[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

The Action of Zinc on the 20,21-Ketol Acetate Group of a Δ^{16}-Pregnene

BY WILLIAM R. NES AND HAROLD L. MASON

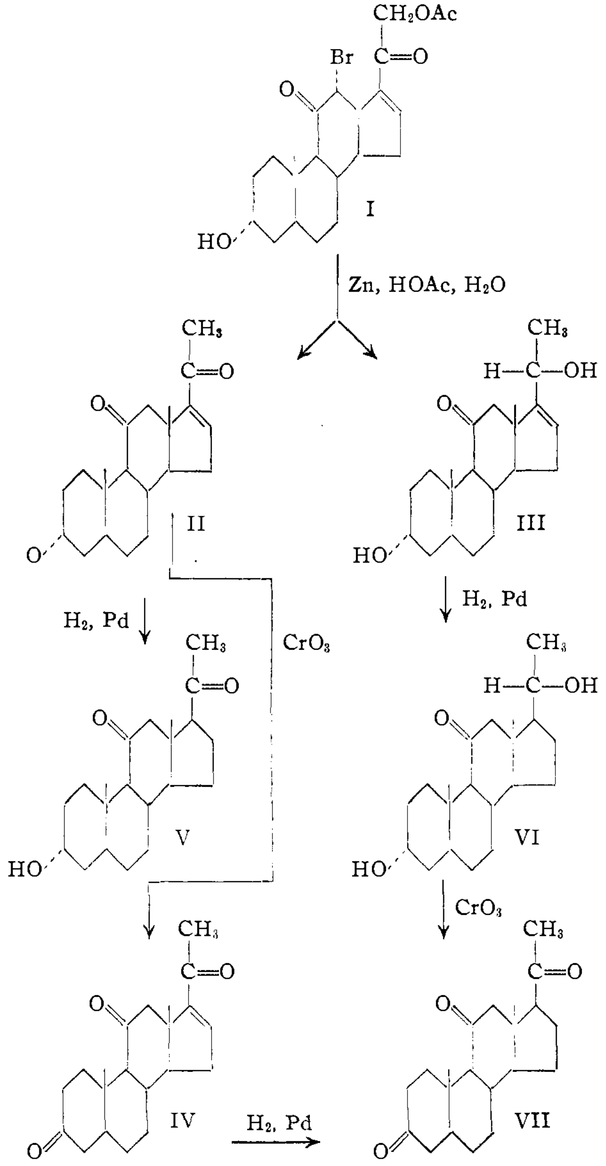
Zinc in the presence of acetic acid and water has been shown to cause reductive removal of the 21-acetoxy group of 3α-hydroxy-21-acetoxy-11,20-diketo-12α-bromo-Δ^{16}-pregnene (I) to yield 3α-hydroxy-11,20-diketo-Δ^{16}-pregnene (II); further action of the zinc reduced the carbonyl at C-20 yielding 3α,20α-dihydroxy-11-keto-Δ^{16}-pregnene (III). II was oxidized to give 3,11,20-triketo-Δ^{16}-pregnene (IV) which on hydrogenation was converted to the known 3,11,20-triketopregnane (VII). Hydrogenation of II afforded 3α-hydroxy-11,20-diketopregnane (V). Similarly III on hydrogenation was converted to 3α,20α-dihydroxy-11-ketopregnane (VI) which was oxidized to VII.

The reductive removal of halogen from the steroid nucleus has been accomplished in a number of cases by the action of zinc and acetic acid. In this manner 3α,21-diacetoxy-11,20-diketopregnane[1] and 11-dehydrocorticosterone acetate[2] have been prepared in excellent yields from the corresponding 12-bromo derivatives. In the case of the latter compound it is of interest to note that a yield of more than 90% was obtained even in the presence of both the α,β-unsaturated ketone in ring A and the ketol acetate side chain. It was, therefore, a considerable surprise to find that in the case of a closely related Δ^{16}-pregnene treatment with zinc and acetic acid caused modification of the 20,21-ketol acetate group in addition to dehalogenation.

When 3α-hydroxy-21-acetoxy-11,20-diketo-12α-bromo-Δ^{16}-pregnene (I) was treated as in the previous cases with zinc in benzene–acetic acid, it was difficult to obtain reproducible results. In all experiments only a small yield of the corresponding 12-methylene compound was obtained, although all of the bromine had been removed. The other products were unidentified. When treatment of I with zinc was carried out in aqueous acetic acid none of the expected 3α-hydroxy-21-acetoxy-11,20-diketo-Δ^{16}-pregnene was isolated, but instead 3α-hydroxy-11,20-diketo-Δ^{16}-pregnene (II) and 3α,20α-dihydroxy-11-keto-Δ^{16}-pregnene (III) were obtained. If treatment with zinc was limited to a few minutes, the principal product was II. After exposure to zinc for a longer period of time a good yield of III was obtained. This result indicates that the primary action of zinc was at C-21 with reductive *removal* of the acetoxyl group and that subsequently the action was at C-20 with reduction of the carbonyl to a carbinol group. It therefore appears that the double bond at position 16,17 activates the ketol acetate side chain.

