+50.3°, λ_{max} 236, 242 mμ, log ε 4.17, 4.19; ν_{max} 1740, 1690, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; O, 12.48. Found: C, 77.77; H, 9.03; O, 12.79.

6α,7α-Oxido-6β,16α-dimethylpregnan-5α-ol-3,20-dione (XIV). (a) *By oxidation of 6,16α-dimethyl-Δ⁵-pregnene-3β,-5α-diol-20-one* (XIa). A solution of compound XIa (0.6 g., m.p. 176–17[illegible] [α]D +50°) in acetone (60 cc.) was oxidized over a perio[illegible]-5 min. by titration with 8 *N* chromic acid in 8 *N* sulfuric acid[8] at 0 to 5°. Addition of water and extraction with ethyl acetate gave a semicrystalline residue. This material was chromatographed on neutral alumina (30 g.) whereby elution with benzene afforded a compound (350 mg.) with m.p. 235–245°. An analytical sample of the oxido ketone XIV was obtained by crystallization from acetone-ether: needles with m.p. 252–253°, [α]D +40.4°, ν_{max} 3650, 1720, 1700 cm.$^{-1}$. It showed no selective high ultraviolet absorption.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.97; H, 8.89; O, 17.51.

(b) *By oxidation of 6,16α-dimethyl-Δ⁵-pregnene-3β,7α-diol-20-one* (XIIa). A solution of XIIa (0.5 g., m.p. 183–185°, [α]D −48.1°) in acetone (60 cc.) was oxidized over a period of 3 min. by titration with 8 *N* chromic acid in 8 *N* sulfuric acid[8] at 0 to 5°. Isolation by addition of water and extraction with ethyl acetate furnished a crystalline crude product which was purified by chromatography on neutral alumina. By elution with benzene, crystals with m.p. 218–250° (200 mg.) were obtained. Further purification by crystallization from acetone-ether provided an analytical sample as fine needles with m.p. 248–250°, [α]D +45.8°, ν_{max} 3600, 1720, 1700 cm.$^{-1}$, and without characteristic ultraviolet absorption. This compound showed an infrared spectrum completely identical to that presented by the product isolated in the preceding experiment (a) and its melting point was not depressed on admixture of such a specimen.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.61; H, 9.27; O, 17.35.

Elution with ether and crystallization from acetone–ether gave needles (80 mg.) of *6β,16α-dimethyl-Δ⁴-pregnene-6α,7β-diol-3,20-dione* (XVI) with m.p. 250–252°, [α]D +111.8° (dioxane), λ_{max} 244, log ε 4.11, ν_{max} 3600, 3320, 1700, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.67; H, 8.81; O, 17.39.

6α,7α-Oxido-6β,16α-dimethylpregnane-3β,5α-diol-20-one (XVIIa). 6,16β-Dimethyl-Δ⁶-pregnene-3β,5α-diol-20-one 3-acetate (XIb) (350 mg., m.p. 180–181°) dissolved in acetone (150 cc.) was oxidized at 5° by titration with 8 *N* chromic acid in 8 *N* sulfuric acid.[8] The oxidation product was isolated after 4 min. by addition of water and extraction with ethyl acetate. The crude material (270 mg.) had m.p. 175–178°, raised by two crystallizations from acetone-ether to 220–222° (150 mg.). An analytical sample of the *3-monoacetate* XVIIb prepared by further recrystallization had m.p. 230–232°, [α]D +23.8° (dioxane), ν_{max} 3650, 1720, 1690, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.84; H, 9.09; O, 19.09.

The saponification of the acetate XVIIb (100 mg.) was carried out by heating under reflux for 1 hr. with a 1% methanolic potassium hydroxide solution (40 cc.). Neutralization with acetic acid, addition of water and extraction with ethyl acetate gave a crude crystalline material with m.p. 200–205°, raised to 233–237° (60 mg.) by two crystallizations from acetone-ether. Recrystallization from the same provided an analytical sample of the *oxidodiol* XVIIa with m.p. 248–250°, [α]D +27° (dioxane), ν_{max} 3500, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.29; H, 9.57; O, 17.03.

