fate and concentrated at room temperature under reduced pressure to dryness. The sirup that resulted was crystallized from toluene and had m.p. 110° alone or when mixed with an authentic sample of penta-*O*-acetyl-D-gluconic acid.

Preparation of *aldehydo*-D-Arabinose Hexa-*O*-acetate.—The sirup obtained from the decarboxylated silver salt of penta-*O*-acetyl-D-gluconic acid (2.0 g.) was dissolved in 10 ml. of toluene, 2.0 g. of dry silver acetate[14] was added and the mixture heated under reflux for five minutes. After standing overnight at room temperature the mixture was filtered and two volumes of petroleum ether (b.p. 35–55°) added to the filtrate. A gummy solid separated. This was separated by decantation and dissolved in chloroform (25 ml.). The chloroform solution was extracted with half-saturated sodium bicarbonate solution (two 10 ml. portions), ice-water (10 ml.) and then dried over anhydrous sodium sulfate, filtered and concentrated at room temperature under reduced pressure. Crystals were obtained from ethanol, m.p. 89–90°, $[\alpha]^{21}D$ +29° ($CHCl_3$, *c* 5) in accord with the values reported for *aldehydo*-D-arabinose hexa-*O*-acetate.[15] The melting point showed no depression upon admixture with *aldehydo*-D-arabinose hexa-*O*-acetate prepared from D-arabinose.[8]

Reduction with Lithium Aluminum Hydride.—Two grams of the sirup obtained from the decarboxylation of silver penta-*O*-acetyl-D-gluconate was reduced in 50 ml. of anhydrous ether with excess lithium aluminum hydride[16] (1 g.) at room temperature for 2 hours.

After treatment with 20 ml. of water and 50 ml. of acetic acid, the ether was removed and the aqueous solution concentrated to dryness under reduced pressure at 35–40°. The dry powder so obtained was acetylated by adding it to a chilled (0°) 50-ml. solution of acetic anhydride and 2 ml. of *concd.* sulfuric acid and then allowing the mixture to stand at room temperature overnight. The acetylation mixture was poured into 500 ml. of ice-water containing 4 g. of sodium acetate, which after several hours was extracted with chloroform (four 50 ml. portions). The chloroform solution was dried over anhydrous sodium sulfate and concentrated to dryness to yield a sirup which crystallized from ethanol; m.p. 75°, $[\alpha]^{22}D$ +35° ($CHCl_3$, *c* 5).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.96; H, 6.11. Found: C, 49.53; H, 6.08.

The compound showed no depression in melting point when mixed with arabitol penta-*O*-acetate prepared from D-arabinose by sodium borohydride[17] reduction and acetylation.

Acknowledgment.—We wish to thank Mrs. P. P Wheeler for the microanalyses.

(14) R. S. Tipson, *J. Biol. Chem.*, **130**, 55 (1939).

(15) E. M. Montgomery, R. M. Hann and C. S. Hudson, THIS JOURNAL, **59**, 1124 (1937).

(16) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4547 (1950).

(17) M. Abdel-Akher, J. K. Hamilton and F. Smith, *ibid.*, **73**, 4691 (1951).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

"Enamine" Derivatives of Steroidal Carbonyl Compounds. IV. Structural Considerations[1]

BY JAMES L. JOHNSON, MILTON E. HERR, JOHN C. BABCOCK, ANNE E. FONKEN, JAMES E. STAFFORD AND FREDERICK W. HEYL

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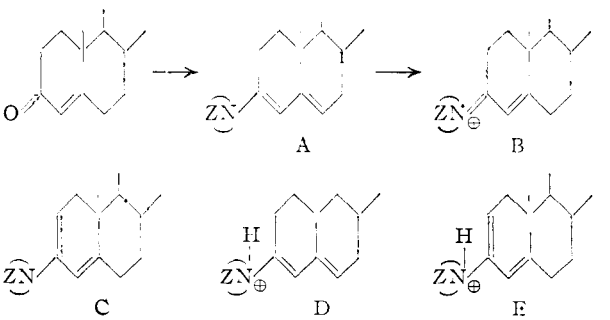
The condensation products of secondary amines with Δ^4-3-ketosteroids are shown to be 3-amino-3,5-dienes. In the presence of strong acids these "enamines" isomerize to ternary iminium salts: $>C=C-C=C-N< \rightarrow H-C-C=C-C=N^{\oplus}<$. Reactions with alkyl halides in non-polar solvents yield the normal quaternary salts: $>C=C-C=C-N^{\oplus}<-R\ X^{\ominus}$. The ultraviolet, polarimetric, infrared and chemical data which support these conclusions are discussed. A simplified preparation of enamines is described.

Condensation of aldehydes and ketones with secondary amines was first described by Mannich and Davidsen.[2] The reaction was subsequently modified and applied to steroids by Heyl and Herr,[3] who found that selectivity in the protection of aldehyde or ketone functions of polycarbonyl steroids could be achieved by a suitable choice of amine reagent. Primarily on the basis of their strong levorotation the enamines formed from Δ^4-3-ketosteroids were inferred to be 3,5-dienes (A) rather than the alternative 2,4-dienes (C).[1] Other evidence was reported, however, which appeared to favor the homoannular diene structure.[4]

Further study has shown these enamines of α,β-unsaturated ketosteroids to be highly reactive and labile compounds, the specific structures of which are determined by their solvent environment. The heteroannular system (A) has been established as the species existing in neutral solvent. In



strongly acid solutions these enamines rearrange rapidly to the stable ternary iminium salts (B). Upon reaction with alkyl halides in non-polar solvents, on the other hand, the enamines yielded the normal N-alkyl quaternary salts. These transformations were accompanied by diagnostic changes in rotation and in ultraviolet and infrared absorption.

Ultraviolet and Infrared Absorption Studies.—In ether solution the pyrrolidinyl enamines of Δ^4-3-ketosteroids (Table I) exhibited ultraviolet absorp-

(1) Paper III, M. E. Herr and F. W. Heyl, THIS JOURNAL, **75**, 5927 (1953).

