pendently and there is little or no interaction between them.

Terminal *gem*-dinitro compounds are ionized in alkali, in water aqueous solvents, alcohols, and ordinary acetonitrile. The ions give rise to new, highly intense absorption bands near 380 mμ.[1] In carefully dried acetonitrile the new bands disappear and in dried alcohols the ionization is sufficiently small so that it may be neglected in determining the molar absorptivities of the unionized molecules at 280 mμ.

In inactive solvents the wave lengths as well as the molar absorptivities of the 280 mμ bands in dinitroparaffins decrease with an increase in polarity or dielectric constant; *e.g.*, the blue shift of the maxima (in each case) for cyclohexane → hydrochloric acid is of the order of 4 mμ and the hypochromic shift about 10 units of molar absorptivity. The transition therefore may be classified, as in the case of simple nitroparaffins, as a *blue-shift* band.[9]

Active solvents cause only a slight increase in the molar absorptivities of 2,3-dimethyl-2,3-dinitrobutane but have very pronounced effects in increasing the absorptivities of *gem*-dinitro compounds. In the latter cases the 280 mμ band is completely submerged, possibly because of a simultaneous blue shift of the band (Fig. 1). Regrettably, solvent absorption in the active solvents imposes considerable limitations on measurements in the short wave length region.

In all cases examined, the molar absorptivities of the maxima increase with molecular weight as was observed for the monofunctional compounds.

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

Steroids. LXXXVI.[1] Synthesis of Monofunctional 11-Ketones

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Syntheses of the four monofunctional 11-keto steroids, androstan-11-one (IVa), testan-11-one (IVb), allopregnan-11-one (VIa) and pregnan-11-one (VIb) are described.

In this paper the synthesis of the four monofunctional steroidal 11-ketones—androstan-11-one (IVa), testan-11-one (IVb), allopregnan-11-one (VIa) and pregnan-11-one (VIb)—are described. The first[3] and the last[4] of these have been prepared previously in milligram quantities, whereas the other two are new. This project was undertaken at the request of Dr. Samuel Hall of the U.S. Public Health Service, Bethesda, Md.

For the preparation of androstan-11-one (IVa), we employed allopregnane-17α,21-diol-3,11,20-trione 21-acetate (Ia) as starting material, a substance readily prepared by the hydrogenation of cortisone acetate.[5] Saponification of the acetate Ia produced the diol IIa, which on side-chain degradation by the excellent Rigby-Norymberski sodium bismuthate method[6] smoothly yielded androstane-3,11,17-trione (IIIa). This route to the triketone compares very faborably as regards yield and availability of starting materials with those described previously.[3,7] Finally, reduction of IIIa by the Huang-Minlon modification of the Wolff-Kishner procedure[8] without employing specially dried hydrazine furnished a mixture of androstane and androstan-11-one (IVa), from which the latter was separated in *ca.* 30% yield by chromatography. Although it has been shown that under particular experimental conditions the Huang-Minlon reduction may result in the removal of the 11-keto group,[9] it has generally been assumed that the usual conditions[8] do not affect this function. The structure of the 11-ketone IVa was confirmed by the elemental analysis (one oxygen function) by the infrared spectrum (six-membered ketone) and by the close agreement in melting point with the sample prepared by Steiger and Reichstein[3] from androstane-3,11,17-trione (IIIa) by reduction to androstane-3β,17β-diol-11-one by means of hydro-

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(8) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(9) R. B. Moffett and J. H. Hunter, *J. Am. Chem. Soc.*, **73**, 1973 (1951); D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

gen and Raney nickel, followed by dehydration *via* the xanthate and hydrogenation. It is interesting to note that this route was chosen, since direct Clemmensen reduction of the triketone IIIa, followed by hydrogenation and reoxidation, had yielded androstan-17-one (in addition to much androstane)[10] instead of androstan-11-one.

For the preparation of testan-11-one (IVb), pregnane-17α,21-diol-3,11,20-trione 21-acetate (Ib), an intermediate in the commercial synthesis of cortisone,[11] was saponified and degraded by the Rigby-Norymberski procedure[6] to testane-3,11,17-trione (IIIb). As in the allo series, this route to the normal triketone is an improvement over those described previously.[12] Huang-Minlon reduction of IIIb then produced testan-11-one (IVb) in *ca.* 65% yield.

11α-Hydroxyprogesterone, readily prepared by the microbiological oxidation of progesterone,[13] served as the starting material for the synthesis of both allopregnan-11-one (VIa) and pregnan-11-one (VIb). While chromic acid oxidation[14] followed by hydrogenation[15] produced allopregnane-3,11,20-trione (Va), the reversal of these two steps, hydrogenation followed by oxidation,[16] yielded pregnane-3,11,20-trione (Vb). The two triketones on being subjected to the Huang-Minlon modification of the Wolff-Kishner reduction[8] furnished the required allopregnan-11-one (VIa) and pregnan-11-one (VIb), respectively. The last mentioned substance agreed well in properties with the compound obtained in somewhat poorer yield from pregnane-3,11,20-trione by desulfurization of the 3,20-dicycloethylenemercaptal.[4]

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(11) *Cf.* G. Rosenkranz and F. Sondheimer, *Progr. Chem. Org. Nat. Prod.*, **10**, 274 (1953); C. Djerassi, *Vitamins and Hormones*, **11**, 205 (1953).