A solution of 6α,7α-oxido-6,16α-dimethylpregnane-3β,-5α-diol-20-one (XVIIa) (50 mg.) dissolved in acetone (30 cc.) was treated for 3 min. at 0 to 5° with 8 *N* chromic acid in 8 *N* sulfuric acid.[8] The reagent was added dropwise until a yellow color persisted in the acetone solution. The mixture was then poured into water and the product extracted with ethyl acetate. Evaporation of the extract gave a crystalline residue (43 mg.) with m.p. 174–175°. Purification by chromatography on neutral alumina (15 g.) afforded, by elution with benzene-ether (19:1), needles (32 mg.) with m.p. 253–255°. The analytical sample exhibited m.p. 256–257°, [α]D +61° (dioxane), no selective high ultraviolet absorption, ν_{max} 3640, 1730, 1700 cm.$^{-1}$. This compound was found to be identical by infrared and mixture melting point comparisons, with that obtained by oxidation of XIa and XIIa as described above.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.44; H, 8.97; O, 17.95.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Preparation of Some Steroidal Enamines[1]

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Received September 8, 1961

The preparation of some α-(aminomethylene)keto steroids is described. Observed ultraviolet spectral and optical rotatory relationships are discussed.

The discovery that steroidal [3,2-*c*]pyrazoles are effective anabolic agents while exhibiting minimal androgenic side effects[2] prompted us to prepare another series of nitrogen-containing steroids, some α-aminomethylene derivatives of keto steroids.

J. Meier[3] has reported 2-(1-pyrrolidylmethylene)testosterone as a crude intermediate in the preparation of 2-(1-pyrrolidylmethyl)testosterone.

(1) Steroidal Heterocycles. V. For preceding paper, see R. O. Clinton, R. L. Clarke, F. W. Stonner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. & Ind.*, (London), 2099 (1961).

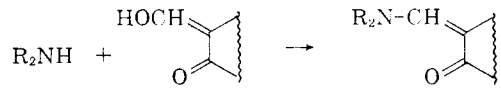
(2) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959). (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*; **83**, 1478 (1961).

(3) J. Meier, *Chimia*, **13**, 65 (1959).

deStevens and Halamandaris[4] have made 17β-hydroxy-2-(1-pyrrolidylmethylene)-5α-androstan-3-one. Ketcheson and Taurins[5] have described five 16-aminomethylene derivatives of 3β-hydroxy-androst-5-en-17-one. Finally a communication from the Syntex group reports three such derivatives of 17β-hydroxy-17α-methyl-5α-androstan-3-one.[6] Of the three, the 2-diethylaminomethylene and the 2-(*N*,*N*-diethylaminoethylaminomethylene) derivatives were described as potent anabolic agents.

Birch and Robinson[7] used *N*-methylanilinomethylene derivatives of ketones to block certain methylene groups in polycyclic systems.

The compounds presently reported may be divided into three categories all of which were prepared by the reaction of an α-hydroxymethylene-ketone with an amine.



The first group, described in Table I, consists of enamine derivatives of saturated (No. 9 and 10 excepted) 2-hydroxymethylene-3- keto steroids. A/B-*cis* as well as A/B-*trans* ring fusions are to be found. Preparation of the novel 2-aminomethylene-A/B-cis-3-keto steroids was possible as a result of the observation that A/B-*cis*-3-keto steroids are formylated at C-2.[8] The compounds described in this table are relatively stable under neutral conditions but dissolve in aqueous formic, methanesulfonic, or hydrochloric acids with immediate decomposition and precipitation of the parent hydroxymethylene compound.

Conjugation in the structures under discussion produces ultraviolet absorption at 332–334 mμ with ε values from 14,100 to 23,300.[9] The presence of a Δ^5-bond in compounds 9 and 10 results in absorption at 328 mμ. Compound 11, a pyrrolidine derivative, is exceptional with its maximum at 339 mμ. This bathochromic shift may be due to relief of internal hydrogen repulsions in the pyrrolidine (but not piperidine) ring by orbital overlap of the nitrogen's electron pair with the double bond system.[10] A similar shift is noted for the pyrrolidine derivatives at C-16 as described below.

The second group, described in Table II, consists of enamine derivatives of 2-hydroxymethylene-Δ^4-3-keto steroids; one of these, No. 5, contains a Δ^6-bond and another, No. 8, contains a 17β-CH(OH)CH_3 group. The ultraviolet spectra of these compounds show two maxima, the first at 248–250 mμ (ε range of 14,600–17,600) and the second at 366–373 mμ (ε range of 10,400–15,300). The ε value for the lower wave-length peak is always greater than that for the higher wave-length peak. The ultraviolet spectrum of compound No. 4 with its unsubstituted amino group is different, showing maxima at 245 and 352 mμ. Compound No. 5 has a $\Delta^{4,6}$ structure and shows three absorption peaks.

