After decomposition of the excess hydride by cautious addition of ethyl acetate, the steroid was isolated with ether and chromatographed on alumina (120 g.). Elution with petroleum ether–benzene (10:1) afforded an oil (0.48 g.) which failed to crystallize. Elution with petroleum ether–benzene (1:1) have a gummy solid (1.21 g.), $[\alpha]^{25}D$ +37°, which after five recrystallizations from aqueous acetone gave 3α-chloro-5α-cholestan-5-ol, m.p. 115-118°, $[\alpha]^{25}D$ +17°. The melting point of this material was depressed upon admixture with a sample of 3β-chloro-5α-cholestan-5-ol.

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LOS ANGELES, CALIF.
SYDNEY, AUSTRALIA

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE & CO.]

Azasteroids. I[1,2]

BY ROBERT H. MAZUR

RECEIVED AUGUST 25, 1958

The conversion of the readily available plant steroid, hecogenin, to a C-ring lactam is described. The latter could serve as the precursor for modified steroid hormones.

Hecogenin (I), 3β-hydroxy-5α,22a-spirostan-12-one,[3] is among the most readily available sapogenins, being found in various species of Agave.[4] It has been used successfully as a starting material for the synthesis of cortisone[5] and would seem to be an attractive substance for the preparation of steroids modified in ring C.[6,7] One such modification could be the introduction of nitrogen into ring C.

The physiological activity of steroid hormones depends on a number of factors. Among those of primary importance are stereochemistry and the over-all shape of the molecule. Thus, any really fundamental change in the steroid nucleus should alter the stereochemistry as little as possible. Models indicate that expansion of ring C from six- to seven-membered has little effect on the molecule's general shape and no change in the configuration at any asymmetric center need be made.

The preparation of steroids containing nitrogen in the ring system has been limited to few examples. Bolt[8] synthesized 4-aza analogs of cholestane and 17β-hydroxypregnane. Schenck[9] has carried out Beckmann rearrangements of ring ketoximes derived from bile acids. Barnes, *et al.*,[10] and Falco, *et al.*,[11] have prepared B-ring lactams in the lanosterol series while Kaufmann,[12] Heusser, *et al.*,[13] Regan and Hayes[1] and the present author[1] have synthesized various 17a-aza-D-homo steroids.

Hecogenin (I) was converted to the acetate II which gave the oxime III. The oxime failed to rearrange at room temperature with *p*-toluenesulfonyl chloride in pyridine, but heating at 100° gave 3β-acetoxy-12a-aza-C-homo-5α,22a-spirostan-12-one (IV). An examination of models showed that although the assigned structure of the oxime and resulting lactam was the more probable, the alternative oxime (*syn* to the C-18 methyl group) and lactam (a 12-aza-12a-one) was not precluded. More about the structure of the lactam was learned from the following sequence of reactions.

Hecogenin acetate was oxidized by selenium dioxide in *t*-butyl alcohol[14] to 3β-acetoxy-5α,22a-spirost-9(11)-en-12-one (V).[15] The oxime VI was more reactive than its saturated analog III and yielded with *p*-toluenesulfonyl chloride in pyridine at room temperature 3β-acetoxy-12a-aza-C-homo-5α,22a-spirost-9(11)-en-12-one (VII). The latter on catalytic hydrogenation gave IV. Thus, the two series II→III→IV and II→V→VI→VII→IV both lead to a common end-product and the second sequence goes through an intermediate whose structure should be capable of unambiguous proof, namely, the unsaturated lactam VII. It should be possible to distinguish between VII and the alternative 12-aza-9(11)-en-12a-one (an enamine lactam) by the ultraviolet spectrum.

Not enough examples of α,β-unsaturated amides and lactams and of α,β-unsaturated amines are in the literature to permit an unambiguous interpretation of the ultraviolet spectrum of VII. The more pertinent data, summarized in Table I, lead to the tentative conclusion that α,β-unsaturated lactams have their strong maxima at low wave lengths (around 200 mμ) while α,β-unsatu-

(1) R. H. Mazur, U. S. Patent 2,738,350 (March 13, 1956); compare B. M. Regan and F. N. Hayes, THIS JOURNAL, **78**, 639 (1956).

(2) R. H. Mazur, U. S. Patent 2,806,028 (September 10, 1957).

