chloro ketone **4a**, m.p. 91–92°, $[\alpha]^{25}D$ 0° (*c* 0.200, ethanol), $\nu_{max}^{CCl_4}$ 1748 (C=O stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}ClO$: C, 76.71; H, 10.65; Cl, 8.71. Found: C, 76.51; H, 10.51; Cl, 8.40.

3β-Bromo-6-norcholestan-7-one (4b).—To a solution of 100 mg. of 3,5-cyclo-6-norcholestan-7-one (**3**) in 10 ml. of acetic acid was added 1 ml. of 48% aqueous hydrobromic acid. After standing overnight, the separated crystalline material was collected by filtration. Crystallization under refrigeration from a small volume of methanol was slow (2 weeks), and an additional crystallization gave 65 mg. of pure bromo ketone **4b**, m.p. 84–85°, $[\alpha]^{25}D$ −5.3° (*c* 1.00, ethanol), $\nu_{max}^{CCl_4}$ 1745 (C=O stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}BrO$: C, 69.16; H, 9.60; Br, 17.70. Found: C, 69.20; H, 9.40; Br, 17.34.

Acknowledgment.—The authors are grateful to Miss Paula M. Parisius, Microanalytical Laboratory (under the direction of Dr. W. C. Alford), National Institutes of Health, Bethesda, Maryland, for the elemental analyses.

Some Steroid Ternary Iminium Salts and Their Conversion to 17β-(N-Pyrrolidinyl) Steroids

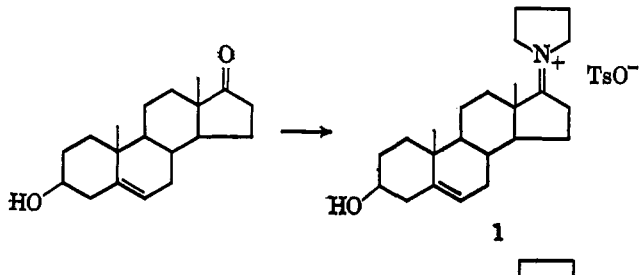
RICHARD M. SCRIBNER

Contribution No. 1085 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

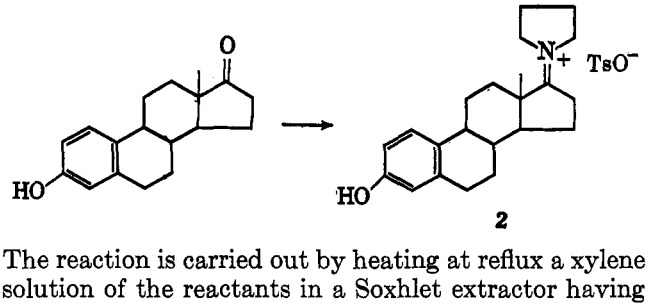
Received April 1, 1965

The enamines of 17-keto steroids, with few exceptions, are notoriously difficult to prepare.[1] By using the high-boiling amine, 4-methylpiperidine, Goldkamp[2] was able to convert several 17-keto steroids to the corresponding enamines, but even under forcing conditions yields were low.

We have found that 17-keto steroids react smoothly with pyrrolidine in the presence of a molar equivalent of *p*-toluenesulfonic acid to afford ternary iminium salts, *i.e.*, protonated enamines,[3] in better than 95% yield.



1

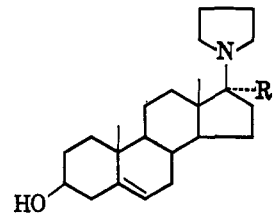


2

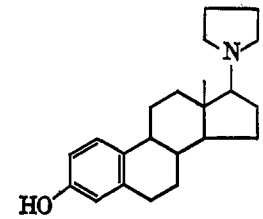
The reaction is carried out by heating at reflux a xylene solution of the reactants in a Soxhlet extractor having calcium carbide in the thimble as a dehydrating agent. After about 10 hr. the insoluble steroid salt is isolated simply by filtration.