The third group, described in Table III, consists of enamine derivatives of 16-hydroxymethylene 17-ketones. Compound 4 contains a Δ^5-bond, Ultraviolet absorption maxima exhibited by these compounds seem to be related to the nature of the amino group. Thus, the pyrrolidine derivatives, Nos. 3, 4, and 5, absorb at 328 mμ whereas the dimethylamine derivative absorbs at 319 mμ and the primary amine derivatives, Nos. 2, 8, and 9, absorb at 314–318 mμ. If the bathochromic shift found in the pyrrolidines is related to relief of hydrogen repulsions in a five-membered ring as described above, the unstrained piperidine compound should absorb at a position corresponding to that of the dimethylamino compound; it does, at 320 mμ. The hexamethyleneimine derivative, N. 7, would likewise be expected to absorb at 320 mμ but it absorbs at 324 mμ.

One bisenamine was prepared. Formylation of androst-4-ene-3,17-dione produced 2,16-bis(hydroxymethylene)androst-4-ene-3,17-dione which was treated with pyrrolidine to give 2,16-bis(1-pyrrolidylmethylene)androst-4-ene-3,17-dione.

There is evidence that the hydroxymethylene precursors to the enamines form amine salts prior to reaction to form the enamines. Thus, if 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one is added to an excess of diethylamine and the excess amine is evaporated, a solid residue remains which is water-soluble, possesses infrared bands at 3.75, 4.05, and 4.18 μ ascribable to a salt form,[11] shows $\lambda_{max}^{C_2H_5OH}$ 314 mμ (ε 12,700) and is decomposed in water solution by carbon dioxide with precipitation of the hydroxymethylene compound. The $[\alpha]^{25}D$ value for this salt in chloroform solution drops from +16.6° to −13.5° in a twenty-four hour period. An ultraviolet absorption of $\lambda_{max}^{C_2H_5OH}$

(4) G. deStevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1614 (1961).

(5) B. G. Ketcheson and A. Taurins, *Can. J. Chem.*, **38**, 972 (1960).

(6) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magnana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. & Ind.*, (London), 1625 (1960).

(7) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

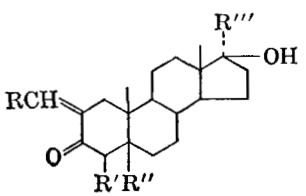
(8) See ref. of footnote 1. Formylation at C-2 rather than C-4 is in accord with other examples of steric control of Claisen type reactions. *Cf.*, G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957).

(9) Infrared spectra of α-aminomethylene ketones are described by J. Weinstein and G. M. Wyman, *J. Org. Chem.*, **23**, 1618 (1958), and by N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949). N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959), discuss the infrared and ultraviolet spectra of salts of these compounds.

(10) *Cf.*, M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1961).

(11) *Cf.*, L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," J. Wiley and Sons, New York, 1959, pp. 259–260.

