similarity of the $\Delta[M]_D$ values (see Table III) for N-carbamyl and N-acyl groups is confirmatory evidence.

(28) H. M. Powell, *J. Chem. Soc.*, 2658 (1954).

(29) We thank Dr. C. A. Kelly of this Institute for these results.

(30) G. Dedichen, *Ber.*, **39**, 1831 (1906).

(31) We are grateful to Drs. A. L. Beyler, A. Arnold and G. O. Potts of this Institute for permission to publish these preliminary results.

potency ratios[32] for anabolic/androgenic activity are eight and one hundred and twenty, respectively.[33] The latter data have been confirmed clinically in humans.[34]

Both anabolic and androgenic activities fell off abruptly in the 17α-alkyl-17β-hydroxyandrostano[3,2-c]pyrazoles when the 17α-alkyl group was larger than ethyl, indicating rather severe restrictions on "fit" to the cellular receptor site in the presence of the [3,2-c]pyrazole ring. The series of 17α-alkyl-17β-hydroxyandrostano[3,2-c]pyrazoles was completely devoid of estrogenic or progestational activities, even at high dose levels. Furthermore, N-methylation also decreased both androgenic and anabolic activities in comparison with the parent steroidal[3,2-c]pyrazole. On the other hand, acylation of the pyrazole ring had the unexpected effect of imparting a low degree of *estrogenicity*[35] to the androstano[3,2-c]pyrazoles, *without* affecting the anabolic/androgenic ratios.

The series of androst-4-eno[3,2-c]pyrazoles and androsta-4,6-dieno[3,2-c]pyrazoles had anabolic/androgenic ratios comparable to their saturated analogs in the androstano[3,2-c]pyrazole series; that is, high ratios for the lower members of the series and a rapid decrease in activities above 17α-ethyl. In these two series of compounds, however, the parent non-acylated pyrazoles were inherently estrogenic—in fact, somewhat more so than the androstano[3,2-c]-N-acylpyrazoles. 17α-Ethinyl-17β-hydroxyandrost-4-eno[3,2-c]pyrazole was less progestational (orally) and considerably more estrogenic than its progenitor, Ethisterone.

The most conspicuous effect of the [3,2-c]-pyrazole moiety on endocrinological activity was observed when substitutions were made in the steroid nucleus in the androstano- and androst-4-eno[3,2-c]pyrazoles. For example, it is known that the introduction of a 6α-methyl substituent[36] or of the 9α-fluoro-11β-hydroxy groups[37] into 17α-methyltestosterone produces a marked increase in the androgenic and/or anabolic activities. However, in the present work similar substitutions produced an *opposite* effect: 6α,17α-dimethyl-17β-hydroxyandrost-4-eno[3,2-c]pyrazole and 11β,17β-dihydroxy-9α-fluoro-17α-methylandrost-4-eno-[3,2-c]pyrazole were both considerably *less* active, androgenically and anabolically, than the parent 17β-hydroxy-17α-methylandrost-4-eno-[3,2-c]pyrazole. Analogous decreases in the observed androgenic and anabolic activities were noted with 4-methylation, and with the 19-norsteroidal[3,2-c]pyrazoles.

It is thus apparent that a high degree of specificity attaches to the steroidal[3,2-c]pyrazoles considered herein, and that the greatest latitude for change is at C_{17} or on the pyrazole ring. These observations are possibly of some significance in relation to such problems as the nature of enzymatic bonding, the spatial requirements for substrates, and the cellular mechanisms of androgenic and anabolic activities.

Some of the simple 2-hydroxymethylene-3-keto-17α-alkylandrostanes and their Δ^4-analogs had a fair to good degree of oral anabolic activity, and gave good anabolic/androgenic ratios. In all cases, however, the anabolic activities of the 2-hydroxymethylene-3-keto progenitors were less interesting than those of their steroidal[3,2-c]-pyrazole derivatives.[31] It is pertinent to point out that one of these compounds, *viz.*, 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one, has shown oral anabolic activity in humans.[38]

Acknowledgment.—We are indebted to Dr. F. C. Nachod and Miss Catherine Martini for the spectral determinations, and to Mr. K. D. Fleischer and staff for analytical services.

Experimental[39]

2-Hydroxymethylene-3-ketosteroids. Method A.—The 3-ketosteroid was treated with sodium hydride and ethyl formate in benzene solution, under essentially the same conditions as those described by Weisenborn, *et al.*[40] Often there were minor variations in quantities or in the duration of the reaction; these are noted below in connection with a specific compound.

Method B.—The above method A was modified as follows: to the stirred suspension of sodium hydride in benzene was added 5 to 25 mole per cent. (based on the sodium hydride) of absolute methyl alcohol. After 0.5 hour the remaining components were added, and the reaction was completed as in method A.

Method C.—The formylation procedure described by Johnson and Posvic,[41] involving the use of methanol-free sodium methoxide in benzene, was modified only by changes in the duration of the reaction, or by the use of commercial sodium methoxide in place of material prepared *in situ*.

Method D.—To a solution of 15 millimoles of the 3-ketosteroid in 100 ml. of dry pyridine, held under nitrogen, was added 8.0 ml. (100 millimoles) of ethyl formate (distilled from phosphorus pentoxide) followed by a solution of 0.66 g. (30 millimoles) of sodium in 6 ml. of absolute methyl alcohol. The resulting solution was then kept at room temperature under nitrogen for several hours (usually overnight). Reaction was evidenced by the appearance of a deep color and/or the formation of an insoluble precipitate.

The mixture was poured into a cold solution of 75 ml. of glacial acetic acid in 700 ml. of water, and the resulting precipitate was extracted into benzene or methylene dichloride. The organic layer was washed with water and then extracted

(32) The anabolic activity was based upon multiple dose-level assays (nitrogen retention in castrate rats) and the androgenic activity was determined by the ventral prostate weight gain in castrate rats. With 17β-hydroxyandrostano[3,2-c]pyrazole the reference standard was testosterone propionate (all administrations given subcutaneously) and with 17β-hydroxy-17α-methylandrostano[3,2-c]pyrazole the reference standard was 17α-methyltestosterone (all administrations given orally).

(33) A. Arnold, A. L. Beyler and G. O. Potts. *Proc. Soc Exptl. Biol. Med.*, **102**, 184 (1959); G. O. Potts, A. L. Beyler and D. F. Burnham, *ibid.*, **103**, 383 (1960).

(34) R. P. Howard, L. N. Norcia, J. A. Peter and R. H. Furman. Paper presented at the 41st Meeting of the Endocrine Society, Atlantic City, N. J., 1959.

(35) Measured by the degree of vaginal cornification and uterine growth in female rats.

(36) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(37) M. E. Herr, J. A. Hogg and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956); S. C. Lyster, G. H. Lund and R. O. Stafford, *Endocrinol.*, **58**, 781 (1956).

(38) H. A. Burke, Jr., and G. W. Liddle, *Abstr. Endocrine Society Meeting*, Atlantic City, N. J., 1959, p. 45.

(39) Melting points were taken in a Hershberg-type apparatus and are corrected. Rotations were determined in chloroform solution at 25°, $c \sim 1\%$ (except where noted); ultraviolet spectra were taken in 95% ethanol (Cary) and infrared spectra in a potassium bromide disk (Perkin-Elmer 21). In the chromatographic purifications below, the silica gel used was Davison Type 923, 100–200 mesh. The sources of other absorbents are listed in the text.

(40) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).

(41) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947); compare L. Ruzicka, V. Prelog and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948); J. A. K. Quartey, *J. Chem. Soc.*, 1710 (1958).

with 3 × 100 ml. of 2% potassium hydroxide solution. The combined basic extracts were washed with ether and acidified with 10 ml. of glacial acetic acid. The product was then isolated by filtration or extraction in the usual manner.

Method E.—Method D was modified by the substitution of an equivalent amount of methanol-free sodium methoxide for the sodium methoxide–methanol solution. The reaction mixture was stirred mechanically.

In the following section certain of the 2-hydroxymethylene-3-keto-steroids are characterized in detail. Those compounds not so specifically listed will be found discussed below with the appropriate derived pyrazole, or in Table IV.