The structure of compound II was shown by oxidation with chromium trioxide to give 3,11,20-triketo-Δ^{16}-pregnene (IV) and by hydrogenation catalyzed with palladium to give the known 3α-hydroxy-11,20-diketopregnane (V).[3] Hydrogenation of IV with palladium and hydrogen afforded 3,11,-20-triketopregnane (VII).[4]

The structure and configuration of III were proved by hydrogenation in the presence of palladium which gave 3α,20α-dihydroxy-11-ketopregnane (VI).[5,6] The hydroxyl group at C-20 in this isomer has been assigned the alpha configuration by Sarett.[6] This diol (VI) was oxidized to 3,11,20-triketopregnane (VII)[4] and the product proved to be identical with that prepared from the unsaturated ketone (IV).



Experimental

Micro-analyses were performed by Joseph F. Alicino. Melting points were determined with the Fisher–Johns electrically heated block and are reported as read. Optical rotations were taken in approximately 1% solutions and are accurate to ±2°. Methanol solutions were used for measurement of the ultraviolet absorption spectra. Nujol mulls

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[1] Unpublished work from this Laboratory.

[2] V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

[3] J. von Euw, A. Lardon and T. Reichstine, *Helv. Chim. Acta*, **27**, 821 (1944).

[4] P. Hegner and T. Reichstein, *ibid.*, **26**, 727 (1943).

[5] H. L. Mason, *J. Biol. Chem.*, **172**, 783 (1948).

[6] L. H. Sarett, THIS JOURNAL, **71**, 1165, 1175 (1949).

were used for determination of infrared spectra which were obtained with a Perkin–Elmer infrared spectrometer, Model 12-C.

3α-Hydroxy-11,20-diketo-Δ^{16}-pregnene (II).—In a solution of 30 ml. of acetic acid and 10 ml. of water, 3.065 g. of 3α-hydroxy-21-acetoxy-11,20-diketo-12α-bromo-Δ^{16}-pregnene (I) was stirred for ten minutes at 15° with 6 g. of zinc dust. The suspended material was removed by filtration, washed with methanol and the combined filtrates were evaporated under reduced pressure nearly to dryness. Addition of water precipitated material which weighed 1.9 g. Crystallization four times from methanol–water gave material which melted at 220–222°, $[\alpha]^{24^\circ}\mathrm{D}$ +91° ($CHCl_3$), $\lambda_{\max.}$ 235 mμ, ε 7,400. Ninety-eight per cent. of the theoretical amount of bromide ion was present in the aqueous phase.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.34; H, 9.15. Found: C, 76.10; H, 9.07.

When treatment with zinc was carried out at 15° for three minutes a 71% yield of II was obtained, m.p. 208–212°, $[\alpha]^{24^\circ}\mathrm{D}$ +87° ($CHCl_3$).

3α,20α-Dihydroxy-11-keto-Δ^{16}-pregnene (III).—The combined mother liquors from the preceding experiment (II from 3.065 g. of I) were concentrated under reduced pressure and yielded 800 mg. of crystalline solid. Recrystallization from ethyl acetate gave a product which melted at 183–185°, $[\alpha]^{24^\circ}\mathrm{D}$ +61° ($CHCl_3$).

When treatment with zinc was extended to 130 minutes at 30–38°, the yield of crude material, m.p. 178–180°, $[\alpha]^{24}\mathrm{D}$ +60° ($CHCl_3$), was 43%. Recrystallization several times from ethyl acetate raised the melting point to 189–190°, $[\alpha]^{24}\mathrm{D}$ +57° ($CHCl_3$). This compound did not have an absorption maximum between 225 and 250 mμ and did not show an acetate band in the infrared spectrum. It gave a negative α-ketol test with alkaline 2,3,5-triphenyltetrazolium chloride reagent and a positive test for unsaturation with tetranitromethane.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.72; H, 9.58.

3,11,20-Triketo-Δ^{16}-pregnene (IV).—To a solution of 990 mg. of 3α-hydroxy-11,20-diketo-Δ^{16}-pregnene in 4 ml. of chloroform and 1 ml. of acetic acid was added 0.33 ml. (130%) of 23.7 *N* aqueous chromic acid. After vigorous stirring for 15 minutes at 0°, 0.33 ml. of 18 *N* sulfuric acid was added and the mixture was stirred for one hour at 0°. Water and chloroform were added and the organic phase was washed with dilute hydrochloric acid, a 5% solution of sodium carbonate, and with water, dried and evaporated under reduced pressure. Crystallization from methanol afforded 446 mg. of product which melted at 196–198°. Addition of water to the methanol gave 306 mg. as a second crop, m.p. 180–185°. Recrystallization of the first crop from methanol raised the melting point to 205–210°, $[\alpha]^{24}\mathrm{D}$ +110° ($CHCl_3$); $\lambda_{\max.}$ 235 mμ, ε 8,900.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.80; H, 8.59. Found: C, 76.97; H, 8.57.