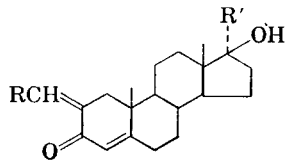
TABLE I



	R	R′	R″	R‴	M.P.°	$[\alpha]^{25}D$°	$\lambda_{max}^{C_2H_5OH}$ mμ	ε	% Yield	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[a]	$N(C_2H_5)_2$	H_2	βH	H	181.5–188.5[b]	+232.4	333	21,500	28	$C_{24}H_{39}NO_2$	77.18	77.3	10.44	10.7	3.75	3.7
2[ac]	$NCH_3(C_2H_5)$	H_2	βH	H	176–182[d]	+231.8	333	18,600	31	$C_{23}H_{37}NO_2$	76.83	77.0	10.37	10.1	3.90	3.8
3[e]	$N(C_2H_5)_2$	H_2	βH	CH_3	176.5–180[f]	+195.6	333	22,600	43	$C_{25}H_{41}NO_2$	77.46	77.8	10.66	10.6	3.61	3 6
4[e]	$N(n\text{-}C_4H_9)_2$	H_2	βH	CH_3	140.5–143[g]	+145.0	334	23,200	40	$C_{29}H_{49}NO_2$	78.48	78.8	11.13	11.2	3.15	3.2
5[eh]	$N(CH_2C_6H_5)_2$	H_2	βH	CH_3	157–161.5[b]	+48.1	332	21,900	26	$C_{35}H_{45}NO_2$	82.15	82.5	8.87	8.9	2.74	2.7
6[ei]	$N(CH_2)_5$	H_2	βH	CH_3	190–198[f]	+236.3	334	21,900	62	$C_{26}H_{41}NO_2$	78.18	78.2	10.34	10.3	3.50	3.4
7[e]	$N(CH_2)_2CHCH_2$ (NHCOCH₃)	H_2	βH	CH_3	140–147[b]	+143.0	334	17,600	23	$C_{28}H_{44}N_2O_3$	73.66	73.4	9.64	9.4	6.13	5.9
8[j]	$N(CH_3)_2$	$(CH_3)_2$	αH	H	238–242[k]	−189.9	333	15,300	57	$C_{24}H_{39}NO_2$	77.16	77.5	10.52	10.4	3.75	3.5
9[l]	$N(CH_3)_2$	$(CH_3)_2$	Δ⁵	H	197.5–217.5[k]	−222.0	328	18,400	28	$C_{24}H_{37}NO_2$	77.58	77.7	10.04	9.9	3.77	3.7
10[mn]	$N(CH_3)_2$	$(CH_3)_2$	Δ⁵	CH_3	212–214[k]	−233.5	328	18,800	41	$C_{25}H_{39}NO_2$	77.87	77.9	10.20	10.0	3.63	3.6
11[o]	$N(CH_2)_4$	H_2	αH	CH_3	224–231.5[p]	−109.6	339	23,400	67	$C_{25}H_{39}NO_2$	77.87	78.0	10.20	9.9	3.63	3.6
12[n,o,q]	$N(CH_2)_5$	H_2	αH	CH_3	232–239[e]	−266.8	333	21,100	41	$C_{26}H_{41}NO_2$	78.14	78.0	10.34	10.1	3.51	3.4
13[oh]	$N(CH_2)_6$	H_2	αH	CH_3	219–222.5[r]	−205.0	334	23,300	57	$C_{27}H_{43}NO_2$	78.40	78.7	10.48	10.4	3.39	3.4

[a] Prepared from 17β-hydroxy-2-hydroxymethylene-5β-androstan-3-one, ref. 6. [b] From ether. [c] The required quantity of amine hydrochloride was added to the benzene solvent along with 10% excess of sodium methoxide and 1 equiv. of methanol. The mixture was stirred for one hour and the general preparative procedure followed thereafter. [d] From acetonitrile. [e] Prepared from 17β-hydroxy-2-hydroxymethylene-17α-methyl-5β-androstan-3-one, R. O. Clinton, R. L. Clarke, F. W. Stonner, D. K. Phillips, K. F. Jennings, and A. J. Manson, to be published. [f] From acetone. [g] From ether–pentane. [h] Reaction mixture was refluxed for six hours. [i] To effect crystallization, the residual oil from the general procedure was dissolved in ether and the solution was diluted with pentane. [j] Prepared from 4,4-dimethyl-17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one, ref. 2b. [k] From methanol–ethyl acetate. [l] Prepared from 4,4-dimethyl-17β-hydroxy-2-hydroxymethyleneandrost-5-en-3-one, ref. 2b. [m] Prepared from 17β-hydroxy-2-hydroxymethylene-4,4,17α-trimethylandrost-5-en-3-one, ref. 2b. [n] Reaction mixture was refluxed for four hours. [o] Prepared from 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one, H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959). [p] From ethyl acetate. [q] The preparation of the compound resulted from refluxing a mixture of 1.8 g. (5.4 mmoles) of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one, 25 ml. of acetone, 1.7 g. (20 mmoles) of piperidine, and 1.2 g. (20 mmoles) of acetic acid for seventy-two hours in an attempt to prepare a benzo steroid. The mixture was cooled and the enamine collected by filtration. [r] Reported,[s] m.p. 219–221°, $[\alpha]D$ −256°. [s] From ethanol. [t] From methanol, ethyl acetate, then methanol–ether.