(2) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

(3) Reference 1 and preceding papers.

(4) Reference 1, footnote 6.

TABLE I

REPRESENTATIVE SPECTRAL DATA FOR ENAMINES PREPARED FROM Δ^4-3-KETO STEROIDS

Pyrrolidinyl enamine of	Infrared ν of C=C, cm.$^{-1}$ (mull)	Ultraviolet λmax, mμ (ϵ) Methanol	Methanol–HCl	Ether
Stigmastadienone	1640, 1609	281	278 (22,400)	280 (24,075)
Progesterone	1636, 1607	277 (20,925)	277 (20,475)	281 (22,725)
11-Ketoprogesterone	1630, 1610	276 (20,425)	274 (20,175)	282 (25,825)
Androstenedione	1633, 1600	276 (19,000)	276 (18,925)	281 (23,200)
11α-Hydroxyandrostenedione	1634, 1609			284 (24,775)
Adrenosterone	1635, 1602		274 (19,775)	282 (23,325)
Piperidyl enamine of				
3-Ketobisnor-4-cholen-22-al (a 3,22-bis-enamine)	1648, 1613	264	280.5 (24,650)	268.5 (21,850)
Stigmastadienone	1638, 1607			271 (19,900)
Morpholinyl enamine of				
Adrenosterone	1635, 1607	266 (19,700)	282 (19,800)	269 (21,300)
11-Ketoprogesterone	1642, 1610	265 (20,000)		268 (21,100)
Testosterone	1639, 1612	263.5 (19,600)	286 (23,150)	267 (20,850)

tion maxima in the range 280–284 mμ with molecular extinction coefficients of 19,000–26,000. Although it was not possible to distinguish between the linear-conjugated 3-amino-3,5-diene and the cross-conjugated 3-amino-2,4-diene structures by the position of the ultraviolet absorption,[5] the extinction coefficients were in the range of transoid (14,000–28,000) rather than cisoid (5,000–15,000) dienes.[7]

The work of Bowden, *et al.*, suggested that the bathochromic contribution of nitrogen could be eliminated by salt formation.[8] In this event, the absorption maxima of the enamine salts would be expected near the wave lengths of the parent dienes (230–250 mμ for the heteroannular system or 265–285 mμ for the homoannular system[6]) and would permit a choice between structures A and C.

Studies carried out in pursuit of this point revealed that the conjugate acids (D), with the positive charge largely on nitrogen, underwent rapid tautomerization to the ternary iminium compounds (B) with the positive charge distributed on nitrogen, C_3 and C_5. In a single case[9] the prototropic shift to C_6 was sufficiently slow that transient absorption near 239 mμ was detected (Table II). In general, however, the ternary iminium ions formed very rapidly affording maxima near 280 mμ with extinction coefficients in excess of 20,000. The transient absorption at 239 mμ and the high extinction coefficients near 280 mμ contraindicated structure E for the conjugate acids of these enamines.

TABLE II

RATE OF PROTOTROPIC CHANGE OF ENAMINES IN ACIDIC METHANOL[a]

	Compound	Time, min.	ϵ_{239}	$\epsilon_{280.5}$
1	3,22-Bis-(N-piperidyl)-3,5,20-(22)-cholatriene	4	11,525[b]	11,775
		15	9,425	17,425
		30	8,025	22,875
		39	7,175	24,300
		49	6,375	24,650
		480	6,500	24,800
2	3-(N-Pyrrolidinyl)-3,5-pregnadien-20-one	0	.... ϵ_{281}	20,425
		4	.... ϵ_{278}	22,450
		210	.... ϵ_{278}	22,400

[a] 0.5 ml. of concd. HCl in 99.5 ml. of absolute methanol. [b] Maxima also occurred at 232 and 247 mμ with ϵ 10,300 and 9,800, respectively, at 4 minutes.

The ultraviolet absorption characteristics of the enamines of ergosterone and isoergosterone (III and IV, Table III) and of their salts contributed to the conclusion that the conjugate acids of enamines of Δ^4-3-ketosteroids have structure B. Ergosterone 3-pyrrolidinyl enamine possessed an absorption maximum at 360 mμ (ether). This maximum, at so long a wave length, must be attributed to extended conjugation of the amine fragment with a 3,5,7-triene IIIb: a cross-conjugated 3-amino-2,4,6-triene would be expected to absorb at shorter wave length. Furthermore, upon addition of acid, the maximum shifted to 274 mμ the same wave length observed for enamines of Δ^4-3-ketosteroids in acid. The disruption of extended conjugation which is responsible for the shift in ultraviolet absorption would not be expected to occur with the 2,4,6-triene but may be accounted for by addition of a proton at C_6 of the 3,5,7-triene to give IIId (Table III). These conclusions were supported by the fact that the addition product of isoergosterone and pyrrolidine (IVb) formed a conjugate acid (IVd, λ_{max} 228, 328 mμ) different from that obtained from ergosterone enamine.

(5) K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946). These authors observed that conjugation of simple conjugated systems with a tertiary amine function led to bathochromic shifts somewhat larger than those obtained by conjugation with an additional double bond. 1-Diethylamino-1,3-butadiene, a conjugated aminodiene, was reported to absorb at 281 mμ (ϵ 24,000). A cross-conjugated steroidal 3-amino-2,4-diene would be expected to absorb near 278 mμ: 253 mμ (homoannular diene) + 5 mμ (exo bond) + 20 mμ (four substituents).[6]

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Pub. Corp., New York, N.Y., 1949, pp. 185–198.

(7) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(8) N-Butenylpiperidine, in which the electron pair on nitrogen was conjugated with the double bond, gave maximum absorption at 228 mμ as compared with 185 mμ for 3-octene. In acidic solution, where conjugation was eliminated by salt formation, only weak end absorption was observed.[5]

(9) This compound was the 3,22-bis-piperidyl enamine of 3-keto-bisnor-4-cholen-22-al. The chromophore $>CH-CH=\overset{\oplus}{N}Z$ did not contribute significantly to the transient absorption near 239 mμ since the 22-monoenamine (ϵ_{240} 21,500) exhibited an absorption in acidified alcohol (ϵ_{242} 17,200) almost identical to that of the parent aldehyde (ϵ_{241} 16,500).