2-Hydroxymethyleneandrostan-17β-ol-3-one.—Method A (3 days) gave a 92% yield, method C (3 days) a 49% yield, and method E (overnight) a 99% yield (all yields are crude, but the material was of sufficient quality for conversion to the pyrazole). The properties of the pure compound were in excellent agreement with those reported subsequent to the completion of the present work by Edwards and Ringold,[8d] but differed substantially from the properties reported for the same compound by Weisenborn and Applegate.[8c,42]

TABLE IV

2-HYDROXYMETHYLENE-3-KETOSTEROID INTERMEDIATES

2-Hydroxymethylene derivative of	Method[a]	Time	Yield, %
17α-Ethinylandrostan-17β-ol-3-one	A, C	2 days	35–36
	D, E	2 days	81–83[b]
17α-Ethylandrostan-17β-ol-3-one[c,d]	C	1 day	100
17α-Propinylandrostan-17β-ol-3-one	C	3 days	85
17α-Propylandrostan-17β-ol-3-one	A	7 days	98[e]
4,4,17α-Trimethylandrostan-17β-ol-3-one[f]	D	1 day	77[g]
6α,17α-Dimethylandrostan-17β-ol-3-one[h]	C	1 day	100[i]
4,4-Dimethylandrostan-17β-ol-3-one[f]	E	1 day	77[j]
19-Norandrostan-17β-ol-3-one[k]	D	4 hr.	100[l]
17α-Methyl-19-norandrostan-17β-ol-3-one[k]	C	2 days	100[m]
17α-Ethyl-19-norandrostan-17β-ol-3-one[k]	E	4 hr.	60[n]
17α-Ethinylandrost-4-en-17β-ol-3-one[o]	E	1 day	50[p]
17α-Vinylandrost-4-en-17β-ol-3-one[q]	A, B	3 days	88–94
17α-Ethylandrost-4-en-17β-ol-3-one[r]	A	3 days	100[s]
17α-Allylandrost-4-en-17β-ol-3-one[t]	D	4 days	83
4,4-Dimethylandrost-5-en-17β-ol-3-one[f]	D	3 days	71[u]
4,4-Dimethyl-17β-methoxyandrost-5-en-3-one[cc]	E	1 day	85[v]
4,4,17α-Trimethylandrost-5-en-17β-ol-3-one[f]	D	1 day	83[w]
Androst-4-ene-11β,17β-diol-3-one[x]	A	4 days	50[y]
9β,11β-Epoxy-17α-methylandrost-4-en-17β-ol-3-one[z]	E	2 days	100[aa]
Androsta-4,6-dien-17β-ol-3-one[bb]	A	4 days	95[ee]
17α-Ethylandrosta-4,6-dien-17β-ol-3-one[cc]	A	3 days	98[dd]

[a] See Experimental. [b] M.p. 170.8–177.5°. [c] See ref. 8b. [d] The intermediate 17α-ethylandrostan-17β-ol-3-one had m.p. 149.8–151.6°, [α]D 13.7°; L. Ruzicka, M. W. Goldberg and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935), reported m.p. 137–138°. [e] Method B (3 days), 98% yield, m.p. about 80°. [f] For the intermediate 3-ketosteroid see H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957); *cf.* W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956). [g] Method C (1 day) gave no product; the crude material had m.p. 150–154°, λ_{max}^{EtOH} 294 mμ (7200). [h] For the 3-ketosteroid, see Experimental. [i] M.p. 190.8–199.8° (from acetone), [α]D 54.3°, λ_{max}^{EtOH} 285 mμ (9200); λ_{max}^{KBr} 3.18, 3.82, 6.23 μ. *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.93; H, 9.63. [j] M.p. 157–159° (from isopropyl alcohol), [α]D 37.5°, λ_{max}^{EtOH} 294 mμ (8100). *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 75.80; H, 9.42; O, 13.30. [k] Intermediate 3-ketosteroid: A. Bowers, H. J. Ringold and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958). [l] Resinous, λ_{max}^{EtOH} 281 mμ (7800). [m] M.p. 206.2–210.6°, [α]D 96.1°, λ_{max}^{EtOH} 283 mμ (7800); *cf.* ref. 8b. [n] Method C (2 days) gave no product; the (hydrated) compound had m.p. 72–115°, λ_{max}^{EtOH} 282 mμ (6800). [o] *Cf.* ref. 8d. [p] M.p. 182–188°, λ_{max}^{EtOH} 252 (11700) and 307 mμ (5200). [q] Intermediate 3-ketosteroid: L. Ruzicka and P. Muller, *Helv. Chim. Acta*, **22**, 755 (1939); E. B. Hershberg, E. P. Oliveto, C. Gerold and L. Johnson, *J. Am. Chem. Soc.*, **73**, 5073 (1951). [r] Intermediate 3-ketosteroid: L. Ruzicka and H. R. Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936). [s] Isolated as the sodium salt: m.p. 200–230° dec.; gave analyses for a monohydrate. [t] The intermediate 3-ketosteroid *hemihydrate* had m.p. 95.4–109.8°, [α]D 75.4; the compound was dried 8 hours at 110° *in vacuo* before the formylation. See A. Butenandt and D. Peters, *Ber.*, **71**, 2688 (1938). [u] M.p. 148–154°, λ_{max}^{EtOH} 279 mμ (6800). [v] M.p. 138.8–139.6° (from isopropyl alcohol), [α]D −44.1°, λ_{max}^{EtOH} 279 mμ (7500). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; OCH_3, 8.66. Found: C, 77.36; H, 9.26; OCH_3, 8.32. [w] M.p. 164.2–166.0° (from isopropyl alcohol), [α]D −59.2°, λ_{max}^{EtOH} 279 mμ (7600). *Anal.* Calcd. for $C_{23}H_{34}O_2$: C, 77.05; H, 9.56. Found: C, 76.81; H, 9.35. [x] Intermediate 3-ketosteroid: M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **75**, 5928 (1953). [y] M.p. 168–190°, λ_{max}^{EtOH} 251 (11700) and 307 mμ (5200). [z] Intermediate 3-ketosteroid: M. E. Herr, J. A. Hogg and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956); see also ref. 65. [aa] M.p. 80–115°, λ_{max}^{EtOH} 253 (9200) and 312 mμ (5500). [bb] Intermediate 3-ketosteroid: A. Wettstein, *Helv. Chem. Acta*, **23**, 388 (1940); H. H. Inhoffen and G. Zuehlsdorf, *Ber.*, **76**, 233 (1943); C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950). [cc] Intermediate 3-ketosteroid: see Experimental. [dd] Isolated as the water-insoluble sodio-derivative the free 2-hydroxymethylene compound was resinous. [ee] λ_{max}^{EtOH} 290 (9900) and 334 mμ (4900).

2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one.—Method A (2 days) 27% yield, methods B and C (2 days) 90–95%, method E (overnight), 99%. The use of potassium *t*-butoxide in *t*-butyl alcohol gave a 31% yield. The reported[1] properties of the compound are substantially in agreement with those given by Ringold, *et al.*,[8b] except for the optical rotation. Subsequent preparations have shown [α]D values in agreement with that reported by Ringold, *et al.*[8b] The pure compound is apparently somewhat unstable; a sample stored in a screw-capped vial for 3 years showed an increase in [α]D value of 6°, a 30° drop in melting point, and a 21% decrease in the ε value at 280 mμ. The infrared spectrum showed new bands at 6.00, 6.37 and 7.00 μ.

2-Hydroxymethylene-17α-methylandrost-4-en-17β-ol-3-one was obtained by method A (5 days), 90%. The compound can best be isolated as the slightly-soluble sodium salt after the initial quench in water. The pure compound

(42) The compound reported by the latter authors[8c] is actually *2-methoxymethyleneandrostan-17β-ol-3-one*, formed when *crude* (containing traces of occluded hydrochloric acid from the precipitation) 2-hydroxymethyleneandrostan-17β-ol-3-one is recrystallized from methanol. The enol ether is differentiated from its parent 2-hydroxymethylene compound by the hypsochromic shift in the ultraviolet maximum to 277 mμ (11800), and in the infrared spectrum by the loss of the broad chelate bands at 3.7–3.8 and 6.1–6.25 μ and the appearance of a new strong band at 5.99 μ (C=C—C=O). The compound had m.p. 199.2–200.6°, [α]D +48.7°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; OCH_3, 9.33. Found: C, 76.12; H, 9.40; OCH_3, 9.96.

had m.p. 178.6–179.8°, $[\alpha]_D$ + 14.0°, λ_{max} 252, 307 mμ (12000 and 6000, respectively); *cf.* Ringold, *et al.*[1]

Attempts to Form Isomeric 2-Hydroxymethylene-3-ketosteroids.—The ultraviolet spectra of 2-hydroxymethylenetestosterone, 2-hydroxymethyleneandrosta-4,6-dien-17β-ol-3-one and 4,4-dimethyl-2-hydroxymethyleneandrost-5-en-17β-ol-3-one were determined in anhydrous ethereal solution; to each stock solution was then added slightly more than one mole equivalent of anhydrous hydrogen chloride, and the ultraviolet spectra of appropriate dilutions were taken at intervals over a 72-hour period. No changes in band positions or intensities were observed during this time with 2-hydroxymethylenetestosterone or 4,4-dimethyl-2-hydroxymethyleneandrost-5-en-17β-ol-3-one. With 2-hydroxymethyleneandrosta-4,6-dien-17β-ol-3-one, although the band at 290 mμ was unchanged in position or intensity, the band at 324 mμ disappeared completely. Preparative experiments with 2-hydroxymethylenetestosterone and 4,4-dimethyl-2-hydroxymethyleneandrost-5-en-17β-ol-3-one, wherein these compounds were subjected to the experimental conditions outlined by Holker, *et al.*,[10] and by Tsuda and Nozoe,[11] gave in every case a quantitative recovery of unaltered starting material.

Preparation of the Steroidal[3,2-c]pyrazoles.—To a solution of 0.01 mole of the 2-hydroxymethylene-3-ketosteroid in 100 ml. of ethanol was added 0.015–0.02 mole of hydrazine hydrate (85–100%). The resulting solution was then refluxed for 2 to 6 hours.[43] Frequently the product crystallized out on cooling the reaction mixture. In other cases the solution was evaporated to dryness *in vacuo*, and the residue was purified by crystallization or by chromatography. With very few exceptions, the yields of the purified steroidal[3,2-c]pyrazoles were greater than 60%.

