[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. XXXII.[1] Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 5). Δ^8-7-Ketones

BY CARL DJERASSI,[2a] O. MANCERA, M. VELASCO, GILBERT STORK[2b] AND G. ROSENKRANZ

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A method is described for the utilization of Δ^8-7-ketones of both the *allo* and *normal* configuration for the partial synthesis of 11-oxygenated steroids. This involves conversion to the enol acetate followed by treatment with monoperphthalic or perbenzoic acid to yield directly the corresponding 3-monoacylated Δ^8-7-one-11α-ol, which is convertible by several pathways into 11-ketosteroids.

Earlier described methods for the introduction of the important C-11 oxygen function into steroids devoid of functional groups in ring C all employed as starting material a $\Delta^{7,9(11)}$-diene which was transformed by various oxidative procedures into a Δ^8-7,11-dione,[3] a Δ^8-7,11-diol[4] or a 9α,11α-oxido-7-one.[5] All of these intermediates are convertible to 11-ketosteroids suitable for the synthesis of cortisone and related adrenal hormones.

As pointed out in a recent Communication to the Editor,[6] the utilization of Δ^8-7-ketones (*e.g.*, I and VII) for the partial synthesis of 11-oxygenated steroids is highly desirable, since such ketones are formed as by-products[3a,6] and sometimes major constituents[3b] in the oxidation of $\Delta^{7,9(11)}$-dien-3-ols of both the *allo* and normal configuration. The present paper records one such useful procedure for converting Δ^8-7-ketones into 11-oxygenated steroids.

Δ^8-Allopregnen-3β-ol-7,20-dione acetate (I),[6] a by-product in the performic acid oxidation of $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate[7] appeared to be a suitable starting material for this purpose. One obvious approach was to transform the Δ^8-7-ketone into the corresponding enol acetate, which most likely would possess the $\Delta^{7,9(11)}$-diene structure II, and then employ some oxidative means for the introduction of the C-11 oxygen function. The conventional acetic anhydride–*p*-toluenesulfonic acid procedure[8] was unsuitable since 20-ketosteroids react under such conditions,[9] but it was found subsequently that isopropenyl acetate[10] in benzene solution[11] smoothly converted the Δ^8-7-ketone (I) (λ_{max}^{EtOH} 252 mμ) into the oily enol acetate II (λ_{max}^{EtOH} 241 mμ)[12] without affecting the 20-keto moiety. When II was treated in ether solution with a slight excess of monoperphthalic acid, there crystallized directly from the solution over a period of two days over 70% of Δ^8-allopregnene-3β,11α-diol-7,20-dione 3-monoacetate (IVa), whose structure was proved by the spectral data (λ_{max}^{EtOH} 252 mμ, $\lambda_{max}^{CHCl_3}$ 1728 cm.$^{-1}$ (acetate band) 1700 cm.$^{-1}$ (20-ketone) and 1670 cm.$^{-1}$ (α,β-unsaturated ketone)[13] as well as free hydroxyl band), and by acetylation to the known[6] diacetate IVb. The direct formation of a 3-monoacylated 3,11-diol is particularly desirable since it permits interconversion by two alternate paths with intermediates employed earlier[3,4] for the synthesis of 11-ketosteroids. Direct oxidation with chromium trioxide or preferably sodium dichromate dihydrate in benzene–acetic acid[14] led to the yellowish Δ^8-allopregnen-3β-ol-7,11,20-trione acetate (V) with the typical[3,4] ultraviolet absorption maximum at 268 mμ, while catalytic hydrogenation of IVa followed by oxidation afforded the saturated trione VIc. That the enol acetate–peracid method is also applicable to normal steroids was demonstrated with methyl Δ^8-3α-hydroxy-7-ketocholenate (VIIa),[3b] formed in 63% yield by performic acid oxidation of methyl $\Delta^{7,9(11)}$-3α-hydroxycholadienate, giving methyl Δ^8-3α-acetoxy-7-keto-11α-hydroxycholenate (VIIIa) further characterized by its diacetate VIIIb. Dichromate oxidation[14] of VIIIa readily yielded the known methyl Δ^8-3α-acetoxy-7,11-diketocholenate (IX), which has already been converted[3a] into 11-ketolithocholic acid, an intermediate in the synthesis of cortisone.