(3) For a discussion of the side chain stereochemistry of the series of sapogenins which includes hecogenin, see M. E. Wall and H. A. Walens, THIS JOURNAL, **80**, 1984 (1958).

(4) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2167 (1947).

(5) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.*, 2807 (1955); J. H. Chapman, J. Elks and L. J. Wyman, *Chemistry & Industry*, 603 (1955), describe some recent developments and given references to the earlier literature.

(6) E. S. Rothman and M. E. Wall, THIS JOURNAL, **77**, 2229 (1955). These authors have prepared a series of compounds containing a 12-carboxy-13-hydroxy-lactone by peracid oxidation of 12-keto steroids.

(7) E. S. Rothman and M. E. Wall, *ibid.*, **78**, 1744 (1956). This paper gives references to the preparation of certain cortical hormone analogs with a 12-keto group starting both from hecogenin and from bile acids.

(8) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938).

(9) M. Schenck, *Z. angew. Chem.*, **42**, 61 (1929).

(10) C. S. Barnes, D. H. R. Barton, J. S. Fawcett and B. R. Thomas, *J. Chem. Soc.*, 2339 (1952).

(11) M. Falco, W. Voser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **35**, 2430 (1952).

(12) S. Kaufmann, THIS JOURNAL, **73**, 1779 (1951).

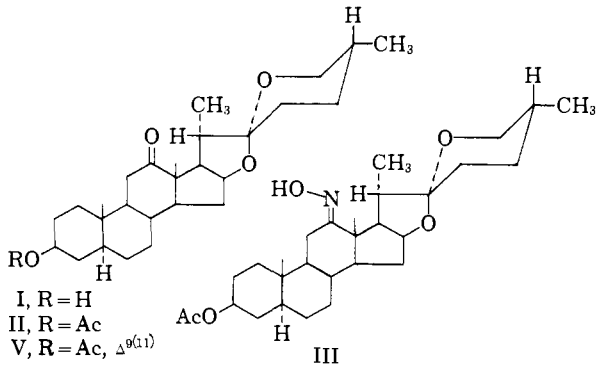
(13) H. Heusser, J. Wohlfahrt, M. Müller and R. Anliker, *Helv. Chim. Acta*, **38**, 1399 (1955); R. Anliker, M. Müller, J. Wohlfahrt and H. Heusser, *ibid.*, **38**, 1404 (1955).

(14) C. Meystre, H. Frey, W. Voser and A. Wettstein, *ibid.*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthmus, M. S. deWinter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

(15) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

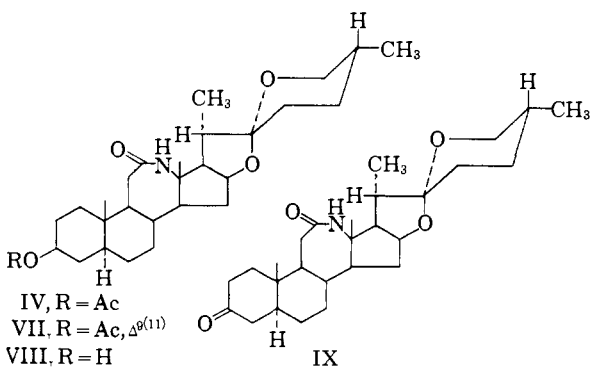
rated amides have their maxima below 200 mμ and thus show end absorption in the usual ultraviolet spectrum. On the other hand, α,β-unsaturated amines and their acyl derivatives have a strong maximum in the range 230–240 mμ. Since compound VII has λ_{max}^{MeOH} 220 mμ, ε 15,800, it is not possible to choose definitely between the lactam and enamine structures.[16]

The lactam IV was saponified under alkaline conditions to the corresponding alcohol VIII which was oxidized with chromic oxide in aqueous acetic acid to 12a-aza-C-homo-5α,22a-spirostane-3,12-dione (IX). In this particular case, Sarett reagent[17] (chromic oxide in pyridine) caused overoxidation, the only product isolated being a small amount of impure starting material.