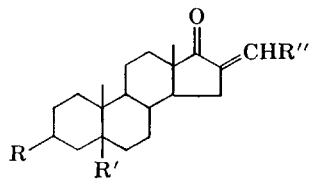
TABLE II



	R	R′	M.P.°	$[\alpha]^{25}D$°	$\lambda_{max}^{C_2H_5OH}$ mμ	ε	% Yield	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[a]	$N(CH_3)_2$	H	233.5–239 dec.[b]	−170.8	248 367	17,200 13,900	77	$C_{22}H_{33}NO_2$	76.92	76.9	9.68	9.9	4.08	3.9
2[a,c]	$N(C_2H_5)_2$	H	192.5–197[d]	−172.9	248 367	17,600 14,500	60	$C_{24}H_{37}>O_2$	77.58	77.9	10.04	9.7	8.61[e]	9.0[e]
3[a,f,g]	$\overline{N(CH_2)_4}$	H	214–225.5[h]	−50.8[i]	250 372	17,600 15,300	61	$C_{24}H_{35}NO_2$	78.00	77.9	9.55	9.5	3.79	3.7
4[j]	NH_2	CH_3	277.5–279	−77.3[k]	245 352	14,600 10,400	6	$C_{21}H_{31}NO_2$	76.55	76.6	9.48	9.1	9.71[e]	9.4[e]
5[l]	$N(CH_3)_2$	CH_3	258–263 dec.[d]	−396.9	271 292 394	15,700 19,900 12,600	22	$C_{23}H_{33}NO_2$	77.70	78.0	9.36	9.6	3.94	3.8
6[m,n]	$N(CH_2)_2N(C_2H_5)_2$	CH_3	181.5–184.5[o]	−101.5	248 366	16,300 14,700	31	$C_{27}H_{44}N_2O_2$	75.65	75.9	10.35	10.1	6.54	6.5
7[m,p]	$\overline{N(CH_2)_4CH(CH_3)}$	CH_3	199.5–214[d]	−322.9	248 373	17,400 15,200	15	$C_{27}H_{41}NO_2$	78.78	78.6	10.04	9.8	3.40	3.4
8[q,r]		H	210–213[d]	0.0	249 368	16,900 13,900	62	$C_{24}H_{37}NO_2$	77.58	77.4	10.08	10.0	3.78	3.7

[a] Prepared from 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one, F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954). [b] From methanol, then acetone. [c] The residual oil from the reaction was dissolved in a minimum quantity of methanol and the solution was allowed to stand to effect crystallization. [d] From acetone. [e] Oxygen analysis. [f] See ref. 3. [g] The residual oil from the reaction was dissolved in benzene and the solution was washed with dilute potassium hydroxide, then concentrated to a residue. This residue was chromatographed on basic alumina, the column being eluted with benzene, ether and finally with ether containing 1% methanol. The yellow crystals so obtained were recrystallized. [h] From acetone, then acetone–methanol. In an evacuated, sealed, Pyrex tube this material melted at 230–231.5°. [i] At 23°. [j] See Experimental section for special procedure. [k] In ethanol. [l] Contains Δ^6-bond. Experimental section contains a description of the precursor. [m] Prepared from 17β-hydroxy-2-hydroxymethylene-17α-methylandrost-4-en-3-one, ref. 1a. [n] The residual oil from the reaction was triturated with ethyl acetate and the solid so obtained was recrystallized twice from ethyl acetate, once from ethanol–ether and was chromatographed on basic alumina. Elution of the column with benzene, ether, and ether containing 1% methanol afforded the product. [o] From acetone, ether–methanol, then acetone. [p] The reaction time was six hours and the residual oil was chromatographed on basic alumina, the column being eluted with benzene and then benzene–ether to remove the product. [q] Prepared from 20-hydroxy-2-hydroxymethylenepregn-4-en-3-one, F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959). [r] Compound has a 17β-$CH(OH)CH_3$ group in place of the 17β-OH.