Regarding the mechanism of the direct formation of IV from the enol acetate II, it seems quite likely that the equivalent of positively charged hydroxyl ion[15] attacks initially the unhindered 11α-position producing the carbonium ion IIIa. Species such as IIIb undoubtedly contribute appreciably to the resulting resonance hybrid and may lead to the unsaturated ketol IV (or VIII) directly with the possible formation of the mixed anhydride of phthalic and acetic acids. The fact that only small

(1) Paper XXXI (Part 4), J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2918 (1952).

(2) Present addresses: (a) Department of Chemistry, Wayne University, Detroit, Michigan; (b) Department of Chemistry, Harvard University, Cambridge, Mass.

(3) (a) L. F. Fieser, J. E. Herz and W. Huang, THIS JOURNAL, **73**, 2397 (1951); (b) L. F. Fieser, J. C. Babcock, J. E. Herz, W. Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951).

(4) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951). The identical procedure has subsequently been reported by H. Heusser and co-workers (*Helv. Chim. Acta*, **34**, 2106 (1951)).

(5) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951).

(6) C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951).

(7) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(8) P. Z. Bedoukian, THIS JOURNAL, **67**, 1430 (1945).

(9) C. W. Marshall, T. H. Kritchevsky, S. Lieberman and T. F. Gallagher, *ibid.*, **70**, 1837 (1948).

(10) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

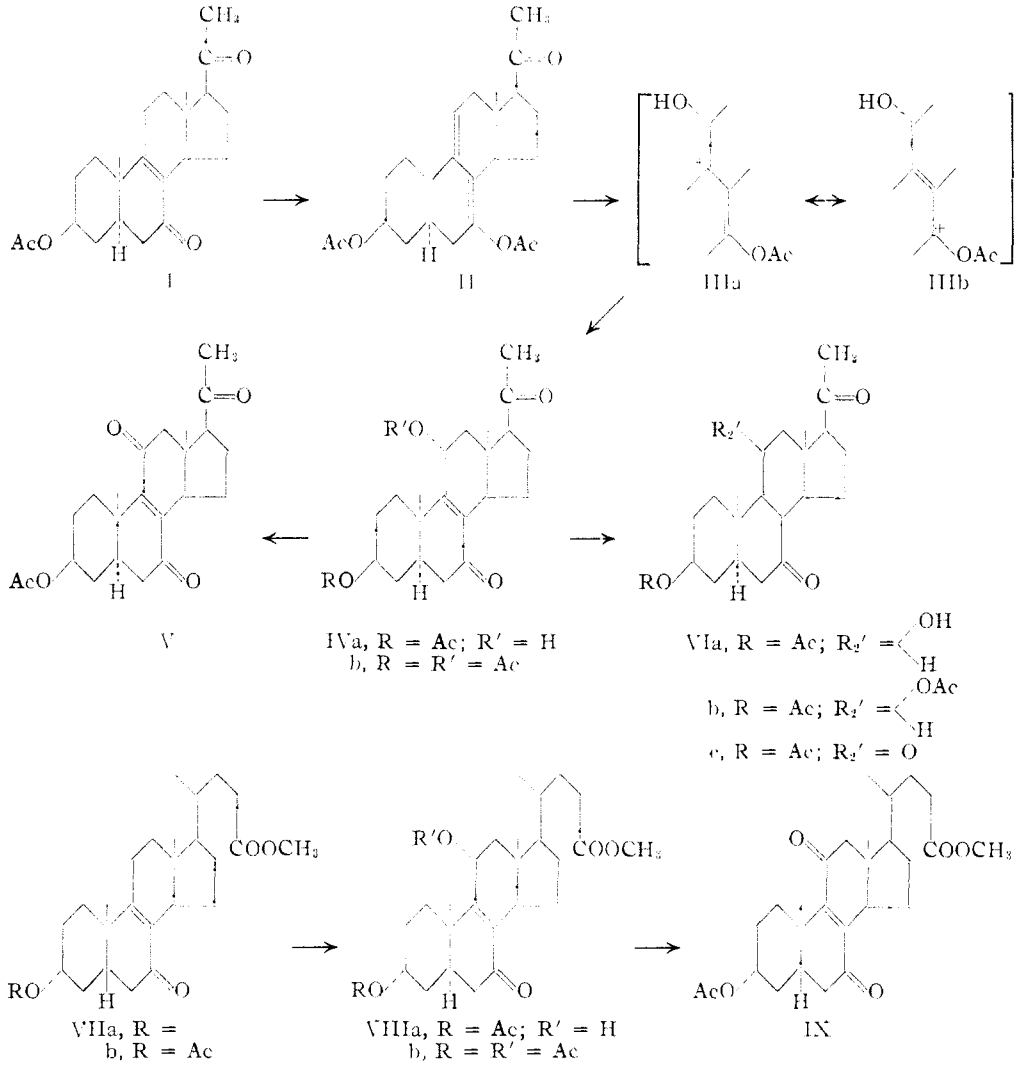
(11) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, THIS JOURNAL, **74**, 2810 (1952); R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952) have shown that in the absence of a solvent, 20-ketosteroids yield the $\Delta^{20(21)}$-enol acetate.