The reaction is probably general for most 17-keto steroids,[4] but efforts to extend it to other heterocyclic nitrogen compounds, such as 4-methylpiperidine,[5] N-methylpiperazine, morpholine, hexamethyleneimine, 4-chloropyrazole, and imidazole, have been unsuccessful.

Ternary iminium salts are known to undergo rapid attack by a wide variety of nucleophilic agents.[6] N-(3β-hydroxyandrost-5-en-17-ylidene)pyrrolidinium *p*-toluenesulfonate (**1**), when suspended in ether and treated with lithium aluminum hydride, gives the corresponding 17β-(N-pyrrolidinyl) steroid **3a** in high yield (Table I).[7] Similarly, reduction of an ethereal suspension of the ternary iminium derivative **2** of estrone gives 3-hydroxy-17β-(N-pyrrolidinyl)estra-1,3,5(10)-triene (**4**).



3a, R=H
b, R=CH_3
c, R=C≡N
d, R=C≡CH



4

Methylmagnesium bromide in ether reacts smoothly with **1** to give the 17α-methyl steroid **3b**. Sodium cyanide in acetonitrile reacts to give the 17α-cyano steroid **3c**. Lithium acetylide etyhlenediamine complex or ethynylmagnesium bromide in ether react with **1** to afford the 17α-ethynyl steroid **3d** in low yields, but action of ethynylmagnesium bromide on the nitrile **3c** in tetrahydrofuran gives **3d** in excellent yield. These reactions are analogous to those observed by Lednicer and Babcock[8] for their steroid 17-N,N-dimethyliminium salts.

Oxidation of the 17β-pyrrolidinyl-5-androsten-3β-ols (**3**) to the corresponding Δ^4-3 ketones (**5**) is readily accomplished with cyclohexanone under Oppenauer conditions.

Treatment of 5α-androstane-3,17-dione with excess pyrrolidine and *p*-toluenesulfonic acid under the conditions described earlier for the preparation of **1**, followed by reduction of the crude product with lithium aluminum hydride in ether, gives 3β,17β-bis(N-pyrrolidinyl)-5α-androstane (**6**).[7]

(1) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918, 5927 (1953); J. L. Johnson and M. E. Herr, *ibid.*, **78**, 430 (1956).

(2) A. Goldkamp, *J. Med. Pharm. Chem.*, **5**, 1176 (1962).

(3) G. Opitz and A. Griesinger, *Ann.*, **665**, 101 (1963).

(4) Shortly after the completion of this work, N. J. Leonard and J. V. Paukstelis [*J. Org. Chem.*, **28**, 3021 (1963)] reported the direct synthesis of ternary iminium salts by reaction of nonsteroidal ketones or aldehydes with the perchloric acid salts of secondary amines, especially pyrrolidine.

(5) The failure of 4-methylpiperidine to afford even a detectable amount of steroid ternary iminium salt under our forcing conditions, in contrast to the success of Goldkamp in preparing enamines with this amine,[2] suggests that the steroid iminium salts are formed directly (as reported in ref. 4) rather than by preliminary formation of enamine followed by protonation.[3]

(6) For example, see N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956); G. Opitz, A. Griesinger, and H. W. Schubert, *Ann.*, **665**, 91 (1963).

(7) M. Davis [U. S. Patent 3,169,093 (1965)] has recently described the preparation of a number of 17β-(N-pyrrolidinyl) steroids, including the compounds designated above as **3a** and **6**, by heating steroid ketones with pyrrolidine and formic acid at about 170°.

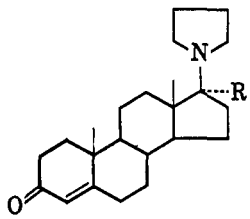
(8) D. Lednicer and J. C. Babcock, *J. Org. Chem.*, **27**, 2541 (1962); D. Lednicer, U. S. Patent 3,107,254 (1963).