I, R = H
II, R = Ac
V, R = Ac, $\Delta^{9(11)}$

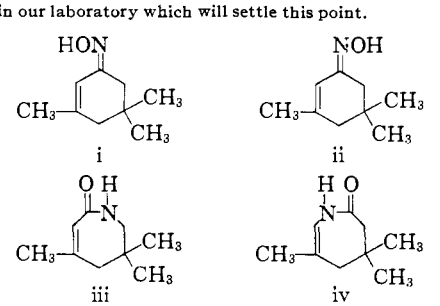
III
VI, $\Delta^{9(11)}$



IV, R = Ac
VII, R = Ac, $\Delta^{9(11)}$
VIII, R = H

IX

(16) An excellent analogy from the standpoint of both ring size and double bond substitution is found in the isomeric isophorone oximes (i, ii) and their Beckmann rearrangement products (iii, iv). These compounds were prepared by R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, **17**, 823 (1952). One lactam had λ_{max}^{EtOH} 218.5 mμ, ε 10,700 and the other λ_{max}^{EtOH} 237 mμ, ε 7320. Unfortunately, insufficient chemical evidence was presented to associate positively a particular ultraviolet spectrum with a particular structure. Work is in progress in our laboratory which will settle this point.



i ii iii iv

(17) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

TABLE I

Compound	Solvent	λ_{max}, mμ	ε
5,6-Dihydro-2(1H)-pyridone[a]	MeOH	204	8400
		240	1200
6-Methyl-5,6-dihydro-2(1H)-pyridone[b]	EtOH	241	1470
1-Methyl-5,6-dihydro-2(1H)-pyridone[a]	MeOH	204	6500
		250	1000
1,6-Dimethyl-5,6-dihydro-2(1H)-pyridone[b]	EtOH	251	1120
trans-2-Methylcrotonamide (tiglamide)[c]	H_2O	End absorption	7000 (213 mμ)
cis-2-Methylcrotonamide (angelamide)[c]	H_2O	End absorption	4660 (200 mμ)
1-Butyl-2-methyl-2-pyrroline[d]	Et_2O[e]	238	7200
1-Ethyl-6-methyl-1,2,3,4-tetrahydropyridine[d]	Et_2O[e]	231	5100
1-(1-Butenyl)-piperidine[d]	Et_2O[e]	228	7500
3β-Acetoxy-17-acetylamino-5,16-androstadiene[f]	EtOH	240	6600

[a] R. Haber, personal communication. [b] O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 683 (1954). The ultraviolet spectra were not reported in the 200 mμ region. [c] A. Castille, *Bull. soc. chim. Belg.*, **39**, 417 (1930). [d] N. J. Leonard and D. M. Locke, THIS JOURNAL, **77**, 437 (1955). [e] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 184, suggest a correction of +7 mμ to compare absorption maxima in ether with those in ethanol. Thus the maxima for the three unsaturated amines would become 245, 238 and 235 mμ, respectively. [f] G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

Experimental[18]

3β-Acetoxy-5α,22a-spirostan-12-one Oxime (III).—Hecogenin (430 g., 1.0 mole) was dissolved in 2600 ml. of pyridine and 200 ml. (2 moles) of acetic anhydride. The solution was heated under reflux for 45 minutes, cooled somewhat and 20 ml. (1.1 moles) of water was added. After the vigorous reaction subsided, 105 g. (1.5 moles) of hydroxylamine hydrochloride was added and the mixture stirred and heated under reflux for one hour. The cooled reaction mixture was poured into a large volume of water, the product removed by filtration, washed with water and dried, yielding 477.5 g. (98%), m.p. 317–321°. The analytical sample was obtained by crystallization from ethanol–chloroform, m.p. 318–321°, $[\alpha]D$ −2.4°; λ_{max}^{KBr} 5.74(s), 6.08(w) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$: C, 71.42; H, 9.30; N, 2.87. Found: C, 71.27; H, 9.15; N, 3.11.

3β-Acetoxy-12a-aza-C-homo-5α,22a-spirostan-12-one (IV).—Hecogenin acetate oxime (477 g.) and 380 g. (2 moles) of *p*-toluenesulfonyl chloride were dissolved in 4 liters of pyridine and the solution heated at 95–105° for three hours. The solution was cooled to 40°, 50 ml. of water added to decompose excess *p*-toluenesulfonyl chloride and the reaction mixture poured into excess cold 6 *N* hydrochloric acid. The product was removed by filtration, washed with water and dried. Crystallization from aqueous ethanol gave irregular plates, 272.5 g., m.p. 224–234°. The material isolated from the mother liquor was chromatographed on silica gel. Elution with 50% ethyl acetate–benzene and subsequent crystallization from aqueous ethanol gave an additional 88.4 g., m.p. 228–234°, for a total yield of 360.9 g. (74%). Recrystallization from aqueous ethanol gave the analytical sample, m.p. 231–234°, $[\alpha]D$ −70°; λ_{max}^{MeOH} 201.5 mμ, ε 7350; λ_{max}^{KBr} 5.75(s), 6.05(s) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$: C, 71.42; H, 9.30; N, 2.87. Found: C, 71.38; H, 9.25; N, 2.89.