The steroidal[3,2-c]pyrazoles are listed in Table V, or in cases where the isolation procedures offered some difficulty, below in the Experimental section.

17β-Propionoxyandrostano[3,2-c]pyrazole.—A mixture of 5.00 g. of 2-hydroxymethyleneandrostan-17β-ol-3-one, 3.80 g. of hydrazine sulfate and 400 ml. of redistilled propionic acid was stirred and heated at 70° for 5 days. The mixture was poured into 800 ml. of water and the product was extracted with ether. The ethereal extracts were washed with water and with saturated sodium bicarbonate solution, and then dried over anhydrous sodium sulfate. Evaporation of the ethereal extract gave a semi-solid residue. Crystallization of the latter from ether–pentane gave 1.82 g. of material melting at 90–98°, resolidifying and melting above 178°. The mother liquors were evaporated *in vacuo* and the residue was chromatographed on 120 g. of silica gel prewet with 1:1 benzene–pentane. Elution with benzene and 10% ether–benzene gave a series of oily fractions. Elution with 20% ether–benzene gave a total of 1.10 g. of additional ester, m.p. 186–196°. The combined crops (2.92 g.) were rechromatographed on 180 g. of silica gel as above. The appropriate fractions were combined and recrystallized four times from ether to give 1.5 g. of the pure compound, m.p. 181.2–195.2°, $[\alpha]_D$ + 40.2°, λ_{max} 223 mμ (5900); λ_{max} 3.18, 5.76, 6.26, 6.38, 6.60, 6.92, 8.43 μ.

Anal. Calcd. for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; O, 8.64. Found: C, 74.45; H, 9.28; O, 8.30.

17β-Propionoxyandrostano[3,2-c]-N-propionylpyrazole.—A mixture of 1.80 g. of 17β-hydroxyandrostano[3,2-c]-pyrazole monoethanolate, 1.43 g. of *p*-toluenesulfonic acid monohydrate, 10 ml. of propionic acid and 25 ml. of redistilled propionic anhydride was allowed to stand at room temperature for 24 hours. The resulting clear solution was poured into 400 ml. of water, and after standing for 1 hour, the precipitated solid was filtered off and washed thoroughly with water. The crude, air-dried product (2.25 g., m.p. 167–175°) was recrystallized from hexane and from ether to give 1.27 g. of white needles, m.p. 180.0–181.8°, $[\alpha]_D$ + 47.2°, λ_{max} 258 mμ (17000).

Anal. Calcd. for $C_{26}H_{38}N_2O_3$: C, 73.20; H, 8.98; N, 6.57. Found: C, 72.92; H, 8.96; N, 6.30.[44]

The N-propionyl group could be removed by heating the O,N-diacyl compound with aqueous acetic acid, as outlined for similar compounds below.

17β-Cyclohexylpropionoxyandrostano[3,2-c]-N-cyclohexylpropionylpyrazole.—To a solution of 5.00 g. of 17β-hydroxyandrostano[3,2-c]pyrazole (predried at 130° *in vacuo*) in 80 ml. of pyridine was added 15.0 g. of redistilled 3-cyclohexylpropionic anhydride, and the mixture was allowed to stand at room temperature for 20 hours. The reaction was completed by heating on the steam-bath for 0.5 hour. After dilution with a large volume of water, the insoluble material was taken up in ethyl acetate and the extracts were washed with water, dilute hydrochloric acid and saturated sodium bicarbonate solution. The dried (Na_2SO_4) extract was evaporated to dryness *in vacuo* and the crude, oily product (still containing a considerable amount of cyclohexylpropionic anhydride) was chromatographed on 350 g. of silica gel prewet with pentane. Elution with 2.5% ether–pentane gave an initial series of oily fractions, followed by a series of crystalline fractions. Several recrystallizations of the combined solid fractions (6.07 g.) from ether–methanol gave 1.12 g. of colorless needles, m.p. 117.8–120.8°, $[\alpha]_D$ + 41.4°, λ_{max} 258 mμ (17700), λ_{max} 5.80, 6.31, 6.75, 6.91 μ. The mother liquors gave additional material on reworking.

Anal. Calcd. for $C_{38}H_{58}N_2O_3$: C, 77.24; H, 9.89; N, 4.74. Found: C, 77.53; H, 9.73; N, 4.76.

17β-Cyclohexylpropionoxyandrostano[3,2-c]pyrazole.—A mixture of 3.4 g. of the above O,N-dicyclohexylpropionyl derivative (material of purity equivalent to the initial chromatographic fractions) and 40 ml. of 80% (v./v.) aqueous acetic acid was refluxed for 2 hours. The initially insoluble material dissolved completely within 0.5 hour. The clear solution was diluted with water and the mixture was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Evaporation of the ethyl acetate *in vacuo* gave 2.6 g. of semi-crystalline residue. The crude product was chromatographed on 100 g. of silica gel prewet with 5% ether–pentane. After preliminary elution with 10% and 25% ether–pentane, the product was eluted with a 50% ether–pentane mixture. Several recrystallizations from an acetone–methanol mixture gave 1.53 g. of colorless needles, m.p. 236.4–238.6°, $[\alpha]_D$ + 41.9°, λ_{max} 224 mμ (4900).

Anal. Calcd. for $C_{29}H_{44}N_2O_2$: C, 76.94; H, 9.80; N,[45] 3.10. Found: C, 76.82; H, 10.17; N,[45] 3.05.

17β-Acetoxy-17α-methylandrostano[3,2-c]pyrazole.—A solution of 7.00 g. of 17β-hydroxy-17α-methylandrostano-[3,2-c]pyrazole in 100 ml. of acetic anhydride was refluxed for 1.5 hours. The solution was poured into a liter of water, and after 1 hour the gummy precipitate was extracted into methylene dichloride. The methylene dichloride extracts were washed with water and with saturated sodium bicarbonate solution, and then evaporated to dryness *in vacuo*. The resulting glass-like resin was chromatographed on silica gel prewet with 5% ether–pentane. The desired product (7.68 g.) was eluted with 10% ether–pentane. Recrystallization from acetone and from ethyl acetate–heptane gave **17β-acetoxy-17α-methylandrostano[3,2-c]-N-acetylpyrazole**; colorless needles of m.p. 144.4–145.8°, $[\alpha]_D$ + 55.0°, λ_{max} 257 mμ (17400).

Anal. Calcd. for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.80; O, 11.63. Found: C, 72.93; H, 8.55; O, 11.90.

A solution of 5.73 g. of the above O,N-diacetyl derivative in 60 ml. of 80% (v./v.) acetic acid was refluxed for 1.5 hours. The solution was diluted with 400 ml. of ice-water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and with saturated sodium bicarbonate solution, dried, and evaporated to dryness *in vacuo*. Recrystallization of the resulting product from methanol gave the title compound as colorless needles (2.17 g.), m.p. 224.8–226.8°, $[\alpha]_D$ + 44.3°, λ_{max} 224 mμ (5000).

Anal. Calcd. for $C_{28}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56. Found: C, 74.81; H, 9.35; N, 7.51.

17β-Hydroxy-17α-methylandrostano[3,2-c]-1′-methylpyrazole (VII, R = CH_3).—A solution of 1.52 g. of methyl-

(43) The ferric chloride test (on a drop of the solution made just acidic with dilute ethanolic hydrochloric acid) usually became negative in 15 to 30 min.

(44) Kjeldahl or unmodified Dumas analyses of the steroidal-[3,2-c]pyrazoles frequently gave erratic results. This difficulty was solved by premixing the compounds with vanadium pentoxide before the Dumas analysis.

(45) "Basic" nitrogen, as determined by potentiometric titration with perchloric acid in acetic acid solution. With pyrazoles, this is equivalent to the determination of a single nitrogen.