TABLE III

STRUCTURE AND ULTRAVIOLET ABSORPTIONS OF STEROID ENAMINES; EFFECT OF SOLVENT AND *p*H[a]

	Parent compound *a*	Solution of enamine in Ether *b*	Alcohol *c*	Alcohol + H^+ *d*	Alcohol + OH^- *e*
I	Δ^{4}-3-one	$\Delta^{3,5}$	$\Delta^{3,5}$	$\Delta^{3(N^+),4}$	Δ^{4}-3-one
	240	280–284	275–281	274–278	240
II[b]	240	268–271	264	280	240
III	$\Delta^{4,7}$-3-one	$\Delta^{3,5,7}$	$\Delta^{3(N^+),5,7}$	$\Delta^{3(N^+),4,7}$	$\Delta^{4,6}$ + $\Delta^{4,7}$-3-one
	240	239, 360	285	274	244, 289
IV	$\Delta^{4,6}$-3-one	$\Delta^{3,5c}$	$\Delta^{3(N^+),4,6}$	$\Delta^{3(N^+),4,6}$	$\Delta^{4,6}$-3-one
	286	281.5	228, 328	327	286
V[b]	22-al	$\Delta^{20(22)}$	.....	Iso-$\Delta^{22(N^+)}$	Iso-22-al
	No strong u.v.	226		No strong u.v.	No strong u.v.

[a] Upper figures locate positions of unsaturation; lower figures give observed ranges of ultraviolet maximum mμ. [b] Piperidinyl enamines; all others are pyrrolidinyl. [c] 3,7-Bispyrrolidinyl-3,5,22-ergostatriene.

In contrast to the salts obtained from enamines of Δ^4-3-ketosteroids by addition of mineral acids, the salts obtained by the addition of methyl iodide in non-polar solvents were N-alkyl derivatives (see below). When purified, they showed maxima at 222,[10] 240 and 248 mμ characteristic of the 3,5-diene system.

Infrared absorptions in the double-bond region were characteristic for enamines but somewhat less definitive for their salts (Fig. 1). In mulls, enamines showed two bands in this region at about 1640 and 1610 cm.$^{-1}$. In chloroform solution these bands occurred near 1630 and 1603 cm.$^{-1}$ and were not clearly resolved. The salts did not absorb at a consistent frequency in mulls, but in chloroform the relatively small number of compounds studied showed incompletely resolved bands at 1617 and 1605 cm.$^{-1}$. The apparent integrated absorption intensities (3.3–3.8 × 10^4 mole^{-1} liter cm.$^{-2}$) were comparable to those of carbonyl groups and greater than those of simple dienes. This was consistent with the findings of Randall, Fowler, Fuson and Dangl[11] that vinylamine and vinyl alcohol derivatives showed intensified carbon–carbon double bond absorptions. The fact that the intensity of the absorption (4.1–4.8 × 10^4 mole^{-1} liter cm.$^{-2}$) was maintained and even enhanced in the ternary iminium salts afforded evidence for structure B with its strongly absorbing conjugated >C=N$^+$— group.[12,13]

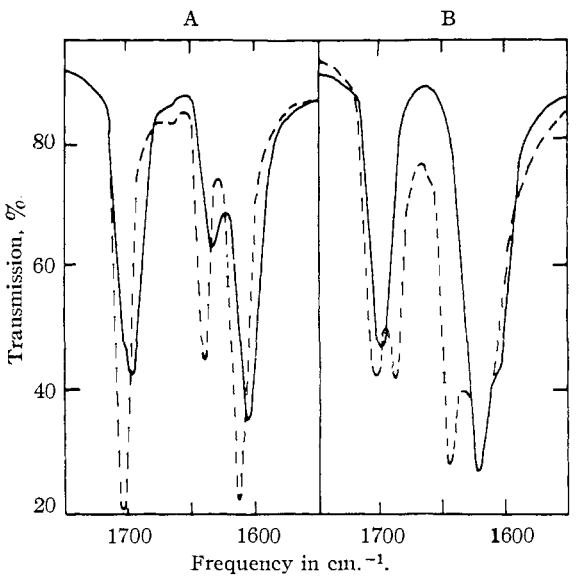
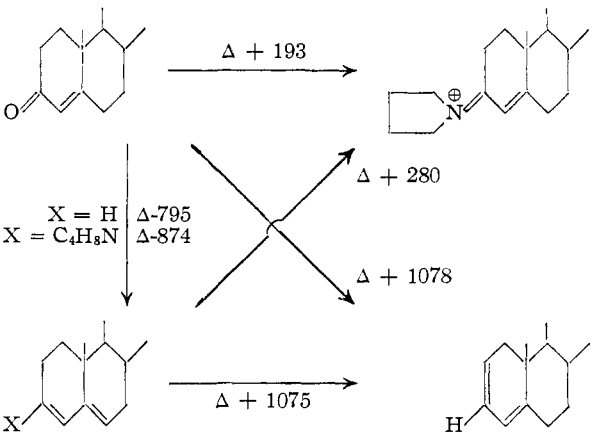


Fig. 1.—Partial infrared spectra: A, 0.7% (w./v.) solutions in chloroform, 0.5-mm. cell: —, 3-pyrrolidinyl enamine of progesterone; ---, its hydrochloride. B, Mineral oil mulls: —, 3-pyrrolidinyl enamine of progesterone; ---, its hydrochloride.

(10) The maximum at 222 mμ is due, at least in part, to absorption by iodide ion.