(12) The ultraviolet absorption maximum is in accordance with this formulation (II), since $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one possesses λ_{max}^{EtOH} 236 and 242 mμ (ref. 7) and the acetoxy substituent should not have any effect on the position of the maximum (*cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 188).

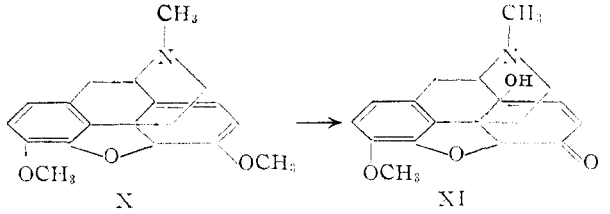
(13) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950).

(14) L. F. Fieser, *ibid.*, **73**, 5007 (1951).

(15) *Cf.* D. Swern, *Chem. Revs.*, **45**, **48** (1949), for leading references.



amounts of phthalic acid (the usual product of the reaction of monoperphthalic acid with an olefin) were isolated affords some substantiation of the above hypothesis. An analogous process may be involved in the conversion of thebaine (X) to 14-hydroxycodeinone (XI) by peracetic acid.[16]



Experimental[17]

Δ^5-Allopregnene-3β,11α-diol-7,20-dione 3-Monoacetate (IVa).—A mixture of 0.5 g. of Δ^5-allopregnen-3β-ol-7,20-dione acetate (I),[6] 0.075 g. of *p*-toluenesulfonic acid monohydrate, 2 cc. of redistilled isopropenyl acetate and 25 cc. of benzene was slowly concentrated to approximately one-half its volume over a period of 4.5 hours by distillation through a short Vigreux column. Additional 1-cc. portions of isopropenyl acetate were added after the second and third hour. The solution was evaporated to near dryness *in vacuo*, the residue was taken up in ether containing two drops of pyridine and washed well with sodium bicarbonate solution and water, dried and evaporated. The resulting yellowish oily enol acetate II (λ_{max}^{EtOH} 241 mμ, log ϵ 4.17),[13] which showed no tendency to crystallize, was dissolved in 5 cc. of ether and treated at room temperature with 3.2 cc. of an ethereal solution of monoperphthalic acid containing 0.071 g. per cc. After two days practically all the peracid had been consumed and the crystalline precipitate which had formed was collected and washed with cold ether; yield 0.37 g. (71%), m.p. 188–191°. Several recrystallizations from hexane–acetone afforded the analytical sample with m.p. 192–194°, $[\alpha]^{20}D$ +14°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.12, $\lambda_{max}^{CHCl_3}$ 1728 cm.$^{-1}$ (acetate), 1700 cm.$^{-1}$ (20-ketone), 1670 cm.$^{-1}$ (α,β-unsaturated ketone)[13] and free hydroxyl band. The yield was reduced to about 60% in large scale experiments and it was advantageous to wash the crude product with hot water in order to remove small amounts of phthalic acid.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.29; H, 8.39.