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(15) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(16) D. H. Peterson, A. H. Nathan, P. D. Meister, S. H. Eppstein, H. C. Murray, A. Weintraub, L. M. Reineke, and H. M. Leigh, *J. Am. Chem. Soc.*, **75**, 419 (1953); O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

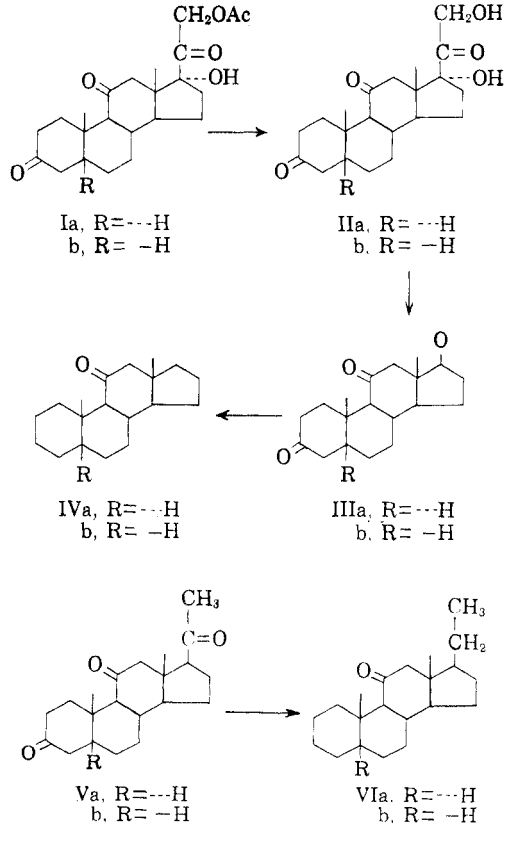
(17) Melting points are uncorrected. Rotations were determined at 20° in chloroform solution. Infrared spectra were also measured in this solvent, on a Perkin-Elmer Model 12 C single beam spectrophotometer with sodium chloride prism. Thanks are due to Miss M. T. Cárdenas for these measurements and to Mrs. A. González for the microanalyses.

EXPERIMENTAL[17]

Androstane-3,11,17-trione (IIIa). A solution of 2.2 g. of potassium hydroxide[18] in 20 cc. of water was added to a suspension of 19 g. of allopregnane-17α,21-diol-3,11,20-trione 21-acetate (Ia)[5] in 1 l. of methanol, the operation being conducted under nitrogen. The mixture was stirred at room temperature for 90 min. (complete solution occurred after *ca.* 30 min.) and 3 cc. of glacial acetic acid were then added. The solution was concentrated to 100 cc. under reduced pressure, 400 cc. of water were added gradually, the mixture was cooled in ice and the resulting precipitate was collected. This procedure furnished 14.64 g. (86%) of allopregnane-17α,21-diol-3,11,20-trione (IIa), m.p. 208–210°, $[\alpha]_D$ + 75°.

Sodium bismuthate (135 g.) was added to a stirred solution of 10 g. of the diol IIa in 340 cc. of glacial acetic acid and 340 cc. of water. The mixture was stirred for a further 30 min. at room temperature, water (1350 cc.) was added, the mixture was cooled to 0° and partially neutralized by the addition of 1400 cc. of 3*N* potassium hydroxide. The product was isolated by extraction with benzene and crystallized from acetone-ether. The resulting androstane-3,11,17-trione (IIIa) (6.23 g.; 75%) showed m.p. 178–180°, $[\alpha]_D$ + 158° (reported for a pure sample:[7] m.p. 180–181°, $[\alpha]_D$ + 155°).

Androstan-11-one (IVa). A mixture containing 6 g. of androstane-3,11,17-trione, 11 cc. of hydrazine hydrate, 7 g. of potassium hydroxide, 7 cc. of water, and 70 cc. of di-



(18) Less than one equivalent of base was sufficient, since the saponification proceeds by ester interchange (*cf.* H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 820 (1956), footnote 11).

ethylene glycol was heated under reflux for 45 min. The open flask was then heated until the temperature of the reaction mixture reached 200°, a reflux condenser was attached and refluxing was continued for a further 2 hrs. The solution was cooled, water was added, and the product was isolated with ether. The oily residue was chromatographed on alumina. Elution with hexane yielded first androstane and then androstan-11-one. The latter was purified most conveniently by pressing between filter paper; it weighed 1.62 g. (30%) and showed m.p. 45–47°, $[\alpha]_D$ + 65°. The analytical sample, obtained by high-vacuum distillation, showed m.p. 49–50°, $[\alpha]_D$ + 65°, ν_{max} 1700 cm.$^{-1}$ (reported:[3] m.p. 50–52°).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.26; H, 10.85.