TABLE III



	R	R'	R''	M.P.°	$[\alpha]^{25}D°$	$\lambda_{max}^{C_2H_5OH}$ $m\mu$	ϵ	% Yield	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[a]	β-OH	α-H	$N(CH_3)_2$	275.5–283[b]	+53.0[c]	319	16,800	67	$C_{22}H_{35}NO_2$	76.47	76.3	10.21	10.1	4.05	4.0
2[a]	β-OH	α-H	$NH(CH_2)_2N(C_2H_5)_2$	173–177[d]	−40.6	315	24,900	34	$C_{26}H_{44}N_2O_2$	74.95	75.3	10.65	10.5	6.72	6.6
3[e,f]	α-OH	β-H	$N(CH_2)_4$	240–244 dec.[g]	+17.5	328	28,700	46	$C_{24}H_{35}NO_3$	74.76	75.0	9.15	9.1	3.63	3.6
4[h]	β-OH	Δ^5	$N(CH_2)_4$	254.5–259 dec.[i]	−105.9	328	28,300	95	$C_{24}H_{35}NO_2$	78.00	77.8	9.55	9.4	3.79	3.8
5[a]	β-OH	α-H	$N(CH_2)_4$	206.5–209.5[j]	−36.7	328	28,550	97	$C_{24}H_{37}NO_2$	77.57	77.4	10.04	9.7	3.77	3.7
6[a]	β-OH	α-H	$N(CH_2)_5$	199.5–202.5[k]	+63.4	320	25,700	98	$C_{25}H_{39}NO_2$	77.86	77.9	10.20	10.1	3.63	3.6
7[e,f]	α-OH	β-H	$N(CH_2)_6$	193–195[l]	+78.6	324	29,200	63	$C_{26}H_{39}NO_3$	75.50	75.8	9.51	9.8	3.39	3.2
8[a,m]	β-OH	α-H	$NHCH(CH_2)_5$	126.4-indet.[n]	−38.3[c]	318	25,700	—	$C_{28}H_{47}NO_3$[n]	75.46	75.3	10.63	10.5	3.14	3.1
9[a,o]	β-OH	α-H	$NH(CH_2)_2N(CH_2)_2O(CH_2)_2$	185–188[l]	−34.8	314	24,700	27	$C_{26}H_{42}N_2O_3$	72.52	72.6	9.83	10.0	6.51	6.5

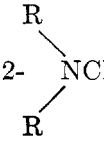
[a] Prepared from 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one, L. Ruzicka, V. Prelog, and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948). [b] From methanol–ethyl acetate, then methanol. [c] At 23°. [d] From methanol, ethyl acetate, and methanol consecutively. [e] Precursor is described in the Experimental. [f] Compound contains a carbonyl group at C-11. [g] From ethyl acetate, then benzene. [h] Prepared from 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one, reference in footnote[a] of this table. [i] From absolute ethanol. [j] From benzene, then ethyl acetate. [k] From benzene, then ethyl acetate–ether. [l] From ethyl acetate. [m] The reaction mixture was refluxed only ten minutes and the residual oil resulting from the usual isolation procedure was dissolved in benzene and chromatographed on basic alumina using benzene, benzene–ether, and finally ether as eluents. The product was recrystallized from ether–pentane, methanol, twice from ethyl acetate ether, and twice from ethanol. [n] Formed a monoethanolate. [o] The oily product was chromatographed on basic alumina using benzene, benzene–ether, ether, and ether–1% methanol as eluents.

TABLE IV

MOLECULAR ROTATORY RELATIONSHIPS

	3-Keto steroid	2-HOCH= [M]D	2-RCH= R	[M]D	Δ[M]D
1	17β-Hydroxy-17α-methyl-5α-androstan-3-one	+126		−425°	−551
				−1067	−1193
				−849	−975
2	17β-Hydroxy-5β-androstan-3-one	+86	$(C_2H_5)_2N-$	+868	+782
3	17β-Hydroxy-17α-methyl-5β-androstan-3-one	+1		+945	+944
4	17β-Hydroxyandrost-4-en-3-one	+164	$(CH_3)_2N-$	−587	−751
5	17β-Hydroxy-17α-methylandrosta-4,6-dien-3-one	−684	$(CH_3)_2N-$	−1409	−725

315 mμ (ε ~ 17,300) has been reported for 2-hydroxymethylene-5α-androstan-3-ones in 0.01 *N* sodium hydroxide solution.[2b]

Introduction of the aminomethylene group at C-2 has produced some unexpected and dramatic optical rotatory effects. Table IV shows the molecular rotations of a representative group of the enamines reported, the rotations of the corresponding hydroxymethylene precursors and the Δ[M]D which accompanies replacement of 2-HOCH= by 2-  NCH=. In the A/B-*trans* series, formation of the enamine is accompanied by a strong levorotatory shift (keto steroid 1) whereas in the A/B-*cis* series this change produces a strong dextrorotatory shift (keto steroids 2 and 3). The presence of double bonds at 4 or 4,6 produces a change analogous to that found in the A/B-*trans* system (keto steroids 4 and 5). There was no evident pattern in the rotational changes which occurred when 16-hydroxymethylene-17-keto steroids were converted to corresponding enamines.