The diacetate IVb was prepared in the usual manner (acetic anhydride–pyridine) and after recrystallization from hexane–acetone exhibited m.p. 216–218°, $[\alpha]^{20}D$ +52°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.09, same carbonyl bands in the infrared as IVa but no free hydroxyl band. The substance proved to be identical (mixed m.p., infrared spectrum) with an authentic specimen[6] obtained from 9α,11α-oxidoallopregnan-3β-ol-7,20-dione acetate.

(16) M. Freund and E. Speyer, *J. prakt. Chem.*, **94**, 135 (1916).

(17) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform solution. We are greatly indebted to Srta. Paquita Revaque and staff for the rotation, ultraviolet and infrared (Perkin–Elmer single beam spectrometer model 12 C with sodium chloride prism) measurements and to Srta. Amparo Barba and assistants for the microanalyses.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.49; H, 7.92.

Δ^8-Allopregnen-3β-ol-7,11,20-trione Acetate (V).—A solution of 0.3 g. of the monoacetate IVa in 10 cc. of acetic acid was oxidized at room temperature for 2 hours with 0.15 g. of chromium trioxide in 5 cc. of 90% acetic acid. Dilution with water, filtration and purification of the precipitate by passage through a short column of alumina followed by recrystallization from hexane–benzene yielded 0.16 g. of the yellowish trione V with m.p. 171–173°, $[\alpha]^{20}D$ +50°, λ_{max}^{EtOH} 268 mμ, log ϵ 3.88.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.63; H, 8.06.

The yield was raised to 70% when the oxidation was carried out with sodium dichromate[14] as described below for IX.

Allopregnane-3β,11α-diol-7,20-dione 3-Monoacetate (VIa).—A solution of 1.0 g. of the monoacetate IVa in 60 cc. of 95% ethanol was shaken for 2 hours with 100 mg. of pre-reduced 10% palladized charcoal catalyst (American Platinum Works, Newark, N. J.) in an atmosphere of hydrogen. Filtration of the catalyst, evaporation to dryness and recrystallization from hexane–acetone led to 0.88 g. of colorless plates with m.p. 184–186°, $[\alpha]^{20}D$ −10°, no selective absorption in the ultraviolet, λ_{max}^{nujol} 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.96; H, 8.85.

The diacetate VIb showed m.p. 155–157°, $[\alpha]^{20}D$ ±0°, $\lambda_{max}^{CS_2}$ 1736 cm.$^{-1}$ (acetate), 1718 cm.$^{-1}$ (7-ketone) and 1710 cm.$^{-1}$ (20-ketone)[13] but no free hydroxyl band. The infrared spectrum proved to be identical with that of an authentic specimen[6] prepared by an alternate procedure from 9α,11α-oxidoallopregnan-3β-ol-7,20-dione acetate.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.51; H, 8.53.

Allopregnan-3β-ol-7,11,20-trione Acetate (VIc).—The oxidation of the monoacetate VIa was carried out exactly as described for the unsaturated analog IVa and proceeded in 80% yield to the desired trione VIc with m.p. 209–211°, $[\alpha]^{20}D$ +20°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.25; H, 8.40.

Methyl Δ^8-3α-Acetoxy-7-keto-11α-hydroxycholenate (VIIIa).—Methyl Δ^8-3α-acetoxy-7-ketocholenate (VIIb)[3] (1.5 g.) was converted by the above described isopropenyl acetate procedure into its oily enol acetate (λ_{max}^{EtOH} 242 mμ, log ϵ 4.20, $\lambda_{max}^{CHCl_3}$ 1736 and 1728 cm.$^{-1}$ but no α,β-unsaturated carbonyl band), which was treated directly in chloroform solution at 5° with 1.2 moles of perbenzoic acid in the same solvent. The peracid consumption was practically complete after 72 hours at which time the solution was washed with sodium bicarbonate solution and water, dried and evaporated. Crystallization from methanol afforded 0.51 g. of colorless crystals with m.p. 170–172°, $[\alpha]^{20}D$ ± 0°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.06, λ_{max}^{nujol} 1736, 1720 and 168 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found C, 70.15; H, 8.55.