Molecular Rotation Differences.—A study of the molecular rotations of Δ^4-3-ketosteroids and their enamines also provided strong evidence for the $\Delta^{3,5}$-structure (A). Conversion of the α,β-unsaturated ketone to enol esters,[14] ethers[15] or thioethers[16] is accompanied by a large levorotatory shift. The difference in molecular rotations between the Δ^4-3-ketosteroids and enamines was also strongly levo, corresponding closely in magnitude to that between cholestenone and 3,5-cholestadiene.[17] Dissolution of enamines in acid, however, produced striking changes in molecular rotation. A strong dextrorotatory shift occurred which could not be accounted for satisfactorily by simple salt formation and pointed to a rapid isomerization of double bonds. In magnitude, the difference corresponded almost identically to that between 3,5- and 2,4-cholestadiene.[18] However, thermodynamic and chemical considerations, as well as ultraviolet and infrared constants, failed to support this interpretation, and the large positive shift in rotation is attributed to formation of the ternary iminium ion.



(11) (a) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 5; (b) R. N. Jones, D. S. Ramsey, D. S. Keir and K. Dobriner, THIS JOURNAL, **74**, 80 (1952); (c) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953); and (d) A. L. Heyden, P. B. Smeltzer and I. Scheer, *Anal. Chem.*, **26**, 550 (1954), observed similar intensifications of the double bond absorptions of steroid enol lactones, enol esters and enol ethers.

(12) N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954).

(13) See the catalog of spectra included in ref. 11a.

(14) U. Westphal, *Ber.*, **70**, 2128 (1937).

(15) A. Serini and H. Koster, *ibid.*, **71**, 1766 (1938).

(16) E. Schwenk, F. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938).

(17) G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(18) E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1939).

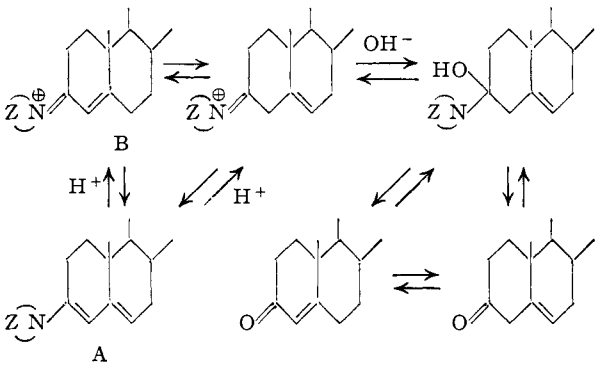
TABLE IV

MOLECULAR ROTATION DIFFERENCES FOR PYRROLIDINYL ENAMINES[a]

Compound	ΔM_D[b] A	B	C
Cholestenone	− 819	192	1021
Stigmastadienone	− 787	132	923
Progesterone	− 710	232	942
Adrenosterone	−1064	200	1263
Androstenedione	−1027	211	1242
9(11)-Dehydroandrostenedione	−1083		
11β-Hydroxyprogesterone	− 814[c]		
11α-Hydroxyprogesterone	−1164		
11-Ketoprogesterone	− 625		
Testosterone	− 727		
Methyltestosterone	− 597		
11α-Hydroxyandrostenedione	−1076		
ΔM_D (average)	− 874	193	1078
M_D (3,5-cholestadiene) − M_D (cholestenone)	− 795		
M_D (2,4-cholestadiene) − M_D (cholestanone)		280	
M_D (2,4-cholestadiene) − M_D (3,5-cholestadiene)			1075

[a] Rotations of the enamines were measured in chloroform except where indicated; the conjugate acids were measured in 95% ethanol containing 5% (vol.) of concd. HCl. [b] A = M_D of enamine − M_D of ketone; B = M_D of HCl salt − M_D of ketone; C = M_D of HCl salt − M_D of enamine. [c] Rotations compared in different solvents.

Chemical Studies.—The chemical properties of enamines of Δ^4-3-ketosteroids and their salts afforded further support for the assigned structures. Unlike enol ethers, these enamines proved stable to strong acid. In the presence of alkali,[19] however, they hydrolyzed rapidly to the unsaturated ketone. The ternary iminium salts, like quaternary salts of Schiff bases,[20] hydrolyzed at a still greater rate in the presence of alkali; this property was consistent with structure B. Hydrolysis probably proceeded by way of the pseudo-base.



A refluxing solution of 3-(N-pyrrolidinyl)-3,5,22-stigmastatriene in 95% ethanol was completely converted to stigmastadienone within 40 minutes. Infrared examination of aliquots removed during the reaction revealed the intermediate existence of non-conjugated ketone, ν_{max}^{Nujol} 1710 cm.$^{-1}$, in the early samples (Fig. 2).

(19) Unpublished experiments of B. J. Magerlein, J. L. Johnson and J. A. Hogg of these laboratories.

(20) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 58.

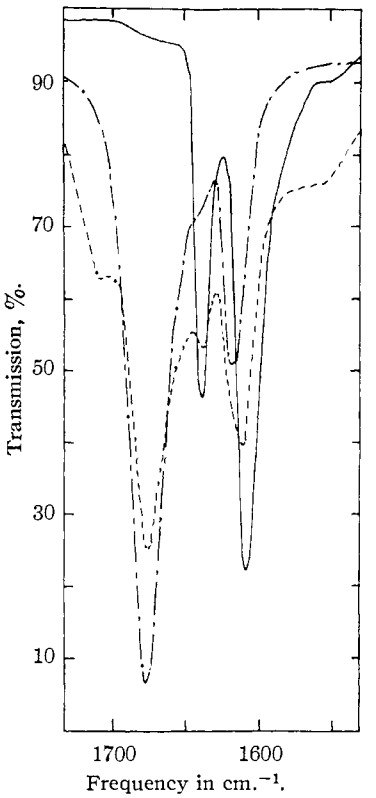


Fig. 2.—Infrared spectra describing hydrolysis of the pyrrolidinyl enamine of stigmastadienone: —, enamine; ---, 10-minute hydrolysis; – – –, stigmastadienone, 40-minute hydrolysis.

Enamines could be regenerated from solutions of their conjugate acids by addition of secondary amines such as piperidine or diethylamine (triethylamine was ineffective).[21] The regenerated enamines were identical with the starting enamines. If the salts had possessed the homoannular structure, C, formation of isomeric enamines might have been expected under these mild conditions. Although highly colored amorphous products of unknown structure were obtained from attempted diene additions of enamines with maleic anhydride or quinone, with methyl maleate only unchanged enamine and dimethyl fumarate were obtained.