TABLE I

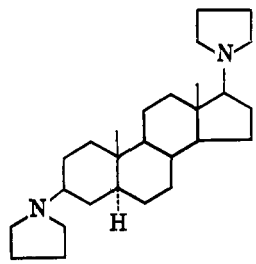
PYRROLIDINYL STEROIDS

Steroid	Yield, %	M.p., °C.	$[\alpha]^{23}D$, deg.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
3β-Hydroxy-17β-(N-pyrrolidinyl)-5-androstene (**3a**)	93	199.5–201.0[a]	−58[b]	80.41	80.61	10.86	10.97	4.08	4.21
3-Hydroxy-17β-(N-pyrrolidinyl)estra-1,3,5(10)-triene (**4**)	40[c]	206.5–209.0[d]	+76[e]	79.26[f]	78.88[f]	9.83[f]	9.68[f]	4.08[f]	4.14[f]
3β-Hydroxy-17α-methyl-17β-(N-pyrrolidinyl)-5-androstene (**3b**)	60	165.5–169.5[g]	−81[b]	80.61	80.91	10.99	11.08	3.92	3.92
3β-Hydroxy-17α-ethynyl-17β-(N-pyrrolidinyl)-5-androstene (**3c**, from **3d**)	80	202.0–203.5[d]	−108[b]	81.69	81.73	10.15	10.29	3.81	3.62
3β-Hydroxy-17α-cyano-17β-(N-pyrrolidinyl)-5-androstene (**3d**)	85	178.0–181.0[a]	...	78.21	78.24	9.85	10.01	7.60	7.39
17β-(N-Pyrrolidinyl)-4-androsten-3-one (**5a**)	60	139.0–140.0[h]	+99[b]	80.88	80.52	10.33	10.13	4.10	4.01
17α-Methyl-17β-(N-pyrrolidinyl)-4-androsten-3-one (**5b**)	46[c]	168.1–169.0[h]	+70[b]	81.07	80.85	10.49	10.64	3.94	3.75
17α-Ethynyl-17β-(N-pyrrolidinyl)-4-androsten-3-one (**5c**)	90	180.5–183.0[i]	+35[b]	82.14	82.17	9.65	9.75	3.83	3.73
3β,17β-Bis(N-pyrrolidinyl)-5α-androstane (**6**)	20[c]	155.0–156.0[i]	+18[b]	81.34	81.76	11.63	11.69	7.03	7.19

[a] Crystallized from benzene–hexane. [b] In chloroform with *c* 1–2. [c] This yield of pure product is based on a single experiment and probably does not represent the maximum yield possible through improved isolation procedures, etc. [d] Crystallized from ethanol. [e] In pyridine, *c* 2.86. [f] Crystallized with 0.5 mole of ethanol. [g] Crystallized from acetone. [h] Crystallized from cyclohexane. [i] Crystallized from hexane. [j] Crystallized from ethanol–water.



5a, R = H
b, R = CH_3
c, R = C≡CH



6

With the exception of the pyrrolidinium salt **1**, which was weakly androgenic and myotrophic, none of these compounds showed steroid sex hormone activity when administered (s.c.) to immature rats. However, the 3β-hydroxy-17β-(N-pyrrolidinyl)-5-androstenes (**3**) were generally toxic at moderate doses, and female rats appeared to be adversely affected at lower doses than male rats. Gaunt and Leatham, *et al.*,[9] have also observed a sex difference in the response of rats to 17-amino-4-androsten-3-one hydrochloride.

Experimental

N-(3β-Hydroxyandrost-5-en-17-ylidene)pyrrolidinium *p*-Toluenesulfonate (**1**).—A solution of 28.9 g. (100 mmoles) of 3β-hydroxyandrost-5-en-17-one, 20.0 g. (105 mmoles) of *p*-toluenesulfonic acid monohydrate, and 15 ml. (12.8 g., 180 mmoles) of pyrrolidine in 700 ml. of xylene was heated at reflux temperature in a Soxhlet extractor having a thimble filled with about 45 g. of 16–20-mesh calcium carbide which had been previously washed with hot xylene. During the fourth hour of the reaction it was necessary to replace the Soxhlet thimble with another containing fresh calcium carbide. After about 10 hr. the reaction mixture was allowed to stand at room temperature for several hours and then was cooled in ice. The crystalline salt was collected by filtration and rinsed thoroughly with ether, giving 49.85 g. (96.7% yield) of almost pure ternary iminium salt. An analytical sample was prepared by recrystallization of 0.5 g. of the salt from 100 ml. of acetonitrile, affording 0.3 g. of colorless, crystalline solid: m.p. 274–275° dec.; ν_{max}^{Nujol} 3350 (OH), 1680 (C=N), 1610, 1645 (C=C), 1210 and 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{44}NSO_4$: C, 69.9; H, 8.62; N, 2.72; S, 6.23. Found: C, 69.9; H, 8.37; N, 2.83; S, 6.34.