The experimental section contains a general procedure (Method A) for preparing enamines using dimethylamine and a general procedure (Method B) used for the remainder of the enamines, with the exception of the ammonia derivative in Table II, which is described separately. Variations from these methods are given in footnotes to the tables. The precursors of the enamines, where known, are recorded in the footnotes to the tables.

Some of the compounds reported here showed mild anabolic activity (subcutaneous route) while others showed a hypotensive action (oral administration). Compound I of Table I was the most active of the hypotensive agents.

EXPERIMENTAL[12]

Method A (for use with dimethylamine). The hydroxymethylene steroid (0.01 mole) was dissolved in 100 ml. of benzene, 10% of the solvent was distilled to dry the solution, and gaseous dimethylamine was added at room temperature until the weight gain corresponded to 0.1 mole. This solution was allowed to stand for 30 min., was heated under reflux for an hour, and concentrated to a residue by warming *in vacuo*. The crystalline residue was recrystallized from the solvent indicated in the tables.

Method B (a general procedure). A mixture of 0.01 mole of the hydroxymethylene steroid, 3 to 6 equivalents of the requisite amine, and 50 ml. of benzene was heated under reflux for 2 hr. with a water separator attached to the system. The solvent was then removed by warming *in vacuo* and the residual oil triturated with ether to obtain a crystalline product.

2-Aminomethylene-17β-hydroxy-17α-methylandrost-4-en-3-one. A solution of 9.4 g. of 17β-hydroxy-2-hydroxymethylene-17α-methylandrost-4-en-3-one[2a] in 500 ml. of benzene was treated with gaseous ammonia for 2 hr. and then left standing at room temperature for 24 hr. The solvent was removed by warming *in vacuo*, and the residual oil was triturated with ethyl acetate to give 2.9 g. of solid. The ethyl acetate washing was concentrated and cooled to give 2.4 g. more solid. Recrystallization of the combined solids from methanol–ethyl acetate gave 1.66 g. of yellow crystals, m.p. 238–249°. Consecutive recrystallizations from methanol–benzene, benzene–ether, and from methanol three times afforded 0.52 g. of yellow crystals described as compound No. 4 of Table II.

17β-Hydroxy-2-hydroxymethylene-17α-methylandrosta-4,6-dien-3-one. A solution of 47 g. (0.156 mole) of 17β-hydroxy-

(12) All melting points are corrected and all rotations are in chloroform unless otherwise noted. We are grateful to Dr. F. C. Nachod and staff for the spectral and optical rotational data, to Mr. K. D. Fleischer and staff for the analytical data, and to Drs. A. L. Beyler and G. O. Potts for the biological data.

17α-methylandrosta-4,6-dien-3-one[2a,13] in 1.1 l. of benzene was boiled down to a 1-l. volume to remove traces of water and was cooled to 25°. Sodium methoxide, 23 g. (0.426 mole), was added with stirring, the system was flushed with nitrogen and 33 ml. (0.40 mole) of ethyl formate was added. The mixture was stirred for 65 hr. at room temperature, filtered, and the filter cake washed with benzene and then with ether. The solid sodium enolate was suspended in water and treated with excess 6 *N* hydrochloric acid. After being stirred 1 hr. the mixture was filtered and the collected solid was air-dried overnight. After an additional 24-hr. drying period over phosphorus pentoxide the fine, powdery solid (52.5 g., 102% yield) melted at 148–154° and apparently contained residual moisture. This material was satisfactory for conversion to pyrazoles[2a] and enamines.

A 10-g. sample (0.03 mole) of the crude product was dissolved in a minimum of methanol, 2.4 g. (0.06 mole) of sodium hydroxide dissolved in a minimum of methanol was added, and the solution was diluted with 1-l. of water. This solution was extracted with benzene and with ether, filtered through a "Celite" bed, acidified with 6 *N* hydrochloric acid, and filtered. The collected product was similarly treated a second time and dried to constant weight *in vacuo* at 64°. It softened to an oil at 85–90° and showed $\lambda_{max}^{C_2H_5OH}$ 291 mμ (ε 16,800), 327 mμ (ε 8,100); $[\alpha]^{25}D$ −208.5° (1% in chloroform). Its analytical values indicated the presence of impurities.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14.61. Found: C, 75.1; H, 8.0; O, 16.8.