Addition of hydrogen cyanide to enamines afforded conjugate acids which were soluble in ether and essentially transparent to ultraviolet light. They did not show the strong infrared absorption in the double bond region characteristic of $>\overset{\oplus}{N}=C<$ and therefore probably possess the more covalent "pseudo-base" structure of a 3-cyano-3-pyrrolidinyl-$\Delta^{(4 \text{ or } 5)}$-steroid. In alcohol, isomerization to the ternary iminium salts with characteristic absorption at 278 mμ occurred. Similarly, crystalline monochlorides could be prepared from equivalent amounts of enamine and gaseous hydrogen chloride in inert solvents, while, with a large excess of hydrogen chloride, products containing two equivalents of chloride were ob-

(21) R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942). These authors observed tertiary vinyl amines to be less basic than secondary amines but more basic than saturated tertiary amines.

TABLE V

ENAMINES OF Δ^4-3-KETOSTEROIDS

Parent steroid	Amine	Method	Recrystn. solvent	M.p. (dec.), °C.	$[\alpha]_D$, ($CHCl_3$)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4,9(11)-Androstadiene-3,17-dione	Pyrrolidine	B		165	−135°	$C_{23}H_{31}ON$	81.84	81.62	9.26	9.09	4.15	4.29
11β-Hydroxyprogesterone	Pyrrolidine	A	Benzene–Skelly C	175–185	−21	$C_{25}H_{37}O_2N$	78.29	78.35	9.73	9.55	3.91	3.72
Ergosterone	Pyrrolidine	A		189	−63	$C_{32}H_{51}N$	85.45	85.93	11.43	11.06	..	..
Isoergosterone[a]	Pyrrolidine	A	Ether	146–147		$C_{47}H_{60}N_2$	83.39	82.79	11.35	10.88	5.26	5.85
Testosterone	Morpholine	A	Acetone	187–195	−89	$C_{23}H_{35}NO_2$	77.20	77.45	9.87	9.83	3.92	4.08
Adrenosterone	Morpholine	A	Acetone	230	+26	$C_{23}H_{31}O_4N$	74.75	74.86	8.46	8.50	3.79	4.12
11-Ketoprogesterone	Morpholine	A	Acetone	173–183	+43	$C_{25}H_{35}NO_3$	75.53	75.60	8.88	8.74	3.52	3.57
3-Ketobisnor-4-cholen-22-al[b]	Piperidine	A	$CHCl_3$–MeOH	198–200	−70	$C_{32}H_{50}N_2$	83.05	82.84	10.89	10.69	6.06	6.46
4,22-Stigmastadien-3-one	Piperidine	C	Ether–MeOH	119–120	−53	$C_{34}H_{55}N$	85.45	85.80	11.61	11.70	2.93	3.32

[a] The product was 3,7-bis-(N-pyrrolidinyl)-3,5,22-ergostatriene. [b] The product with excess amine was 3,22-bis-(N-piperidyl)-bisnor-3,5,10(22)-cholatriene. It was separated from the 22-monoenamine by triturating the product with large volumes of ether and recovering the insoluble material.

tained.[22] Both salts were soluble in methanol (λ_{max} 278 mμ) whereas the bromides and iodides were quite insoluble.[23]

Upon reaction with methyl iodide varying results were obtained.[24] Stigmastadienone, testosterone and progesterone pyrrolidinyl enamines afforded principally the alkali-stable N-methyl iodides (λ_{max} 222, 240 and 248 mμ) contaminated with ternary iminium salts (λ_{max} 278 mμ) in varying amounts depending on the reaction conditions.

The preparation of enamines by azeotropic removal of water from the reaction mixture has been described previously.[1] Extended refluxing was required for complete conversion. Enamines of many 3-keto- or Δ^4-3-ketosteroids have now been found to precipitate in almost quantitative yield on addition of a small excess of pyrrolidine to a hot solution of the steroid in a minimal volume of methanol. Under these conditions, piperidine does not react. Even when piperidine was used as solvent these ketones afforded chiefly recovered starting material and only small amounts of enamines. The greater resistance of piperidine and morpholine to enamine formation appears due in part to the greater steric requirement of 6-membered rings and in part to the greater stability of double bonds exocyclic to 5-membered rings.[25] The latter phenomenon probably accounts for the observed differences in ultraviolet absorptions between pyrrolidinyl and piperidinyl or morpholinyl enamines and between their conjugate acids. In their principal excited states, the free enamine bases contain a double bond exocyclic to the heterocyclic ring. The energy required to reach this level, as measured by the wave length of absorption, is less when the heterocyclic ring is 5-membered (λ_{max} 280–284 mμ) than when it is 6-membered (λ_{max} 267–271 mμ). On the other hand, in the conjugate acids the excited state possesses less double bond character exo to the heterocyclic ring and is reached more readily from the 6-membered heterocycles (λ_{max} 280–286 mμ) than from those with only 5 members (λ_{max} 274–278 mμ). In the transition state of enamine formation where dehydration of the carbinol amine introduces a double bond exo to the heterocyclic ring, these energy differences may be critical in determining the course of the reaction.

Acknowledgments.—We are indebted to Drs. Arnold C. Ott and J. A. Hogg and to Mr. O. R. Woods for their encouragement and interest in this work, and to Mr. W. A. Struck for optical rotation data and elemental analyses.

Experimental

Absorption Spectra.—Ultraviolet measurements were made using a model 11 Cary spectrophotometer. Infrared measurements were made with a Perkin–Elmer model 21 spectrophotometer equipped with a sodium chloride prism.

Preparation of Enamines.—Enamines of Δ^4-3-ketosteroids were prepared according to previously described procedures[3]: (A) by removal of water with a Bidwell–Sterling moisture trap and a water-immiscible solvent; (B) by passing the vapor condensate through a drying agent such as calcium carbide; or (C) by placing of a drying agent in the reaction mixture. Ease of enamine formation increased in the order: piperidyl < morpholinyl < pyrrolidinyl.