N-[3-Hydroxyestra-1,3,5(10)-trien-17-ylidene]pyrrolidinium *p*-Toluenesulfonate (**2**).—Under the conditions of the previous experiment 5.0 g. (18.5 mmoles) of 1,3,5(10)-estratrien-3-ol-17-one, 3.8 g. (20 mmoles) of *p*-toluenesulfonic acid, and 3.0 ml. (36 mmole) of pyrrolidine gave 9.10 g. (99%) of almost pure ternary iminium salt which was analyzed without further purification: ν_{max}^{Nujol} 3150 (OH), 1675 (C=N), 1610, 1570, 1120, 1030, 1010, and 818 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{37}NSO_4$: N, 2.82. Found: N, 2.87.

Reduction of the Ternary Iminium Salts.—To 4.7 g. (124 mmoles) of lithium aluminum hydride in 500 ml. of ether was added 16.0 g. (3 mmoles) of salt **1**, and the mixture was heated at reflux for 3 hr. The cooled reaction mixture was treated cautiously with excess water saturated with sodium sulfate and then filtered. The filter cake was extracted seven times with methylene chloride. Evaporation of the combined organic phases gave 9.92 g. of 3β-hydroxy-17β-(N-pyrrolidinyl)-5-androstene: $\nu_{max}^{CHCl_3}$ 3413 and 1667 cm.$^{-1}$.

A similar procedure was employed for the preparation of 3-hydroxy-17β-(N-pyrrolidinyl)-1,3,5(10)-estratriene from **2** except that the reaction mixture after treatment with water saturated with sodium sulfate was poured into 1 l. of water containing 10% ammonium chloride to neutralize the amphiprotic product. Extraction with methylene chloride gave a troublesome emulsion which could be broken only by slow filtration through sintered glass. Evaporation of the methylene chloride gave the pyrrolidinyl steroid **4** (Table I).

Grignard Reactions.—A solution of ethynylmagnesium bromide in tetrahydrofuran was prepared from 3.65 g. (150 mg.-atoms) of magnesium and 18 g. (165 mmoles) of ethyl iodide in ether followed by an exchange of solvents and introduction of gaseous acetylene at 0° for 1.5 hr. To this was added 9.7 g. (26 mmoles) of 3β-hydroxy-17α-cyano-17β-(N-pyrrolidinyl)-5-androstene (**3d**). The mixture was heated at reflux for 18 hr., concentrated, cooled, and poured into 800 ml. of water. Extraction with ether and introduction of dry HCl into the washed and dried ether solution gave the insoluble amine hydrochloride. The amine hydrochloride was dissolved in methanol and treated with excess aqueous ammonia to give crystalline 3β-hydroxy-17α-ethynyl-17β-(N-pyrrolidinyl)-5-androstene (**3d**): $\nu_{max}^{CHCl_3}$ 3700, 3500, and 3360 cm.$^{-1}$.

A suspension of 24.0 g. (46.8 mmoles) of the pyrrolidinium salt **1** in 550 ml. of ether was mixed with 50 ml. of 3 *M* methylmagnesium bromide and heated at reflux for 2 hr. 3β-Hydroxy-17α-methyl-17β-(N-pyrrolidinyl)-5-androstene (**3b**) was isolated by a procedure analogous to that described in the previous paragraph.

3β-Hydroxy-17α-cyano-17β-pyrrolidinyl-5-androstene.—A mixture of 20 g. (38.9 mmoles) of the pyrrolidinium steroid **1**, 13 g.