The yield was not improved when the reaction was carried out with monoperphthalic acid at room temperature or in the ice-box.

Acetylation with acetic anhydride–pyridine on the steam-bath followed by recrystallization from acetone yielded the **diacetate VIIIb** with m.p. 158–160°, $[\alpha]^{20}D$ +48°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.10, no free hydroxyl band in the infrared.

Anal. Calcd. for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 69.31; H, 8.55.

Methyl Δ^8-3α-Acetoxy-7,11-diketocholenate (IX).—A solution of 0.75 g. of the monoacetate VIIIa in 20 cc. of benzene was treated dropwise at 15° with 1.3 g. of sodium dichromate dihydrate in 20 cc. of glacial acetic acid and the mixture was let stand overnight. After dilution with water, extraction with ether, washing with sodium carbonate solution and water, the extract was dried, evaporated and crystallized from ether giving 0.53 g. of yellowish crystals of the unsaturated diketone IX with m.p. 119–120.5°, $[\alpha]^{20}D$ +36° (dioxane), λ_{max}^{EtOH} 270 mμ, log ϵ 3.94; reported,[3a] m.p. 115°, $[\alpha]^{20}D$ +36° (dioxane). A mixed melting point determination, kindly carried out by Prof. L. F. Fieser of Harvard University, confirmed the identity of the two specimens.

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 71.15; H, 8.41.

LAGUNA MAYRAN 413
MEXICO CITY 17, D. F.

[CONTRIBUTION NO. 246 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Esters of Basically Substituted 3-Pyridols with Physostigmine-like Activity[1]

BY ARTHUR STEMPEL AND JOHN A. AESCHLIMANN

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A series of twenty-four esters of 3-pyridol containing a basic substituent in the 2-position has been prepared in the form of the tertiary and quaternary salts. Several members of both series exhibit potent parasympathomimetic and anti-curare activity. The relationship of structure to activity is discussed.

Although physostigmine, the standard of natural parasympathomimetic drugs, is a monomethyl carbamyl ester of a phenolic tertiary amine, the first successful synthetic substitute, Prostigmin, owed its superiority to our finding that dimethylcarbamyl esters of phenolic *quaternary* ammonium compounds[2] combined pronounced parasympathomimetic action with stability. Salts of the corresponding weak tertiary bases exhibit comparatively low activity. Stedman[3] discovered the activity of monoalkylcarbamyl esters of quaternary phenols and synthesized Miotine which, like physostigmine, is a fairly strong tertiary base containing a monomethyl carbamyl group which is readily hydrolyzed in solution. This instability, along with its toxicity, prevents extensive use of physostigmine.

The preparation of quaternized carbamic esters of 3-pyridol exhibiting interesting anti-cholinesterase and parasympathomimetic activity has recently been reported from several laboratories.[4]

In a recent publication from this Laboratory,[5] the preparation of (3-hydroxy-2-pyridylmethyl)-

(1) Presented at XII International Congress of Pure and Applied Chemistry, New York, N. Y., Sept., 1951.

(2) (a) J. A. Aeschlimann and M. Reinert, *J. Pharm. Exp. Therap.*, **43**, 413 (1931); (b) J. A. Aeschlimann and A. Stempel, Barell Jubilee Vol., 306 (1946).

(3) (a) E. Stedman, *Biochem. J.*, **20**, 719 (1926); (b) A. C. White and E. Stedman, *J. Pharm. Exp. Therap.*, **41**, 259 (1931).

(4) (a) Hoffmann-La Roche A. G., Swiss Patents 246,834, 246,836, 252,486 (1947); (b) H. M. Wuest and E. H. Sakall, THIS JOURNAL, **73**, 1210 (1951); (c) R. D. Haworth, A. H. Lamberton and D. W. Woodcock, *J. Chem. Soc.*, 182 (1947).

(5) A. Stempel and E. C. Buzzi, THIS JOURNAL, **71**, 2969 (1949).