Pyrrolidinyl enamines also were prepared by adding excess amine to a hot, near-saturated solution of steroid in methanol, acetone, pyridine or dimethylformamide (method D). The enamine precipitated rapidly from solution. This method is illustrated as follows: To a solution of 0.5 g. of androstenedione in 2 ml. of methanol near reflux (under nitrogen) was added 0.2 ml. of pyrrolidine. The yellow solution was not heated further; it solidified after a few seconds. After cooling, the mixture was filtered to afford 0.55 g. of 3-(N-pyrrolidinyl)-3,5-androstadien-17-one, m.p. 197° dec.

These conditions were applied to most Δ^4-3-ketosteroids by using only slightly more solvent than was required to dissolve the starting material. The products were generally less soluble and separated nicely.

Piperidine, under the above conditions, yielded mainly starting material.

Table V summarizes the data for the enamines.

Hydrohalides of Enamines.—Monohydrohalides were formed by dropwise addition of excess anhydrous hydrogen chloride or bromide to ether or ether–benzene solutions of enamines (method A). Addition of enamines to ethereal hydrogen chloride[26] afforded salts with analyses approaching those for dihydrochlorides (method B).

(22) These have been tentatively formulated as $\overset{\oplus}{Z}\overset{\frown}{NH}—C(Cl)—C{=}C<$ with $Cl^{\ominus}$.

(23) Enamine salts, like Girard derivatives, are useful in the separation of reactive ketones from non-reactive ketones or non-ketonic material. The enamines may be separated from inert substances by taking advantage of the solubility of the hydrochlorides or the insolubility of other conjugate acids, such as the hydrobromides.

(24) As this work was being completed, similar studies were reported by G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).

(25) H. C. Brown, J. H. Brewster and H. Schechter, *ibid.*, **76**, 467 (1954).

(26) M. E. Herr and F. W. Heyl, *ibid.*, **74**, 3627 (1952).

Although the chlorides were soluble in methanol, the bromides and iodides were only slightly soluble. Addition of hydrobromic or hydriodic acid or their metal salts to solutions of enamines in methanol containing hydrochloric acid afforded the bromides and iodides (method C). The iodides were also obtained by treating the hydrochloride salts of enamines with methyl iodide in methanol (method D). Examples are given below and results summarized in Table VI.

Method A.—A solution of 3-(N-pyrrolidinyl)-3,5-cholestadiene in benzene–ether was treated dropwise with an excess of anhydrous hydrogen bromide in dry ether. The resulting precipitate was washed with ether, dried (m.p. 265–270° dec.) and recrystallized from methylene chloride–Skellysolve B (see Table VI).

Method D.—Two grams of 3-(N-pyrrolidinyl)-3,5,22-stigmastatriene was dissolved in 10 ml. of methanol with the aid of 0.7 ml. of concd. HCl. Methyl iodide (2 ml.) was added and the mixture allowed to stand at room temperature under nitrogen in the dark for 24 hours. The yellow precipitate was filtered and washed with cold methanol; 2.02 g., λ_{max} 278 mμ (see Table VI).

TABLE VI

HYDROHALIDE SALTS OF PYRROLIDINYL ENAMINES OF Δ^4-3-KETOSTEROIDS

Enamine of	Salt	Method	M.p. (dec.), °C.	$[\alpha]_D$ ($CHCl_3$)	Halide, % Calcd.	Halide, % Found
Progesterone	HCl	A	170	219°	8.77	8.62
Progesterone	2HCl	B	145	201	16.1	14.81
11-Ketoprogesterone	HCl	A	130	283	8.48	8.68
11-Ketoprogesterone	2HCl	B	185	254	15.46	13.78
11β-Hydroxyprogesterone	HCl	B	210	124	8.44	9.89
17-Methyltestosterone	HCl	A	125	102	9.05	8.82
Testosterone	HCl	B	225	132	9.38	9.97
Hydrocortisone-21-acetate	HCl	B	180	178	7.18	8.09
Cholestenone	HBr	A	270	94	15.41	15.96
4,22-Stigmastadien-3-one	HCl	A	195	75	7.20	8.04
4,22-Stigmastadien-3-one	HI	C	287	69	21.45	25.81
4,22-Stigmastadien-3-one	HI	D	297	74	21.45	21.69

Hydrocyanides of Enamines, Hydrocyanide of 3-(N-Pyrrolidinyl)-3,5,22-stigmastatriene.—When 1 g. of the pyrrolidinyl enamine of stigmastadienone in 9 ml. of ethanol and 3.2 ml. of acetic acid was treated with 3 g. of potassium cyanide in 5 ml. of water a precipitate separated. The product was recovered by filtration, washed with water, dried and recrystallized from ethyl acetate as needles, m.p. 114–118° dec., $[\alpha]^{24}D$ +2° ($CHCl_3$).

Anal. Calcd. for $C_{34}H_{54}N_2$: C, 83.22; H, 11.09; N, 5.71. Found: C, 83.10; H, 10.98; N, 5.55.

Treatment of the cyanide with aqueous methanolic sodium hydroxide at 26° for 10 minutes gave back stigmastadienone, m.p. 123–125°.

Hydrocyanide of 3-(N-pyrrolidinyl)-3,5-cholestadiene, prepared from the 3-pyrrolidinyl enamine of cholestenone as described above, was crystallized from ethyl acetate as needles, m.p. 123–128° dec., $[\alpha]^{24}D$ +27° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{52}N_2$: C, 82.69; H, 11.28; N, 6.03. Found: C, 82.48; H, 10.76; N, 6.10.

N-Alkyl Derivatives of Enamines, N-(20-Keto-3,5-pregnadien-3-yl)-N-methylpyrrolidinium Iodide.—To a solution of 2.5 g. of 3-(N-pyrrolidinyl)-3,5-pregnadien-20-one in 10 ml. of warm benzene was added 2.5 ml. of methyl iodide with chilling. The yellow solution gradually turned reddish-orange and deposited flat needles which were filtered and washed with ether: 2.1 g., m.p. 198–207° dec. Recrystallization from methanol–ethyl acetate gave orange plates, m.p. 208–214° (s. 199°); $[\alpha]D$ +89° ($CHCl_3$); λ_{max}^{EtOH} 223.5 mμ (16,325), 240 mμ (12,325), 248 mμ (9,600), 278 mμ (5,400).