Testane-3,11,17-trione (IIIb). The saponification of 10 g. of pregnane-17α,21-diol-3,11,20-trione 21-acetate (Ib) suspended in 400 cc. of methanol was carried out by means of 1 g. of potassium hydroxide[18] in 5 cc. of water, as described above in the allo series. Addition of 1.5 cc. of glacial acetic acid, concentration to 200 cc., addition of 800 cc. of water, and ice-cooling resulted in the precipitation of 7.91 g. (88%) of pregnane-17α,21-diol-3,11,20-trione (IIb), m.p. 231–232° (reported:[19] m.p. 233–235°). This material (7.5 g.), dissolved in 300 cc. of glacial acetic acid and 300 cc. of water, was oxidized with 100 g. of sodium bismuthate as described above. The product was isolated by benzene extraction and the dried solution was evaporated and chromatographed on alumina. Elution with benzene and crystallization from ether furnished 4.73 g. (76%) of testane-3,11,17-trione (IIIb), m.p. 130–132°, $[\alpha]_D$ + 144° (reported:[12] m.p. 132–133°, 135–136°, $[\alpha]_D$ + 148°).

Testan-11-one (IVb). Testane-3,11,17-trione (4 g.) was reduced with 8 cc. of hydrazine hydrate in 50 cc. of diethylene glycol in the presence of 5 g. of potassium hydroxide and 5 cc. of water, as described previously. The product was isolated with ether and chromatographed on alumina. Elution with hexane and crystallization from ether yielded 2.41 g. (66%) of testan-11-one, m.p. 118–121°, $[\alpha]_D$ + 54°. The analytical sample showed m.p. 121–122°, $[\alpha]_D$ + 55°, ν_{max} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.91; H, 10.78.

Allopregnan-11-one (VIa). Allopregnane-3,11,20-trione (Va) (4.5 g.)[15] was reduced with 8 cc. of hydrazine hydrate in 80 cc. of diethylene glycol together with 8 g. of potassium hydroxide in 8 cc. of water, as described above for the preparation of IVa. The cooled reaction mixture was diluted with water, the precipitate was collected, dried, and chromatographed on alumina. Elution with hexane and crystallization from ether-methanol led to 2.44 g. (59%) of allopregnan-11-one with m.p. 101–104°. The analytical sample exhibited m.p. 108–109.5°, $[\alpha]_D$ + 60°, ν_{max} 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.74; H, 11.33.

Pregnan-11-one (VIb). Pregnane-3,11,20-trione (Vb) (5 g.)[16] in 100 cc. of diethylene glycol was reduced with 10 cc. of hydrazine hydrate, 10 g. of potassium hydroxide, and 10 cc. of water, as described previously. The product was extracted with ether and chromatographed on alumina. Crystallization of the fractions eluted with hexane from ether-methanol yielded 1.91 g. (42%) of pregnan-11-one, m.p. 106–109°, $[\alpha]_D$ + 52°. A further purified specimen showed m.p. 111–113°, $[\alpha]_D$ + 54°, ν_{max} 1700 cm.$^{-1}$ (reported:[4] m.p. 112–114°, $[\alpha]_D$ + 56°).

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[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XII.[1] Stereoformulas of Tetrahydro-α-santonins[2]

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α, β, and γ-Tetrahydro-α-santonins were reassigned the stereoformulas III, VIII, and I on the basis of chemical evidence. Zinc-alcohol hydrogenation of the 5-dehydro-α-santoninic acid (VI, R = H) gave the Δ^1-3,5-diketo acid (VII, R = H), which was converted to santonic acid (XIV) with alkali. This offered strong support for the previously suggested mechanism of santonic acid formation from α-santonin (see ref. 15).

In the paper IV of this series,[3] it was described that α-santonin was catalytically hydrogenated to a mixture of three tetrahydro compounds, α, β, and γ, which are tentatively formulated as I, II, and III, respectively.

In these formulas, the configurations at the 5-, 6-, and 11-positions are the same as those in the α-santonin structure,[3] of which the former two were well established,[4,5] and the latter one remains obscure.[6] The assignment of the configurations at the juncture of two six-membered rings was based on molecular rotation differences, the relative reactivity toward bromine, and the mode of the preparations. However, these reasons for the formulations became questionable and revision of the above formulas seemed necessary on the following grounds.

(1) As shown in the paper VII of this series,[5]

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(2) This work was supported in part by the Grant in Aid for Scientific Research from the Ministry of Education of Japan.

(3) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(4) For example see R. B. Woodward and P. Yates, *Chemistry & Industry*, 1391 (1954).

(5) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956).

(6) Y. Abe, J. Miki, M. Sumi, and T. Toga, *Chemistry & Industry*, **1956**, 953.