TABLE V

STEROIDAL [3,2-c]PYRAZOLES AND DERIVATIVES

-[3,2-c]pyrazole	M.p., °C. (cor.)	$[\alpha]_D$ ($CHCl_3$)	λ_{max}^{EtOH} mμ	ε	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
17β-Hydroxyandrostano-[a,b,c]	127.6–128.4[d]	55.1	224	4900	$C_{22}H_{36}N_2O_2$[b]	73.29	73.28	10.07	10.06	[e]	[e]
17β-Hydroxy-17α-methylandrostano-[a,f]	229.8–242.0	35.7[g]	223	4700	$C_{21}H_{32}N_2O$	76.78	76.65	9.82	9.73	8.53	8.45
N-acetyl-[a,b,h,i]	111.4–115.4	43.1	258	19000	$C_{25}H_{40}N_2O_3$[b]	72.07	72.40	9.68	9.78	6.73	6.72
N-propionyl-[a]	134.4–148.0	45.1	258	18800	$C_{24}H_{36}N_2O_2$	74.96	75.17	9.44	9.33	7.29	7.30
N-(4-chlorophenoxyacetyl)-[k]	164.8–167.6	35.1	228[l]	14000	$C_{29}H_{37}ClN_2O_3$	[m]	[m]				
17α-Ethinyl-17β-hydroxyandrostano-[a]	237.4–242.0	12.4[n]	223[o]	5100	$C_{22}H_{30}N_2O$	78.06	77.87	8.93	9.20	8.28	8.37
17α-Ethyl-17β-hydroxyandrostano-[a,b,q]	249.0–251.6[q]	32.7	224	5100	$C_{24}H_{40}N_2O_2$[b]	74.18	74.32	10.38	10.28	7.21	7.12
17β-Hydroxy-17α-propinylandrostano-[r,s]	[t]	[u]	224[v]	5400	$C_{23}H_{32}N_2O$	78.36	78.04	9.15	9.10	[w]	[w]
17β-Hydroxy-17α-propylandrostano-[x,y]	217.6–220.8	35.2	224	4800	$C_{23}H_{36}N_2O$	77.48	77.17	10.18	9.87	7.86	7.65
6α,17α-Dimethyl-17β-hydroxyandrostano-[z]	156.0–174.0[aa]	44.8	224	4900	$C_{22}H_{34}N_2O$	77.14	77.35	10.01	10.10	8.18	8.28
17β-Hydroxy-4,4,17α-trimethylandrostano-[bb]	269.2–274.6	[cc]	223	4900	$C_{23}H_{36}N_2O$	77.48	77.46	10.18	10.21	7.86	7.93
4,4-Dimethyl-17β-hydroxyandrostano-[bb]	176.0–179.0	30.0	223	4800	$C_{22}H_{34}N_2O$	77.14	76.24	10.01	9.68	4.09[qq]	4.06[qq]
17β-Hydroxy-19-norandrostano-[a]	248.0–251.5	...	223	5600	$C_{19}H_{28}N_2O$	75.95	75.36	9.39	9.62	9.33	9.49
17α-Ethyl-17β-hydroxy-19-norandrostano-[a,dd]	149.2–150.4	[ee]	223	4700	$C_{21}H_{32}N_2O$	76.78	76.74	9.82	9.90	8.53	8.28
17β-Hydroxyandrost-4-eno-[a]	272.0–276.6	[ff]	261	10600	$C_{20}H_{28}N_2O$	76.88	76.93	9.03	9.03	...	...
N-propionyl-17β-propionate-[h,gg]	148.8–151.6	52.4	237[hh]	7500	$C_{26}H_{36}N_2O_3$	73.55	73.82	8.55	8.55	[ii]	[ii]
17α-Ethinyl-17β-hydroxyandrost-4-eno-[k]	239.6–246.2	29.0[jj]	271	10700	$C_{22}H_{28}N_2O$	78.53	78.44	8.39	8.39	8.33	8.32
17β-Hydroxy-17α-vinylandrost-4-eno-[a,kk]	247.0–259.4	101.2[ll]	261[mm]	11200	$C_{22}H_{30}N_2O$	78.06	78.30	8.93	9.19	8.28	8.36
17α-Ethyl-17β-hydroxyandrost-4-eno-[a]	284.4–290.6	102.1	261	10600	$C_{22}H_{32}N_2O$	77.60	77.88	9.47	9.20	8.23	7.96
17α-Allyl-17β-hydroxyandrost-4-eno-[z]	239.8–248.2	93.7	260	10500	$C_{23}H_{32}N_2O$	78.36	78.28	9.15	9.48	[nn]	[nn]
4,4-Dimethyl-17β-hydroxyandrost-5-eno-[z]	231.0–233.6	−20.1	224	5500	$C_{22}H_{32}N_2O$	77.60	78.17	9.47	9.69	[oo]	[oo]
4,4-Dimethyl-17β-methoxyandrost-5-eno-[pp]	236.4–239.2	−34.2	224	5200	$C_{23}H_{34}N_2O$	77.92	77.88	9.67	9.34	3.95[qq]	4.00[qq]
17β-Hydroxy-4,4,17α-trimethylandrost-5-eno-[bb]	270.4–276.0	[rr]	223	5400	$C_{23}H_{34}N_2O$	77.92	78.23	9.67	9.47	7.90	7.65
11β,17β-Dihydroxyandrost-4-eno-[a,b]	233.2–246.0[ss]	[tt]	262	10700	$C_{22}H_{34}N_2O_3$[b]	70.55[uu]	70.80	9.15	9.37	3.79[qq]	4.00[qq]
N-propionyl-17β-propionate-[h,bb]	107.6–112.6	80.7	238[vv]	7300	$C_{26}H_{36}N_2O_4$	70.88	71.04	8.24	7.90	6.36	6.60
9β,11β-Epoxy-17β-hydroxy-17α-methylandrost-4-eno-[k,ww]	233.2–246.8	−145.0	262	9200	$C_{21}H_{28}N_2O_2$	74.08	74.20	8.29	8.40	4.14[qq]	3.88[qq]
17β-Hydroxyandrosta-4,6-dieno-[xx]	272.8–277.0	[yy]	220[zz]	7600	$C_{20}H_{26}N_2O$	77.38	77.40	8.44	8.42	9.03	9.29
17α-Ethyl-17β-hydroxyandrosta-4,6-dieno-[a]	305–315	[aaa]	221[bbb]	7500	$C_{22}H_{30}N_2O$	78.06	78.07	8.93	8.99	8.28	7.99

[e] Crystallized from ethanol. [b] Monoethanolate. [c] The compound also crystallized as a solvate from benzene, acetone and ethyl acetate. [d] Resolidified and remelted at 217–225°. [e] Calcd.: C_2H_5OH, 12.78. Found: C_2H_5OH, 12.76. [f] The compound crystallized as a solvate, prisms melting at about 148°, resolidifying and remelting at 228–234°; for analysis the compound was dried for 16 hours at 140° *in vacuo*. [g] $[\alpha]_D$ 48.6° (1% in methanol). [h] Prepared by treatment of the pyrazole with the acyl anhydride–pyridine, 24 hours at room temperature. [i] λ_{max}^{KBr} 2.98, 5.78, 6.17, 6.32, 6.75, 6.93 μ. [j] Dried for 8 hours at 95° *in vacuo*. [k] Crystallized from acetone. [l] Further maxima at 260 (18300) and 287 mμ (1700). [m] Calcd.: Cl, 7.13; O, 9.66. Found: Cl, 7.05; O, 9.25. [n] $[\alpha]_D$ 10.2° (1% in pyridine). [o] λ_{max}^{KBr} 3.10, 4.77, 6.15, 6.27, 6.37, 6.68 μ. [p] Dried for 48 hours at 30° *in vacuo* over phosphorus pentoxide. [q] Sintered at 140–150°. [r] Crystallized from ethyl acetate–ether. [s] Dried for 8 hours at 120° *in vacuo*. [t] Decomposed at about 143° to a foam. [u] $[\alpha]_D$ −29.6° (1% in pyridine), $[\alpha]_D$ −29.3° (1% in dimethylformamide). [v] λ_{max}^{KBr} 2.98, 3.12, 4.47, 6.25, 6.36, 6.60–6.70, 6.79, 6.92 μ. [w] Calcd.: O, 4.54. Found: O, 4.64. [x] Crystallized from aqueous ethanol. [y] Dried for 8 hours at 110° *in vacuo*. [z] Crystallized from ethyl acetate. [aa] With decomposition. [bb] Crystallized from methanol. [cc] $[\alpha]_D$ 4.7° (1% in ethanol), $[\alpha]_D$ 5.9° (1% in pyridine). [dd] Purified by chromatography by the method used for the 17α-methyl homolog; see Experimental. [ee] $[\alpha]_D$ 93.0° (1% in pyridine). [ff] $[\alpha]_D$ 147.6° (1% in pyridine). [gg] Crystallized from ether–pentane. [hh] Further maxima at 289 (24800) and 297 mμ (22400). [ii] Calcd.: O, 11.31. Found: O, 11.50. [jj] $[\alpha]_D$ 54.6° (1% in dioxane). [kk] Obtained as a solvate, also from ethyl acetate; dried for 8 hours at 150° *in vacuo*. [ll] $[\alpha]_D$ 93.6° (1% in dioxane). [mm] λ_{max}^{KBr} 3.12, 5.46, 6.15, 6.44, 10.05, 10.92 μ. [nn] Calcd.: O, 4.54. Found: O, 4.80. [oo] Calcd.: O, 4.70. Found: O, 4.94. [pp] Crystallized from isopropyl alcohol. [qq] See ref. 45. [rr] $[\alpha]_D$ −55.0° (1% in ethanol) $[\alpha]_D$ −42° (1% in pyridine). [ss] Solvent loss at about 155°. [tt] $[\alpha]_D$ 167.5° (1% in pyridine). [uu] Calcd.: C_2H_5OH, 12.03. Found: C_2H_5OH, 10.81. [vv] Further maxima at 254 (6000) and 291 mμ (21700). [ww] Dried 16 hours at 140° *in vacuo*. [xx] Crystallized from ethanol-ethyl acetate. [yy] $[\alpha]_D$ −137.2° (1% in ethanol). [zz] Further maxima at 225 (8500), 232 (7800), 296 (22000) and 300 mμ (16600). [aaa] $[\alpha]_D$ −55.4° (1% in pyridine). [bbb] Further maxima at 225 (8500), 232 (7700), 297 (21800) and 308 mμ (16400).

hydrazine sulfate and 1.97 g. of sodium acetate in 80 ml. of water was added to a solution of 3.00 g. of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one in 400 ml. of ethanol, and the resulting mixture (including precipitated sodium sulfate) was refluxed for 30 minutes. The reaction mixture was diluted with 700 ml. of ethyl acetate and 400 ml. of water, and after thorough mixing the ethyl acetate layer was separated. The aqueous layer was re-extracted several times with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residual crystalline solid was recrystallized from acetone–methanol, giving (in two crops) 2.20 g. of material melting at 234–248°. On further recrystallization from methanol the compound was obtained as diamond-shaped crystals (1.53 g.), m.p. 249.6–259.0°, $[\alpha]_D$ + 39.0° (1% in ethanol), λ_{max} 231 mμ (7100).