Anal. Calcd. for $C_{26}H_{40}ONI$: C, 61.29; H, 7.91; N, 2.75; I, 24.91. Found: C, 60.95; H, 7.90; N, 3.13; I, 25.21.

N-(3,5,22-Stigmastatrien-3-yl)-N-methylpyrrolidinium Iodide.—A solution of 1 g. of 3-(N-pyrrolidinyl)-3,5,22-stigmastatriene in 8 ml. of methyl iodide was refluxed 1.75 hours, diluted with 10 ml. of methanol. The methyl iodide was evaporated and the solution diluted with water until turbid. Crystallization did not occur, so the solution was evaporated to a solid residue. Trituration with ethyl acetate afforded 0.72 g. of an amorphous tan solid, m.p. 207–225° dec., $[\alpha]D$ −39.6° ($CHCl_3$); λ_{max}^{EtOH} 222.5 mμ (22,325), 238 mμ (17,650), 249 mμ (13,050); ν_{max}^{Nujol} 1617 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3450, 1626, 970 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{56}IN$: C, 67.41; H, 9.32; I, 20.95. Found: C, 66.46, 66.57; H, 9.25, 9.15; I, 21.37, 21.09.

N-(17β-Hydroxy-3,5-androstadien-3-yl)-N-methylpyrrolidinium Iodide.—To a solution of 3.3 g. of 3-(N-pyrrolidinyl)-3,5-androstadien-17β-ol in 30 ml. of warm benzene was added 2.5 ml. of methyl iodide. The mixture gradually solidified and, after dilution with 20 ml. of ether, was filtered to give 3.4 g. of a tan product, m.p. 182–208°, $[\alpha]D$ +54° ($CHCl_3$); λ_{max}^{EtOH} 222 mμ (21,350), 240 mμ (14,675), 248 mμ (11,900) and 278 mμ (3,025). The crude material was divided into two portions. One was recrystallized from methanol–ethyl acetate to give pale yellow prisms, m.p. 230–235°, $[\alpha]D$ +27° ($CHCl_3$), λ_{max}^{EtOH} 224 mμ (23,450), 240 mμ (20,400), 248 mμ (15,325); ν_{max} 1632, 1604 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}ONI$: C, 59.62; H, 7.92; I, 26.25. Found: C, 59.53; H, 8.00; I, 26.55.

The second portion was triturated with ether–aqueous NaOH mixtures and finally recrystallized from methanol–ethyl acetate as almost white needles, m.p. 195–198°, $[\alpha]D$ −25° ($CHCl_3$), λ_{max}^{EtOH} 225 mμ (23,250), 238 mμ (21,775), 248 mμ (14,875); ν_{max} 1721, 1625, 1604 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}ONI$: C, 59.62; H, 7.92; I, 26.25. Found: C, 59.47; H, 7.99; I, 25.74.

The two apparently different methiodides of testosterone pyrrolidinyl enamine are tentatively considered to be diastereoisomers. Although quaternization of a symmetrically substituted amine would not ordinarily be expected to lead to asymmetry, the possibility of restricted rotation in the severely hindered quaternary salt must be entertained. This subject will be considered in more detail in a future publication.

N-(3-Ketobisnor-4,20(22)-choladien-22-yl)-N-methylpiperidinium Iodide.—A solution of 7.92 g. of 22-(N-piperidyl)-bisnor-4,20(22)-choladien-3-one in 20 ml. of methyl iodide and 20 ml. of ether was allowed to stand at room temperature for 3 days in the absence of air and light. A gelatinous precipitate formed. The mixture was diluted with an equal volume of ether and filtered. After drying in a vacuum desiccator the yield was 8.69 g. (81%), m.p. 194–197° dec., $[\alpha]D$ +51° ($CHCl_3$); ν_{max}^{Nujol} 1665 cm.$^{-1}$, 1617 cm.$^{-1}$; λ_{max}^{MeOH} 222 mμ (21,825), 242 mμ (14,190).

Anal. Calcd. for $C_{28}H_{44}INO$: I, 23.6. Found: I, 27.5, 26.2.

This crude material could not be purified further by recrystallization without extensive decomposition. Some samples melted as high as 215–217° dec.

N-(3,5,22-Stigmastatrien-3-yl)-N-methylpiperidinium Iodide.—Three hundred milligrams of 3-(N-piperidyl)-3,5,22-stigmastatriene in 3.0 ml. of methyl iodide after 3 days yielded 420 mg. of crude quaternary salt, m.p. 191–195° dec., $[\alpha]D$ −74° ($CHCl_3$); λ_{max}^{MeOH} 232 mμ (24,130); flexes 227, 239 and 249 mμ.

Anal. Calcd. for $C_{35}H_{58}IN$: I, 20.5. Found: I, 19.4, 18.7.

Hydrolysis of Enamines.—It was considered possible that the "neutral" hydrolysis of C_3-enamines of Δ^4-3-ketosteroids might represent a facile preparation of Δ^5-3-ketosteroids.[27] That such an intermediate existed, albeit transiently, was shown by the following experiment:

One-half gram of the pyrrolidinyl enamine of 4,22-stigmastadien-3-one suspended in 50 ml. of 95% ethanol was brought to reflux and aliquots taken at 10, 20, 30 and 40 minute intervals. These aliquots were individually and rapidly dried in a vacuum desiccator and examined by infrared. Evidence for the presence of non-conjugated ketone is described in the discussion above.

Upon cooling the remainder of the solution, 4,22-stigmastadien-3-one, m.p. 124–125°, was recovered.

When the hydrolysis was carried out at room temperature

(27) Similar studies were carried out by A. J. Birch, P. Hextall and J. A. K. Quartey, *Austral. J. Chem.*, **6**, 445 (1953).

in dilute dioxane containing one drop of acetic acid, the material which precipitated gradually over several days was a sharp melting mixture (m.p. 150–150.5°) identified by infrared and ultraviolet absorptions as stigmastadienone and the starting enamine.