(9) R. Gaunt, J. H. Leatham, C. H. Tuthill, N. Antonchak, M. Gilman, and A. A. Renzi, *Endocrinology*, **54**, 272 (1954).

of potassium cyanide, and 300 ml. of anhydrous acetonitrile was heated at reflux temperature for 16 hr., cooled, and poured into 500 ml. of water. The precipitate was collected by filtration and washed thoroughly with water, giving 12.1 g. (85%) of cruce 17α-cyano steroid, m.p. 174–178°, which was chromatographed on neutral, activity grade III alumina: $\nu_{max}^{CHCl_3}$ 2220 cm.$^{-1}$ (no bands in carbonyl region).

17β-(N-Pyrrolidinyl)-4-androsten-3-ones.—The following is a typical procedure used for the preparation of the unsaturated ketones **3a–c**. A solution of 8.0 g. (22.4 mmoles) of 3β-hydroxy-17α-methyl-17β-(N-pyrrolidinyl)-5-androstene (**3b**) in 700 ml. of toluene and 100 ml. of cyclohexanone was distilled until 200 ml. of distillate had been removed and then a solution of 8.0 g. of aluminum isopropoxide in 100 ml. of dry toluene was added quickly (5 minutes or less) to the boiling mixture. The yellow-orange mixture was heated at reflux temperature for 30 min., cooled, and extracted with three 150-ml. portions of 5% sodium hydroxide and then with saturated sodium chloride solution. The toluene solution was evaporated to dryness *in vacuo* and the residue was taken up in ether. Filtration of the ether solution and introduction of gaseous hydrogen chloride into the filtrate gave the insoluble amine hydrochloride, which was separated by filtration, dissolved in methanol, and neutralized with aqueous ammonia. Addition of water and extraction with ether gave on evaporation of the ether extract 6.90 g. of crude ketone which was purified by chromatography on basic, activity grade III alumina. **5a–c** had λ_{max}^{EtOH} 240 mμ (ϵ *ca.* 16,000) and 306 mμ (ϵ *ca.* 85).

3β,17β-Bis(N-pyrrolidinyl)-5α-androstane (**6**).—A solution of 8.64 g. (30 mmoles) of 5α-androstane-3,17-dione, 18.0 ml. of pyrrolidine, and 12.5 g. (66 mmoles) of *p*-toluenesulfonic acid monohydrate in 350 ml. of diethylene glycol dimethyl ether (toluene was not satisfactory) was heated at reflux temperature in a Soxhlet extractor having calcium carbide in the thimble. After 4 hr., the Soxhlet head was replaced by a Vigreux column and 200 ml. of distillate was removed. The residue was cooled in an ice bath, and 125 ml. of ether was added and then 5.7 g. (150 mmoles) of lithium aluminum hydride was added with stirring. After the vigorous reaction had subsided, the reaction mixture was kept at room temperature for 24 hr. Excess water saturated with sodium sulfate was added, and the mixture filtered. The filter cake was washed thoroughly with ether, and the combined organic phases were washed with 5% aqueous sodium hydroxide, water, and saturated aqueous sodium chloride. The dry solution was treated with gaseous HCl, giving 11.6 g. of steroid amine hydrochloride as a buff-colored precipitate. The hydrochloride salt was dissolved in methanol and treated with excess aqueous sodium hydroxide. The crude amine that precipitated was chromatographed on 180 g. of basic, activity grade III alumina. Elution with petroleum ether–benzene (3:1 v./v.) gave the diamine **6**, which was crystallized from ethanol–water (Table I).

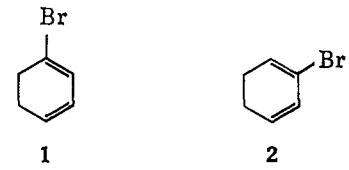
1- and 2-Bromo-1,3-cyclohexadiene[1]

ALBERT T. BOTTINI AND WILLIAM SCHEAR

Chemistry Department, University of California, Davis, California 95616

Received January 25, 1965

It was reported recently that treatment of 1,3-cyclohexadiene with potassium *t*-butoxide in dimethyl sulfoxide results in formation of equal amounts of benzene and cyclohexene.[2] Interestingly, we have noted that similar treatment of 1- or 2-bromo-1,3-cyclohexadiene[3] (**1** and **2**, respectively) at 75° results in formation of an equilibrium mixture consisting of



1 **2**

79% **1** and 21% **2**. Described here are the preparation, characterization, and equilibration of **1** and **2**.