3β-Hydroxy-12a-aza-C-homo-5α,22a-spirostan-12-one (VIII).—The above acetate (69 g., 0.14 mole) in 500 ml. of methanol was treated with 39 g. (0.7 mole) of potassium hydroxide in 200 ml. of 80% methanol. The solution was allowed to stand at room temperature for three hours, acetic

(18) We are indebted to Robert T. Dillon and his associates for analyses and determinations of physical properties. Analytical samples were dried under high vacuum at 118° for one hour. Melting points are uncorrected. Rotations were determined at 25 ± 3° and at a concentration of 1% in $CHCl_3$. Infrared spectra were run at 0.5% in a KBr disk.

acid added to neutrality, and the product precipitated in quantitative yield with 500 ml. of water. The material melted over the range 145–215° and was used directly for oxidation.

12a-Aza-C-homo-5α,22a-spirostane-3,12-dione (IX).—The total crude alcohol (0.14 mole) was dissolved in 500 ml. of 90% acetic acid and the solution cooled to 6°. Chromic oxide (14.0 g., 50% excess) in 100 ml. of 90% acetic acid was added dropwise with good stirring so that the temperature remained below 10°. The solution was allowed to stand at room temperature for three hours, diluted with water and the product isolated by chloroform extraction. The residue was crystallized from aqueous ethanol to give 54.6 g. (88%), m.p. 224–231°, in two crops. Recrystallization from aqueous ethanol yielded transparent blades, m.p. 234–236°; $[\alpha]D$ −55°; λ_{max}^{KBr} 5.82(s), 6.02(s) μ.

Anal. Calcd. for $C_{27}H_{41}O_4N$: C, 73.09; H, 9.32; N, 3.16. Found: C, 73.01; H, 8.96; N, 3.01.

3β-Acetoxy-5α,22a-spirost-9(11)-en-12-one (V).—Selenous acid (7.7 g., 0.06 mole) was dissolved in 150 ml. of *t*-butyl alcohol and 15 ml. of acetic acid. Hecogenin acetate (9.5 g., 0.02 mole) was added and the mixture stirred and heated under reflux for 66 hours. The solvents were distilled, the residue taken up in benzene and chromatographed on silica gel. Elution with 5% ethyl acetate–benzene and crystallization from aqueous ethanol gave long needles, 3.4 g. (36%), m.p. 215–216° (lit.[13] 218–220°), $[\alpha]D$ −0.1°; λ_{max}^{MeOH} 238 mμ, ε 13,200; λ_{max}^{KBr} 5.73(s), 5.96(s), 6.27(m) μ.

3β-Acetoxy-5α,22a-spirost-9(11)-en-12-one Oxime (VI).—The above acetate (1.9 g., 0.004 mole) was converted to the oxime by heating under reflux for two hours with 0.6 g. (0.008 mole) of hydroxylamine hydrochloride in 40 ml. of pyridine. The crude product on crystallization from aqueous ethanol yielded 1.7 g. (87%) of thin plates, m.p. 282–284°, $[\alpha]D$ +36°; λ_{max}^{MeOH} 238 mμ, ε 13,600; λ_{max}^{KBr} 5.77(s), 6.20(w) μ.

Anal. Calcd. for $C_{29}H_{43}O_5N$: C, 71.72; H, 8.93; N, 2.88. Found: C, 71.32; H, 8.44; N, 3.13.

3β-Acetoxy-12a-aza-C-homo-5α,22a-spirost-9(11)-en-12-one (VII).—Oxime VI (0.9 g.) and 0.7 g. (approx. 2 molar equivalents) of *p*-toluenesulfonyl chloride were dissolved in 10 ml. of pyridine and allowed to stand at room temperature for 21 hours. Water was added, the product extracted with chloroform and the residue chromatographed on silica gel. Elution with 30% ethyl acetate–benzene and crystallization from aqueous ethanol yielded feathery clusters, 0.45 g. (50%), m.p. 225–231°. Recrystallization from aqueous ethanol gave irregular prisms, m.p. 228–231°, $[\alpha]D$ −72°; λ_{max}^{MeOH} 220 mμ, ε 15,800; λ_{max}^{KBr} 5.75(s), 6.03(s), 6.21(m) μ.