When the conjugate acids of enamines were treated with dilute alkali, the absorption near 278 mμ was rapidly replaced by the absorption of the Δ^4-3-ketone near 240 mμ. The same change occurred at a somewhat slower rate when enamines were treated directly with alkali.

Recovery of Enamines from Their Conjugated Acids.—An ether suspension of testosterone pyrrolidinyl enamine hydrochloride was treated with excess piperidine and stirred for 10 minutes. The mixture was filtered and the filtrate taken to dryness *in vacuo*. Trituration of the residue with methanol gave testosterone pyrrolidinyl enamine.

Ultraviolet spectra and rotations of the hydrochloride salts of enamines of Δ^4-3-ketones were not altered by addition of triethylamine, but addition of diethylamine or piperidine converted the conjugate acids to the free bases.

Separation of Progesterone from Pregnenolone Using Enamine Salts.—A mixture of 3.14 g. of progesterone and 3.16 g. of pregnenolone was dissolved in 50 ml. of benzene. The solution was treated with 1.67 ml. of pyrrolidine and 20 mg. of *p*-toluenesulfonic acid and stirred at reflux under a water trap for 2.25 hours, during which time 0.18 ml. of water was collected. The reaction mixture was evaporated to dryness *in vacuo* and the residue redissolved in 50 ml. of a mixture of benzene–ether (1:1). An ether solution of anhydrous hydrogen chloride was added slowly with stirring until no further precipitation occurred. The insoluble enamine hydrochloride of progesterone, A, was recovered by filtration, washed with ether and dried, and the filtrate saved.

The hydrochloride A was dissolved in 100 ml. of methanol and 25 ml. of 5% aqueous sodium hydroxide was added. The solution was warmed at 50° for 20 minutes, acidified with glacial acetic acid, and concentrated to dryness *in vacuo*. The residue was recrystallized from dilute methanol to give 2.79 g. of progesterone, m.p. 120–129°, identical with authentic progesterone by melting point and infrared spectrum.

The filtrate B was washed free of acid. Evaporation of the solvent gave 2.98 g. of good quality pregnenolone, m.p. 187–190°, identified by comparison of melting point and infrared spectrum.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Anthrasteroid Rearrangement. IV. The Preparation of Several New Anthrasteroids and Some Observations on the Dehydrobromination of 7-Bromo-Δ^5-steroids[1]

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Anthracholestatetraene, anthracholestatriene, methyl anthrabisnorcholatetraenate and methyl anthrabisnorcholatrienate have been prepared from the corresponding steroidal 5,7,9(11)-trienes. The molecular rotations of these anthrasteroids and those of the corresponding derivatives in the ergosterol series exhibit consistent ΔM_D values for hydrogenation of the conjugated double bond. This is interpreted as evidence for a common position of the conjugated double bond in the various anthrasteroids and, consequently, for a dominant pathway for the over-all conversion. Rearrangement in the 17-ketosteroid series gave in poor yield the corresponding chloroanthrastatrienone. This compound exhibited the normal ultraviolet spectrum of anthrastatrienes and possessed an infrared spectrum which showed the presence of an unconjugated carbonyl group. This is considered as corroborating earlier evidence that anthrasteroids possess an aromatic B-ring and not an aromatic C-ring. A study of the influence of temperature on the dehydrobromination of 7-bromocholesteryl acetate revealed that the yield of $\Delta^{5,7}$-steroid decreases with decreasing temperature while the formation of the 4,6-isomer was not appreciably affected. The isocaproates of cholesterol and dehydroepiandrosterone gave better yields of the corresponding $\Delta^{5,7}$-steroid than did the acetates.

The application of the anthrasteroid rearrangement in the ergosterol and lumisterol[3] series has been described previously.[1a] The present paper deals with the extension of this reaction to the 5,7,9(11)-trienes derived from cholesterol, methyl 3β-hydroxybisnor-5-cholenate and dehydroepiandrosterone.

Applied to compounds I and II, the rearrangement proceeded smoothly and the corresponding anthrasteroids III and IV were obtained. These were reduced to the trienes V and VI, respectively, with platinum oxide in ethyl acetate–acetic acid. Sufficient material was available only in the cholesterol series to carry out dehydrogenation experiments, and anthracholestatetraene (III) was converted readily to an oily anthracene derivative by heating with palladium-on-charcoal.

The molecular rotations of the new anthrasteroids are compared with those of anthraergostatetraene and anthraergostatriene in Table I, and the increments for hydrogenation of the conjugated double bond have been calculated. The consistency of the individual values (+244° ± 6°) suggests strongly that the various samples of the anthrasteroids were homogeneous and, moreover, that all three types have a common position for the conjugated double bond. This is significant for answering the question of the pathway for the over-all conversion, since there is the possibility that more than one unsaturated steroidal intermediate could undergo rearrangement to give isomeric anthrasteroids. The fact, however, that the 5,7,9(11)-trienes appear to be converted principally or solely to but one isomer indicates the predominance of a single pathway.

TABLE I

ΔM_D FOR HYDROGENATION

Side chain related to	M_D of anthrasteroid containing (A) a conjugated double bond	(B) no conjugated double bond	M_D(B) − M_D(A)
Ergosterol	−163°[a]	+80°[b]	+243°
Cholesterol	−128	+110	+238
Methyl bisnorcholenate	−152	+98	+250

[a] Calcd. for M_D of anthraergostapentaene[1a] using an increment of +103° for saturation of the Δ^{22}-bond (D. H. R. Barton, J. D. Cox and N. J. Holness, *J. Chem. Soc.*, 1771 (1949)). [b] See ref. 1a.

(1) (a) Part I, W. R. Nes and E. Mosettig, THIS JOURNAL, **76**, 3182 (1954); (b) part II, *ibid.*, **76**, 3186 (1954); (c) part III, W. R. Nes, *ibid.*, **78**, 193 (1956).