Anal. Calcd. for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; O, 4.76. Found: C, 77.44; H, 9.90; O, 4.90.

17β-Hydroxy-17α-methylandrostano[3,2-c]-2′-methylpyrazole (VIII, R = CH_3).—A solution of 8.5 g. of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one and 2.3 g. of 2-methylsemicarbazide[22] in the minimum amount of boiling 1-butanol was refluxed for 18 hours. The solution was evaporated to dryness *in vacuo*, the residual gum was taken up in methylene dichloride, and the latter solution was washed thoroughly with water. Evaporation of the methylene dichloride left 8.4 g. of resinous material. On trituration with ether there was obtained 4.8 g. of an ether-insoluble powder, which melted with decomposition at about 140° and had λ_{max} 234, 290 mμ (15500, 17300); λ_{max} 2.90, 5.93 (sh.) 6.00, 6.4 μ. The compound, to which we assign the structure IX or X, gave an intense green color with ferric chloride.

The N-methylsemicarbazone (2.7 g.) was heated in an oil-bath at 205° (nitrogen atmosphere) for 6 hours. The resulting black, glassy product was dissolved in benzene and chromatographed on 100 g. of Woelm neutral alumina prewet with benzene. After preliminary elution with benzene and 10% ether–benzene, a mixture of 20% ether–benzene eluted 0.78 g. of product melting at 180–198°. Recrystallization from acetone gave material melting at 186.6–198.0°, $[\alpha]_D$ + 38.3° (1% in ethanol), λ_{max} 229 mμ (4900). The infrared spectrum of this compound was distinctly different from that of the 1′-methyl isomer above.

Anal. Calcd. for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; N, 8.18. Found: C, 77.24; H, 10.17; N, 8.09.

17β-Hydroxy-17α-methylandrostano[3,2-c]-1′,2′-dimethylpyrazolium Iodide.—A mixture of 1.85 g. of 17β-hydroxy-17α-methylandrostano[3,2-c]-1′-methylpyrazole, 10 ml. of methanol and 10 ml. of methyl iodide was sealed in a glass bomb and allowed to stand at room temperature for 60 hours. The bomb was then heated at 100° for 1 hour, cooled, and the solution was evaporated to dryness. The residual solid was a mixture of massive white prisms and yellow spherulites. The latter yellow solid was selectively washed out of the mixture by trituration with a few ml. of methylene dichloride, and the remaining prisms (1.43 g.) were recrystallized from methanol and from acetonitrile to give 1.34 g. of the title compound, m.p. 282.4–291.2° dec., $[\alpha]_D$ + 35.8° (1% in methanol), λ_{max} 222 mμ (16700).

Anal. Calcd. for $C_{23}H_{37}IN_2O$: C, 57.01; H, 7.70; I, 26.20. Found: C, 57.09; H, 7.67; I, 25.87.

The yellow solid by-product (λ_{max} 224 mμ (6700)) was not investigated further.

17β-Hydroxy-17α-methylandrostano[3,2-c]-2′-phenylpyrazole Methanolate (VIII, R = C_6H_5).—A mixture of 3.33 g. of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one, 1.10 g. of phenylhydrazine and 100 ml. of methanol was refluxed for 1.5 hours, and the solution was then concentrated to a volume of 15 ml. The solution was cooled and the precipitated orange solid was filtered off and air dried, giving 3.29 g. of crude product with a melting point of about 103° dec. The compound was recrystallized three times from methyl alcohol and then dried at 30° *in vacuo:* clusters of soft needles, (1.34 g.), m.p. begins to decompose at 99.4° to a foam, $[\alpha]_D$ + 55.0°, λ_{max} 262 (14100).

Anal. Calcd. for $C_{27}H_{36}N_2O \cdot CH_3OH$: C, 77.02; H, 9.23; O, 7.33. Found: C, 76.90; H, 8.96; O, 7.25.

17α-Ethinylandrostan-17β-ol-3-one.[46]—A solution of 5.1 g. of 17α-ethinylandrostane-3β,17β-diol[47] in 125 ml. of pyridine was treated with 5.0 g. of chromium trioxide in the usual way.[48] The crude solid product was recrystallized several times from alcohol to give 2.05 g. of pure material, m.p. 287.4–299.4°, $[\alpha]_D$ −25.4° (1% in pyridine).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.28; H, 9.77; O, 9.95.

An alternative preparation utilized 17α-ethinylandrost-4-en-17β-ol-3-one (Ethisterone) and gave somewhat better over-all yields: Ethisterone was reduced to 17α-ethinylandrostan-17β-ol-3-one by means of lithium in liquid ammonia (*cf.* the preparation of 6α,17α-dimethylandrostan-17β-ol-3-one below) and the crude product, containing some of the 3-hydroxy compound, was oxidized by the Oppenauer procedure.

17α-Vinylandrostan-17β-ol-3-one.—A solution of 3.18 g. of 17α-vinylandrostane-3β,17β-diol[49] in 20 ml. of dry pyridine was treated with 1.33 g. of solid chromium trioxide.[48] From the reaction mixture was obtained 2.50 g. (79%) of product melting above 180° and suitable for formylation. Recrystallization from ethyl acetate gave small white needles, m.p. 183.0–183.6°, $[\alpha]_D$ + 8.8°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11. Found: C, 79.30; H, 10.39; O, 10.50.

17β-Hydroxy-17α-vinylandrostano[3,2-c]pyrazole.—The formylation of the above 3-ketone by method C (3 days) gave yields of 36 and 37%. Method D (2 hours to 2 days) gave 4–15% yields. Using method C and heating at 45–50° for 2 days gave yields of 47 and 53%. The crude 2-hydroxymethylene-3-ketosteroid had m.p. 132–137°.

Condensation of the crude 2-hydroxymethylene-17α-vinylandrostan-17β-ol-3-one with hydrazine hydrate gave a pyrazole derivative which could not be obtained pure by recrystallization. The crude steroidal[3,2-c]pyrazole (2.71 g.) was chromatographed on 100 g. of silica gel prewet with benzene. The column was eluted with the sequence: benzene, ether–benzene, ether, ethyl acetate. Finally, elution with 5% methanol–ethyl acetate produced 1.39 g. of pyrazole. After several recrystallizations from methanol the pure compound (0.94 g.) was obtained as dense prisms, m.p. above 300°, $[\alpha]_D$ + 24.5°, λ_{max} 224 mμ (7100).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23; O, 4.70. Found: C, 77.52; H, 9.70; N, 8.00; O, 4.50.

17α-Propinylandrostan-17β-ol-3-one.—To a stirred suspension of 46.3 g. (0.16 mole) of androstan-3β-ol-17-one in 400 ml. of dry ether and 90 ml. of dihydropyran (redistilled from solid potassium hydroxide) was added 0.9 g. of *p*-toluenesulfonic acid monohydrate. Solution of the steroid was complete after about 20 minutes. The clear solution was allowed to stand for 3 days at room temperature and then cooled in an ice-bath. The first crop of crystalline product (17.0 g., m.p. 160–195°) was filtered off and washed with cold ether; concentration of the filtrate *in vacuo* gave successively two additional crops (16.6 g., m.p. 150–190°, and 4.4 g., m.p. 120–150°). The first two crops of the crude epimeric mixture of 3-tetrahydropyranyl ethers were combined for the next step.

A 2-liter 3-neck flask was fitted with a mechanical stirrer, gas entry tube, and a "Y"-tube carrying a Dry Ice-cooled reflux condenser and a pressure-equalized dropping funnel. The flask was flushed with dry nitrogen and there were introduced 250 ml. of tetrahydrofuran (distilled from sodium) and a solution of 0.3 mole of ethylmagnesium bromide in 100 ml. of ether.[50] Thirty grams of propyne[51] was introduced through the gas entry tube under Dry Ice reflux, and the resulting mixture was then stirred for 1 hour. A solution of the tetrahydropyranyl epimers from above (33.5 g.) in 250 ml. of dry tetrahydrofuran was added slowly through the dropping funnel, and the mixture was refluxed overnight. After cooling, the mixture was treated with 50 ml. of satu-

(46) *Cf.* T. Bersin and I. Loheyde, *Z. Naturforsch.*, **4b**, 195 (1949), these authors do not describe the preparation or properties of the compound.

(47) L. Ruzicka and K. Hofmann, *Helv. Chim Acta*, **20** 1280 (1937).

(48) See G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(49) A. Serini and W. Logemann, *Ber.*, **71**, 1362 (1938).

(50) Arapahoe Chemicals, Inc., Boulder, Colo.