Anal. Calcd. for $C_{29}H_{43}O_5N$: C, 71.72; H, 8.93; N, 2.88. Found: C, 71.32; H, 8.95; N, 3.00.

Reduction.—The lactam VII (0.24 g.) in 15 ml. of acetic acid was hydrogenated over 0.10 g. of Adams platinum catalyst at atmospheric pressure and room temperature for 5 hours. Catalyst was removed by filtration, the filtrate diluted with water, extracted with chloroform and the residue from the chloroform precipitated from aqueous ethanol. The crude product, 0.19 g., was chromatographed on silica gel.[9] The material eluted with 30% ethyl acetate–benzene was crystallized from aqueous ethanol and yielded 0.084 g. of irregular plates, m.p. 230–233°. The melting point was not depressed on admixture with authentic 3β-acetoxy-12a-aza-C-homo-5α-22a-spirostan-12-one, and the infrared spectra of the two samples were identical.

SKOKIE, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Syntheses of Pyrrocolines Unsubstituted in the Five-membered Ring[1]

BY V. BOEKELHEIDE AND R. J. WINDGASSEN, JR.[2]

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New methods for the synthesis of pyrrocolines having no substituents in the five-membered ring are presented. An unusually simple synthesis for pyrrocoline itself is described.

For the synthesis of cycl[3,2,2]azine described in an accompanying paper,[3] it was necessary to prepare 5-methylpyrrocoline (III). Unfortunately, the Chichibabin reaction,[4] which is the standard method, fails in the case of pyrrocolines bearing no substituents in the five-membered ring. For this reason new methods for the synthesis of pyrrocolines were investigated and it is the purpose of the present paper to report these findings.

The original synthesis of pyrrocoline by Scholtz[5] involved heating α-picoline with acetic anhydride to form "picolide" which, on hydrolysis, gave pyrrocoline. Even though the yields by this procedure are very low, it has persisted as a method of choice for preparing pyrrocoline itself and it seemed desirable in the present instance to subject 2,6-lutidine to the Scholtz procedure in order to obtain an authentic sample of 5-methylpyrrocoline. When 2,6-lutidine and acetic anhydride were heated at 215° in a sealed tube, two products were formed. The first of these was the expected 1,3-diacetyl-5-methylpyrrocoline (I) and the second was a monoacetyl derivative, presumably II. Acidic hydrolysis of II, as is usual for 1- or 3-acetylpyrrocolines, removed the acetyl group and gave the desired 5-methylpyrrocoline (III).

The assignment of structure II to the monoacetyl derivative is based on the further observation that treatment of 5-methylpyrrocoline with acetic anhydride gave a new monoacetyl derivative. Since simple alkylpyrrocolines are known to undergo acetylation at the 3-position,[6] the structure of this product has been assumed by analogy to be IV. Therefore, the monoacetyl derivative from the Scholtz reaction must be 1-acetyl-5-methylpyrrocoline (II). It is of interest that the mechanism proposed by Chichibabin and Stepanow[7] to explain the Scholtz reaction would require II as an intermediate in the formation of the diacetyl derivative I.

Recently, it was reported that the pyrolysis of 1-(2′-pyridyl)-1,3-diacetoxypropane provided a con-

(1) Supported in part by the Office of Ordnance Research, Army Ordnance Contract No. DA-30-115-O.R.D.-723.

(2) National Science Foundation Predoctoral Fellow, 1956–1958.

(3) R. J. Windgassen, Jr., W. H. Saunders, Jr., and V. Boekelheide, THIS JOURNAL, **81**, 1459 (1959).

(4) A. E. Chichibabin, *Ber.*, **60**, 1607 (1927).

(5) M. Scholtz, *ibid.*, **45**, 734 (1912); *cf.* E. T. Borrows and D. O. Holland, *Chem. Revs.*, **42**, 611 (1948), for a summary of the earlier methods.

(6) E. T. Borrows, D. D. Holland and J. Kenyon, *J. Chem. Soc.*, 1083 (1946).

(7) A. E. Chichibabin and E. N. Stepanow, *Ber.*, **62**, 1068 (1929).