3α-Hydroxy-16-hydroxymethylene-5β-androstane-11,17-dione 3-acetate. Sodium methoxide was prepared by dissolving 6.9 g. (0.3 g.-atom) of sodium in 175 ml. of methanol in a 500 ml. three neck flask, distilling the methanol and drying the residue for 1 hr. at 165° (15 mm.). A mixture of 10.4 g. (0.03 mole) of 3α-hydroxy-5β-androstane-11,17-dione acetate, 300 ml. of dry benzene, and 32 ml. (0.4 mole) of dry ethyl formate was added, the flask was flushed with nitrogen, and the mixture was stirred for 1 hr. at room temperature, then allowed to stand overnight. A gas was slowly evolved. The mixture was poured into 500 ml. of water, the layers were separated, the benzene layer was washed with water and the combined water layer and water, washings were washed with benzene. The water layer was filtered, acidified with diluted hydrochloric acid, and the precipitated product was collected, washed with water and dried at 70°; 9.8 g., 98% yield crude, m.p. 238–243° dec. (uncorr.).

The crude product was dissolved in 100 ml. of acetic acid, and the solution was diluted with 150 ml. of water, treated with Darco G-60, and filtered while hot, diluted to a 1-l. volume with water, and the precipitated gum allowed to crystallize. The solid was dissolved in dilute sodium hydroxide and the solution was filtered. The product was reprecipitated with dilute hydrochloric acid, collected, washed well with water, air-dried, and dissolved in 200 ml. of hot 95% ethanol. Addition of sufficient water to produce turbidity, then cooling gave a crystalline product which was collected and dried at 110° *in vacuo* for 8 hr. The 7.53 g. of the title compound melted at 244–246°, $[\alpha]^{28.5}D$ +50° (1% in acetic acid).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.3; H, 8.7.

2,16-Bis(hydroxymethylene)androst-4-ene-3,17-dione. This compound was prepared from 26.0 g. (0.094 mole) of androst-4-ene-3,17-dione, 51 g. of sodium methoxide, and 109 ml. of ethyl formate in 900 ml. of benzene in the manner described immediately above. The gummy product, initially precipitated by hydrochloric acid, was collected and dissolved in hot methanol; the solution was treated with Darco G-60, concentrated, and cooled to give 20.8 g. of light yellow solid. Concentration of the filtrate afforded a second crop of 3.3 g. (83% crude yield).

Treatment of a methanolic solution of the crude product with Darco G-60 a second time did not remove the color from this solution, but, instead, caused it to become darker. It was diluted with hot water to produce turbidity, filtered, diluted to produce further turbidity, filtered, etc., until the filtrate was light yellow in color. The solution was cooled and the tan crystals collected. Three recrystallizations of the solid from ethyl acetate gave a tan product, m.p. 198–205° dec., $[\alpha]^{25}D$ +35.1° (1% in chloroform).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66; O, 18.68. Found: C, 73.5; H, 7.5; O, 19.1.

2,16-Bis(1-pyrrolidylmethylene)androst-4-ene-3,17-dione. This compound was prepared from 2,16-bis(hydroxymethylene)androst-4-ene-3,17-dione and pyrrolidine by Method B. The solid was recrystallized from ethyl acetate–methanol to give 3.6 g. (69% yield) of yellow crystals, m.p. 256–263°, $[\alpha]^{25}D$ −245.3°, $\lambda_{max}^{C_2H_5OH}$ 249 mμ (ε 18,200), 331 mμ (ε 32,900), 373 mμ (ε 16,300).

Anal. Calcd. for $C_{29}H_{40}N_2O_2$: C, 77.63; H, 8.99; N, 6.25. Found: C, 77.5; H, 9.2; N, 6.2.

Diethylamine salt of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one. 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (5 g.) was mixed with 15 ml. of diethylamine; the mixture became warm. The excess diethylamine was boiled off by brief warming. The solid residue was heated to boiling with 260 ml. of acetone, 0.2 g. of insoluble material was removed by filtration and the filtrate was cooled to give 1.7 g. of pale yellow title compound, m.p. 114.5–116.5° dec., $[\alpha]^{25}D$ +16.6° (1% in chloroform) (value dropped to −13.5° after 24 hr. in solution), $\lambda_{max}^{C_2H_5OH}$ 314 mμ (ε 12,700), λ_{max}^{KBr} 3.75, 4.05, and 4.18 μ.

Anal. Calcd. for $C_{25}H_{43}NO_3$: C, 74.02; H, 10.69; N, 3.42. Found: C, 74.2; H, 10.9; N, 3.2.

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(13) J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959).