(51) The Matheson Co., Inc., East Rutherford, N. J.

rated ammonium chloride solution. The inorganic salts were filtered off, washed thoroughly with ethyl acetate, and the combined filtrate and washings were evaporated to dryness *in vacuo*. The residual solid was taken up in 300 ml. of ethanol, 5 ml. of 85% phosphoric acid was added, and the clear solution was stored at room temperature for 2 days. Slow dilution of the resulting solution with water gave a crystalline precipitate; recrystallization of the dried precipitate from acetone–ether and from benzene afforded 22.6 g. (76%) of crude 17α-propinylandrostane-3β,17β-diol, m.p. above 150°. After oxidation by means of the complex from 18.0 g. of chromium trioxide and 300 ml. of pyridine, there was obtained a 66% over-all yield of the title compound; massive transparent prisms from methanol, m.p. 192.8–197.0°, $[\alpha]_D$ −18.7°, $[\alpha]_D$ −28.2° (1% in pyridine).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83; O, 9.74. Found: C, 80.72; H, 10.01; O, 9.50.

17α-Propylandrostan-17β-ol-3-one.—The stepwise hydrogenation of 17α-allylandrost-5-ene-3β,17β-diol[52] utilizing a 22% palladium–strontium carbonate catalyst in ethanol solution (*via* the isolated intermediate 17α-propylandrost-5-ene-3β,17β-diol[53]), gave an excellent over-all yield of **17α-propylandrostane-3β,17β-diol**[54]; needles from ethyl acetate, m.p. 188.6–191.0°, $[\alpha]_D$ −5.3°.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.20; H, 11.47.

Oxidation of the latter diol by means of the chromium trioxide–pyridine complex gave the title compound in excellent yield; prisms from ethyl acetate, m.p. 131.8–132.4° $[\alpha]_D$ +15.5°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.20; H, 10.92.

6α,17α-Dimethylandrostan-17β-ol-3-one.—To 1 liter of liquid ammonia, contained in a 3-liter 3-neck flask surmounted by a Dry Ice condenser and a mechanical stirrer, was added slowly a solution of 10 g. (0.0316 mole) of 6α,17α-dimethylandrost-4-en-17β-ol-3-one[55] in a mixture of 150 ml. of anhydrous ether and 150 ml. of anhydrous tetrahydrofuran. To this mixture was added 2.5 g. (0.361 mole) of lithium metal in small pieces, and the resulting blue-black solution was stirred for 50 minutes. There was then added, in portions, a total of 20 g. of solid ammonium chloride, and the ammonia and most of the ether were evaporated by means of a steam-bath. The residual pasty mixture was stirred with 2.5 liters of water and the resulting white precipitate was filtered off, washed thoroughly with water, and dried at 60° *in vacuo*. The crude product[56] (9.87 g.) was dissolved in 100 ml. of dry pyridine and the solution was treated with 10.0 g. of solid chromium trioxide. After the heterogeneous mixture had been stirred overnight, it was diluted with ethyl acetate, filtered, and the insoluble solids were repeatedly triturated with hot ethyl acetate. The combined extracts were washed several times with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. Recrystallization of the crude product (7.96 g.) from ethyl acetate gave 3.47 g. of material with the melting point 177–181° (sufficiently pure for formylation). Further recrystallization from ethyl acetate gave the analytical sample as massive prisms, m.p. 181.6–184.6°, $[\alpha]_D$ + 10.3°, λ_{max} 2.88, 5.86 μ.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.43; H, 11.00.

17β-Hydroxy-17α-methyl-19-norandrostano[3,2-c]pyrazole.—The pure 2-hydroxymethylene-17α-methyl-19-norandrostan-17β-ol-3-one gave a crude pyrazole which could not be purified by recrystallization. The product was chromatographed on silica gel prewet with 10% ether–pentane. Elution with 20% acetone–methylene dichloride gave a series of oily fractions followed by a series of crystalline fractions. The latter were combined for recrystallization. The pyrazole formed solvates extensively, *e.g.*, an ethanol solvate of m.p. 146–156°, an acetone solvate of m.p. 148° dec. and an ethyl acetate solvate of m.p. 125–126° dec. (The latter solvate contained 14.3% of ethyl acetate, whereas a sesqui-solvate would contain 12.3% of ethyl acetate.) The pure, solvent-free pyrazole was obtained by drying the ethyl acetate solvate at 110° *in vacuo* for 48 hours, and then had m.p. 140.4–152.4°, $[\alpha]_D$ + 90.0°, λ_{max} 224 mμ (4800).

Anal. Calcd. for $C_{20}H_{30}N_2O$: C, 76.38; H, 9.62; N, 8.91. Found: C, 76.07; H, 9.62; N, 8.98.

17β-Propionoxyandrost-4-eno[3,2-c]pyrazole.—A solution of 2.33 g. of 17β-propionoxyandrost-4-eno[3,2-c]-N-propionylpyrazole in 50 ml. of 80% (v./v.) acetic acid was refluxed for 1.5 hours. The solution was diluted with water and the resulting precipitate taken up in ether. The ethereal solution was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The crude solid product was chromatographed on silica gel prewet with methylene dichloride. The crystalline fractions eluted by 5% ether–methylene dichloride were combined and recrystallized from acetone–hexane to give the pure compound, m.p. 166.6–172.0°, $[\alpha]_D$ + 99.5°, λ_{max} 261 mμ (10900); λ_{max} 2.84, 3.20, 5.80, 8.35, 6.13 μ.

Anal. Calcd. for $C_{28}H_{32}N_2O_2$: C, 74.96; H, 8.75; N,[45] 3.80. Found: C, 73.83; H, 8.63; N,[45] 3.85.

17-Ketoandrost-4-eno[3,2-c]pyrazole.—To a solution of 5.0 g. of 17β-hydroxyandrost-4-eno[3,2-c]pyrazole in 200 ml. of methanol was added 15 ml. of ether containing 0.016 mole of hydrogen chloride followed by 40 ml. of water. To the resulting clear solution, at room temperature, was added a solution of 1.3 g. of potassium cyanate in 10 ml. of water; within a few minutes a copious crystalline precipitate began to appear. After the mixture had been allowed to stand overnight, the precipitate was filtered off and washed well with water. The crude, dried product (4.2 g.) had m.p. 225–227°. One recrystallization from methanol gave, with but little loss, pure **17β-hydroxyandrost-4-eno[3,2-c]-N-carbamylpyrazole**, m.p. 227.0–228.0°, $[\alpha]_D$ + 83.4° (1% in pyridine), λ_{max} 236 and 280 mμ (8500 and 23600, respectively).

Anal. Calcd. for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 71.08; H, 8.37; N, 12.19.

A stirred, partial suspension of 8.0 g. of 17β-hydroxyandrost-4-eno-[3,2-c]-N-carbamylpyrazole in 500 ml. of glacial acetic acid was cooled to about 14°, and there was added dropwise during 10 minutes a solution of 3.2 g. of chromium trioxide in a mixture of 8 ml. of water and 24 ml. of glacial acetic acid. The mixture was stirred a further 2 hours at 14°, and then for 3 hours at room temperature. After dilution with water, the crude product was filtered off, washed thoroughly with water, and dissolved in chloroform (extraction of the aqueous filtrates with chloroform in the usual way gave additional material). The chloroform solution was filtered and concentrated to a small volume; on cooling there was obtained a first crop of crystalline product (4.8 g.) with m.p. 270–272°. The analytical sample of **17-ketoandrost-4-eno[3,2-c]-N-carbamylpyrazole** crystallized from chloroform in clusters of tiny needles, m.p. 273–274°, $[\alpha]_D$ + 136.3°, $[\alpha]_D$ + 142.2° (0.25% in pyridine).

Anal. Calcd. for $C_{21}H_{27}N_3O_2$: N, 11.89. Found: N, 11.61.

Oxidation of the 17β-hydroxy compound by means of the pyridine–chromium trioxide reagent did not result in improved yields, whereas the use of N-bromoacetamide in acetone solution gave a product containing bromine.[57]

A mixture of 4.57 g. of 17-ketoandrost-4-eno[3,2-c]-N-carbamylpyrazole, 1800 ml. of ethanol and 10 ml. of concentrated hydrochloric acid was refluxed for 6 hours. The alcoholic solution was concentrated to 900 ml., diluted with 600 ml. of water and 20 ml. of concentrated ammonium hydroxide solution, and the remaining alcohol was removed by distillation *in vacuo*. The precipitate was filtered off, washed with water and air-dried, yielding 3.95 g. of product

(52) S. Kuwada and M. Yago, *J. Pharm. Soc. Japan*, **56**, 625 (1936); A. Butenandt and D. Peters, *Ber.*, **71**, 2688 (1938).

(53) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1191 (1951).

(54) The corresponding 3-acetate, m.p. 125–126°, $[\alpha]_D$ −6° (1% in acetone), has been reported by V. Wenner and T. Reichstein, *Helv. Chim. Acta*, **27**, 24 (1944).

(55) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(56) Chromatography of a similar run indicated that the material at this point consisted of a 3:2 mixture of the ketone with the corresponding 3-hydroxy derivative.