2,3-Dibromocyclohexene[4] (**3**) with quinoline at 125 and at 175° gave different liquid products with the same boiling point (43° at 15 mm.). The product obtained at 125° appeared to be a single compound when analyzed by gas–liquid partition chromatography (g.l.p.c.), but similar analysis of the product obtained at the higher temperature indicated that it was a mixture of two compounds in a ratio of 2:1. The major component was the same compound that was obtained pure at the lower temperature, and the minor component was obtained pure by preparative-scale g.l.p.c.

Both compounds had the empirical formula C_6H_7Br. Considering their origin, the product obtained at 125° was assigned the 2-bromo-1,3-cyclohexadiene (**2**) structure, and its isomer was assigned the 1-bromo-1,3-cyclohexadiene structure. The structural assignments seem reasonable because formation of **2** can be pictured as occurring by β elimination of the elements of hydrogen bromide from **3**, and formation of **1** can be rationalized as occurring by a slower, base-induced, prototropic rearrangement of **2**. Evidence supporting the structural assignments was obtained by carrying out an additional reaction at 175° with a reaction time of 25 instead of 18 hr.; the product obtained consisted of 46% **1** and 54% **2**.[5]

The infrared, n.m.r., and ultraviolet spectra of **1** and **2** are in accord with the bromo-1,3-cyclohexadiene structure. The infrared spectrum of **1** possesses absorptions in the 1630-cm.$^{-1}$ region characteristic of a conjugated diene without a center of symmetry,[6] *i.e.*, bands of moderate intensity at 1580 and 1640 cm.$^{-1}$. The infrared spectrum of **2** possesses similar absorptions at 1575 and 1680 cm.$^{-1}$. The n.m.r. spectrum of **1** at 60 Mc. has considerable fine structure and consists of two series of lines from 402–361 (=CH, 3H) and 196–142 (CH_2, 4H) c.p.s. downfield from the tetramethylsilane (TMS) resonance. The n.m.r. spectrum of **2** consists of a broad band from 373–348 c.p.s. with peaks at 369 and 361 c.p.s. (=CH, 3H) and a broadened band ($\omega_{1/2} \sim 4$ c.p.s.) centered at 140 c.p.s. (CH_2, 4H). The ultraviolet spectra of **1** and **2** are similar but distinguishable: **1** has λ_{max} 269 mμ (ϵ 7900), and **2** has λ_{max} 268 mμ (ϵ 7600).[7]

As prototropic rearrangements of alkenes occur at particularly favorable rates in dimethyl sulfoxide,[9]

(1) This research was supported by Grant GM-10606 from the National Institute of General Medical Sciences of the U. S. Public Health Service.

(2) J. E. Hofmann, P. A. Argabright, and A. Schriesheim, *Tetrahedron Letters*, No. **17**, 1005 (1964).

(3) R. Cornubert, A. Rio, and P. Senechal [*Bull. soc. chim. France*, **46** (1955)] noted that a small amount of a rather impure material, which they suggested might be **1** or **2**, was obtained as a minor product from the reaction of 2,3-dibromocyclohexyl acetate with potassium acetate.

(4) J. Sonnenberg and S. Winstein, *J. Org. Chem.*, **27**, 750 (1962).

(5) The greater elution time (on octyl phthalate) of **2**, which has the higher dipole moment, is also consistent with the structural assignments.

(6) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 59.

(7) *Cf.* the ultraviolet spectra of 1,3-cyclohexadiene, λ_{max} 256.5 mμ (ϵ 8000),[8] and a number of alkyl substituted 1,3-cyclohexadienes summarized by H. H. Jaffé and M. Orchin ["Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 202].

(8) V. Henri and L. W. Pickett, *J. Chem. Phys.*, **7**, 439 (1939).

(9) A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3164 (1962).