(57) *Cf.* C. Musante, *Gazz. chim. ital.*, **78**, 178 (1948); E. Buchner and M. Fritsch, *Ann.*, **273**, 262 (1893).

melting at 244–255°. Recrystallization from acetone gave brilliant prismatic crystals of the title compound, m.p. 258.6–263.8°, $[\alpha]_D$ + 209.4°, $[\alpha]_D$ + 211.8° (1% in pyridine), $[\alpha]_D$ + 199.1° (1% in ethanol), λ_{max} 261 mμ (11300).

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.49; H, 8.65; N, 8.97.

17β-Hydroxy-17α-methylandrost-4-eno[3,2-c]pyrazole.—Prepared in high yield from 2-hydroxymethylene-17α-methylandrost-4-en-17β-ol-3-one (see above), the pure pyrazole derivative crystallized from alcohol in rhomboidal plates, m.p. 250.0–258.0°, $[\alpha]_D$ + 133.2° (1% in pyridine), $[\alpha]_D$ + 103.5° (1% in methanol), λ_{max} 260 mμ (11600).

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26. Found: C, 77.26; H, 9.31.

When the latter steroidal [3,2-c]pyrazole was treated with acetic anhydride–pyridine (48 hours at room temperature) the crude acetyl derivative was obtained as a colorless resin. When crystallized from ethanol **17β-hydroxy-17α-methylandrost-4-eno[3,2-c]-N-acetylpyrazole** formed a reproducible hemi-ethanolate (Found: C_2H_5OH, 5.8[58]) which melted at 92.0–100.2° to a glass. The solvent-free compound could not be obtained in a crystalline form; the pure compound (dry basis) had $[\alpha]_D$ + 67.1°, $[\alpha]_D$ + 87° (1% in pyridine); λ_{max} 237, 255 and 289 mμ (7600, 5300, 26000, respectively).

Anal. (Sample dried at 97° for 20 hours *in vacuo*). Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.20; H, 8.85; N, 7.56.

17β-Hydroxy-17α-methylandrost-4-eno[3,2-c]-1′-methylpyrazole (VII, R = CH_3, $\Delta^{4,5}$).—The reaction of 2-hydroxymethylene-17α-methylandrost-4-en-17β-ol-3-one with methylhydrazine (from equivalent amounts of methylhydrazine sulfate and sodium acetate) in aqueous ethanol gave a 44% yield of the pure steroidal[3,2-c]pyrazole, prisms from acetonitrile, m.p. 175.2–193.2°, $[\alpha]_D$ + 103.6°, $[\alpha]_D$ + 132.9° (1% in pyridine), λ_{max} 272 mμ (10400).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.26; H, 9.62; N, 8.00.

17β-Hydroxy-17α-methylandrost-4-eno[3,2-c]-1′,2′-dimethylpyrazolium Iodide.—A mixture of 5.25 g. of 17β-hydroxy-17α-methylandrost-4-eno[3,2-c]-1′-methylpyrazole, 10 ml. of methanol and 15 ml. of methyl iodide was placed in a bomb-tube and heated at 100° for 2.5 hours. The solvent and excess methyl iodide were removed *in vacuo*, and the residual solid was recrystallized from absolute ethanol with decolorization (Darco G-60). After a further recrystallization from ethanol there was obtained 2.05 g. (28%) of pale yellow crystals, m.p. 257.8–261.6° dec., $[\alpha]_D$ + 13.3° (1% in methanol), λ_{max} 220, 287 mμ (23100, 15500, respectively).

Anal. Calcd. for $C_{23}H_{35}IN_2O$: C, 57.25; H, 7.31; I, 26.30. Found: C, 57.41; H, 7.50; I, 26.74.

17β-Hydroxy-17α-propargylandrost-4-eno[3,2-c]pyrazole.—The formylation of 17α-propargylandrost-4-en-17β-ol-3-one[58] (m.p. 135.8–143.2°, $[\alpha]_D$ + 65.2) by method B (6 days) gave an 84% crude yield of product as a yellow solid. The crude 2-hydroxymethylene derivative when condensed with hydrazine hydrate produced a resinous pyrazole derivative. The latter was purified by chromatography on silica gel prewet with benzene. Elution with mixtures of 5% ether–benzene through 25% ether–benzene gave trace of resin; the title compound was eluted by means of a 50% ether–benzene mixture. Recrystallization of the pooled fractions from dilute ethanol gave the pure pyrazole, crystallizing as transparent prisms of m.p. 130.4–140.6°, $[\alpha]_D$ +75.4°, λ_{max} 261 mμ (9700).

Anal. Calcd. for $C_{23}H_{30}N_2O$: C, 78.81, H, 8.63; N, 7.99. Found: C, 78.73; H, 8.70; N, 8.11.

17β-Hydroxy-17α-propylandrost-4-eno[3,2-c]pyrazole.—The Oppenauer oxidation of 17α-propylandrost-5-ene-3β,17β-diol[59] (m.p. 188.0–192.8°, $[\alpha]_D$ −59.2°) by the procedure of Butenandt and Peters[60] gave **17α-propylandrost-4-en-17β-ol-3-one**, transparent rectangular plates from benzene–hexane, m.p. 114.6–116.0°, $[\alpha]_D$ + 75.4°, λ_{max} 241 mμ (16800).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 80.10; H, 10.64; O, 9.75.

Formylation of the 17α-propyltestosterone by method A (3 days) gave an 86% yield of the 2-hydroxymethylene derivative as a crystalline solid. The condensation of the latter compound with hydrazine hydrate was carried out as usual and the crude product was then triturated with 2 *N* hydrochloric acid to remove gummy impurities. The resulting material, after washing and drying, was chromatographed on silica gel prewet with benzene. Elution with benzene through 20% ether–benzene gave traces of resinous materials, whereas elution with 30% ether–benzene removed a small amount of crystalline material (see below). The desired product was eluted with 50% ether–benzene. Recrystallization from dilute ethanol afforded the pure title compound as fibrous plates, m.p. 223.0–232.4°, $[\alpha]_D$ + 89.5°, λ_{max} 260 mμ (9800).

Anal. Calcd. for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90. Found: C, 78.08; H, 9.78; N, 7.58.

The above crystalline fraction eluted by 30% ether–benzene formed flattened needles from ethanol, m.p. 203.0–212.0°, λ_{max} 260 mμ (8100). Analyses indicated that this compound was a dehydration product of the title compound, and infrared evidence confirmed this fact. Additionally, the infrared data indicated that the new double bond was probably endocyclic. The compound was therefore assigned the structure **17-methyl-17-propylandrosta-4,12(13)-dieno-[3,2-c]pyrazole.**

Anal. Calcd. for $C_{23}H_{32}N_2$: C, 82.09; H, 9.59; N, 8.33. Found: C, 81.77; H, 9.42; N, 8.26.

The dehydration product was probably formed during the treatment of the crude product with dilute hydrochloric acid; the position assignment of the double bond was based upon analogy with the recent work of Herzog, *et al.*,[61] in another series.

6α,17α-Dimethyl-17β-hydroxyandrost-4-eno[3,2-c]pyrazole.—The formylation of 6α,17α-dimethylandrost-4-en-17β-ol-3-one[43] by method A (5 days) gave an 85% crude yield of the 2-hydroxymethylene derivative with m.p. 145–165°, λ_{max} 257 mμ (7200) and 353 mμ (broad) (4100). Condensation of the 2-hydroxymethylene derivative with hydrazine hydrate gave a crude pyrazole which could not be purified by crystallization. The compound was chromatographed by a method similar to that used with 17β-hydroxy-17α-propylandrost-4-eno[3,2-c]pyrazole above. The desired product was eluted by means of a 50% ether–benzene mixture. Recrystallization of the pooled crystalline fractions from ethyl acetate gave the product as feathery needles, m.p. 170.0–178.6° dec., λ_{max} 262 mμ (9200).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.59; H, 9.47; N, 8.23. Found: C, 77.30; H, 9.69; N, 8.33.

17β-Hydroxy-6α-methyl-17α-propinylandrost-4-eno-[3,2-c]pyrazole.—The treatment of 6α-methyl-17α-propinylandrost-4-en-17β-ol-3-one[62] by the procedure of method D (2 days) gave a quantitative crude yield of the 2-hydroxymethylene derivative with m.p. 108–130°; λ_{max} 250 mμ (8300), 296 mμ (5400) and 379 mμ (5100). The derived steroidal[3,2-c]pyrazole was resinous; chromatographic purification was carried out on silica gel prewet with 10% ether–pentane. Elution with 3:1 methylene dichloride–ether through 1:1 methylene dichloride–ether gave a series of crystalline fractions, which were combined and recrystallized from methanol. The pure compound had m.p. 166.2–170.6°, $[\alpha]_D$ + 7.6°, λ_{max} 261 mμ (10500); λ_{max} 3.14, 4.48, 6.27, 6.67, 6.89 μ.

Anal. Calcd. for $C_{24}H_{32}N_2O$: C, 79.07; H, 8.85; N,[45] 3.85. Found: C, 79.22; H, 8.64; N,[45] 3.90.

4,4-Dimethyl-17β-methoxyandrost-5-en-3-one.—The mother liquors from the preparation of 4,4-dimethylandrost-5-en-17β-ol-3-one[63] were chromatographed on Merck

(58) Inadvertently reported in the Communication[1] as a solvate containing 15.8% ethanol.

(59) Prepared by the catalytic reduction (10% palladium-on-Darco G-60) of 17α-allylandrost-5-ene-3β,17β-diol, in ethanol solution, *cf.* ref. 53.

(60) A. Butenandt and D. Peters, *Ber.*, **71**, 2688 (1938).

(61) H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg and D. H. R. Barton, *J. Org. Chem.*, **22**, 1413 (1957).

(62) A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. Pharmacol.*, **9**, 929 (1957); S. P. Barton, D. Burn, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.*, 1957 (1959).

(63) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957); *cf.* W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956).

aluminum oxide prewet with benzene. Elution with benzene gave a series of crystalline fractions, which were combined and recrystallized from methanol. The pure compound (12% yield based upon testosterone) formed slender needles of m.p. 134.4–138.2°, $[\alpha]_D$ −15.0°; λ_{max} 5.86, 6.05 μ (no hydroxyl band).[64]

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; OCH_3, 9.39. Found: C, 80.33; H, 9.95; OCH_3, 9.23.

11β,17β-Dihydroxy-9α-fluoro-17α-methylandrost-4-eno[3,2-c]pyrazole.—Method E (6 days) when applied to 9α-fluoro-17α-methylandrost-4-ene-11β,17β-diol-3-one[65,66] gave a quantitative crude yield of the 2-hydroxymethylene derivative. The compound was a glassy resin. The condensation of the latter compound with hydrazine hydrate was carried out in methanolic solution; the desired pyrazole derivative was obtained as an orange resin. Chromatographic purification of the crude material on silica gel, as outlined above for 17β-hydroxy-17α-propylandrost-4-eno[3,2-c]pyrazole, gave a series of crystalline fractions (eluted by pure ether). These were combined and recrystallized from acetone and from ethyl acetate; m.p. 281° dec., $[\alpha]_D$ +101.3° (1% in ethanol).

Anal. Calcd. for $C_{21}H_{29}FN_2O_2$: C, 69.97; H, 8.11; F, 5.27; N,[45] 3.88. Found: C, 69.85; H, 7.53; F, 5.32; N,[45] 3.59.

9α-Fluoro-17β-hydroxy-11-keto-17α-methylandrost-4-eno[3,2-c]pyrazole.—The reaction of 9α-fluoro-17α-methylandrost-4-en-17β-ol-3,11-dione[67] with ethyl formate, utilizing method B (5 days), gave a 75% crude yield of the 2-hydroxymethylene derivative. The derived pyrazole was an amorphous solid, which was purified by chromatography on silica gel (see above). The series of crystalline fractions eluted by pure ether were pooled and recrystallized from acetone. The pure compound had m.p. 292–300° dec., $[\alpha]_D$ +119.6° (0.15% in ethanol), λ_{max} 260 mμ (10000), λ_{max} 2.80, 3.08, 5.81, 6.10, 6.38, 6.66, 6.89μ.

Anal. Calcd. for $C_{21}H_{27}FN_2O_2$: C, 70.36; H, 7.59; F, 5.30. Found: C, 70.85; H, 7.73; F, 4.63.

17β-Hydroxy-17α-methyl-19-norandrost-4-eno[3,2-c]-pyrazole Hemi-ethanolate.—The steroidal[3,2-c]pyrazole was prepared from the intermediate 2-hydroxymethylene-17α-methyl-19-norandrost-4-en-17β-ol-3-one[8b] (λ_{max} 247 mμ (10800)). The crude product was chromatographed on silica gel prewet with 10% ether–pentane and the title compound was eluted by means of a 3:1 methylene dichloride–acetone mixture. Recrystallization from ethanol gave needles of m.p. 111.0–126.1° dec., $[\alpha]_D$ + 0.2°, λ_{max} 260 mμ (10500).

Anal. Calcd. for $(C_{20}H_{28}N_2O)_2 \cdot C_2H_5OH$: C, 75.18; H, 9.32; N,[45] 4.18; OC_2H_5, 6.72. Found: C, 75.30; H, 9.41; N,[45] 4.21; OC_2H_5, 6.98.

The N-propionyl derivative of 17β-hydroxy-17α-methyl-19-norandrost-4-eno[3,2-c]pyrazole was prepared by treatment of the hemi-ethanolate with excess propionic anhydride in pyridine solution for 48 hours at room temperature. The compound crystallized from methanol as a solvate, m.p. 105–134°. After prolonged drying at 80° *in vacuo* the compound was obtained free of solvent; m.p. 131.8–134.2°, $[\alpha]_D$ −6.4°; λ_{max} 239 mμ (7700), 245 mμ (7500), 257 mμ (6800), 290 mμ (20700).

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.73; H, 9.05; N, 7.76.

(64) The infrared band at 6.05 μ is characteristic for the C_8-double bond in this and similar compounds.

(65) We wish to thank Drs. D. I. Weisblat and H. G. Kolloff of the Upjohn Co., Kalamazoo, Mich., for a generous supply of this compound.

(66) We are indebted to Dr. J. Fried of the Squibb Institute for Medical Research, New Brunswick, N. J., for a supply of this compound.

(67) M. E. Herr, J. A. Hogg and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956).

17α-Ethyl-17β-hydroxy-19-norandrost-4-eno[3,2-c]pyrazole.—The formylation of 17α-ethyl-19-norandrost-4-en-17β-ol-3-one[68] by method B (4 days) gave an 85% crude yield of the corresponding 2-hydroxymethylene derivative (solvated by water), m.p. 87–100°, λ_{max} 247 mμ (8900) and 300 mμ (4100). Condensation of the 2-hydroxymethylene derivative with hydrazine hydrate gave a resinous product, which was purified by chromatography on silica gel prewet with methylene dichloride. The column was eluted with 19:1 methylene dichloride–methanol. After a series of oily fractions, the product was eluted in crystalline form. This material was recrystallized twice from methyl ethyl ketone; m.p. from 147° with gradual decomposition, $[\alpha]_D$ +59.1° (1% in pyridine), λ_{max} 261 mμ (5700).

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58. Found: C, 77.04; H, 9.08; N, 8.66.

17β-Hydroxy-17α-methylandrosta-4,6-dieno[3,2-c]pyrazole.—Method C (3 days) when applied to 17α-methylandrosta-4,6-dien-17β-ol-3-one[1,69] gave a quantitative crude yield of the 2-hydroxymethylene derivative, m.p. from 87° with gradual decomposition, λ_{max} 291 and 327 mμ (16800 and 8100, respectively), $[\alpha]_D$ −208.5°. Reaction of the 2-hydroxymethylene-17α-methylandrosta-4,6-dien-17β-ol-3-one with hydrazine hydrate furnished a 52% yield of the pure pyrazole derivative, pale yellow plates from ethyl acetate, m.p. 279.2–284.0°, $[\alpha]_D$ −126.1° (1% in pyridine)[70]; λ_{max} 226, 232, 297, 308 mμ (9200, 8200, 24300, 18400, respectively).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.64. Found: C, 77.92; H, 8.53; N, 8.35.

A solution of 17β-hydroxy-17α-methylandrosta-4,6-dieno[3,2-c]pyrazole in pyridine containing an excess of acetic anhydride was allowed to stand at room temperature for 24 hours. The mixture was then poured into water, and the resulting precipitate was filtered off, washed thoroughly with water and dried at 65°. The crude product was purified by chromatography on silica gel prewet with methylene dichloride. Elution with 5% ether-methylene dichloride gave a series of crystalline fractions, which were combined and recrystallized from ether–pentane. The pure 17β-hydroxy-17α-methylandrosta-4,6-dieno[3,2-c]-N-acetylpyrazole had m.p. 151.8–154.8°, $[\alpha]_D$ −244°, $[\alpha]_D$ −192° (1% in pyridine); λ_{max} 264, 310, 323 mμ (9200, 33300, 30200, respectively).

Anal. Calcd. for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.42; H, 8.19; N, 7.69.

17α-Ethylandrosta-4,6-dien-17β-ol-3-one.—The bromination of 17α-ethyltestosterone[71] by means of N-bromosuccinimide and the subsequent dehydrobromination of the 6-bromo derivative by means of collidine were carried out in the usual manner. The product crystallized from ethanol in pale yellow, flattened needles, m.p. 177.4–182.2°, $[\alpha]_D$ +14.9°, $[\alpha]_D$ +73.1° (1% in pyridine), λ_{max} 285 mμ (26300).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.55; H, 9.79.

(68) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *ibid.*, **79**, 1123 (1957). We are grateful to Dr. Byron Riegel for a generous sample of this compound.

(69) This compound was prepared in 47% over-all yield from 17α-methyltestosterone by bromination with N-bromosuccinimide in carbon tetrachloride solution and subsequent dehydrobromination of the 6-bromo derivative by means of refluxing technical collidine. The pure dienone crystallized from acetone in leaflets, m.p. 196.0–197.6°, $[\alpha]_D$ +36.2°, $[\alpha]_D$ +75.8° (1% in pyridine), λ_{max} 283 mμ (26000). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.49. The compound has also been prepared by the direct dehydrogenation of 17α-methyltestosterone by means of chloranil. J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959).

(70) Inadvertently reported[1] as $[\alpha]_D$ −162.1° (1% in pyridine).

(71) L. Ruzicka and H. R. Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936).