3α-Hydroxy-11,20-diketopregnane (V).—Hydrogenation of 500 mg. of 3α-hydroxy-11,20-diketo-Δ^{16}-pregnene was carried out in 10 ml. of methanol with 1.5 g. of 2% palladium hydroxide on calcium carbonate at room temperature and atmospheric pressure. After 11 minutes the catalyst was filtered out, the solution was concentrated under reduced pressure, the product was precipitated with water and recrystallized from ethyl acetate. The crystals, 220 mg., melted at 175–177°, $[\alpha]^{24}\mathrm{D}$ +114° ($CHCl_3$). The reported melting point is 172–174°.[3] The melting point was not depressed by admixture with an authentic sample of V. The infrared spectrum of this product was identical with that of a sample of V previously prepared in this Laboratory.

3α,20α-Dihydroxy-11-ketopregnane (VI).—In a solution of 5.0 ml. of methanol 280 mg. of 3α,20α-dihydroxy-11-keto-Δ^{16}-pregnene (III) was hydrogenated at room temperature and pressure in the presence of 506 mg. of 2% palladium hydroxide on calcium carbonate. After nine minutes the catalyst was filtered out, the filtrate was evaporated under reduced pressure, and the residue was crystallized from ether–petroleum ether. The compound [179 mg. (64%), m.p. 203–205°], after recrystallization from methanol–acetone, melted at 214–217°, $[\alpha]^{24}\mathrm{D}$ +63° (alcohol). The melting point of a mixture with an authentic sample of VI was 216–219°. The reported constants[5,6] are m.p. 217–219° and 219–221°, $[\alpha]^{27}\mathrm{D}$ +59° and $[\alpha]^{25}\mathrm{D}$ +61° (alcohol). The ether–petroleum ether filtrate yielded 61 mg. (22%) of needles melting at 171–172°. This material was not investigated further.

3,11,20-Triketopregnane (VII).—Hydrogenation of 100 mg. of 3,11,20-triketo-Δ^{16}-pregnene (IV) by the procedure given for the preparation of VI from III yielded 71 mg. of VII which was crystallized from ether–petroleum ether, m.p. 160–162°, $[\alpha]^{24}\mathrm{D}$ +113° (acetone). The reported[4] melting point is 154–156°, $[\alpha]^{20}\mathrm{D}$ +119° (acetone).

3,11,20-Triketopregnane (VII).—Oxidation of 100 mg. of 3α,20α-dihydroxy-11-ketopregnane with 0.085 ml. of 23.7 *N* aqueous chromic acid and 0.07 ml. of 18 *N* sulfuric acid in chloroform–acetic acid yielded, after crystallization from ether, 67 mg. of VII, m.p. 160–161°, $[\alpha]^{24}\mathrm{D}$ +114° (acetone). The melting point was not depressed when this product was mixed with the sample of VII prepared from IV. The infrared spectra of the two preparations were identical.

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Dicyclic Hydrocarbons. III. Diphenyl- and Dicyclohexylalkanes through C_{15}

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The synthesis and properties including heats of combustion and viscosities are described for a series of dicyclic alkanes prepared in a purity of 99 mole % or higher. The series, starting with diphenylmethane, extends through the diphenylpropanes and comprises a total of fourteen hydrocarbons including the corresponding dicyclohexylalkanes. Melting or freezing point values are reported for each member of the series, eight of these being indicated for the first time. Three new compounds, namely, 2-cyclohexyl-2-(cyclohexan-4-ol)-propane, 2-cyclohexyl-2-(cyclohexen-3-yl)-propane and 2-phenyl-2-cyclohexylpropane are also described.

Several classes of dicyclic hydrocarbons have been synthesized and purified at this Laboratory as part of a program concerned with investigating possible components of aviation fuel. The present paper describes all the diphenyl- and dicyclohexylalkanes from C_{13} through C_{15}; previously reported are some substituted alkylbiphenyls[1] and alkylbicyclohexyls.[2]

Although most of the hydrocarbons prepared in the present work are not new compounds, melting points and viscosities necessary for evaluating the usefulness of these materials as possible fuels, were generally not available. Also, lack of information concerning purity and the fact that the values of the boiling points, densities and refractive indices of many of these hydrocarbons were not in agreement[3,4] made it virtually impossible to distinguish

[1] I. A. Goodman and P. H. Wise, THIS JOURNAL, **72**, 3076 (1950).

[2] I. A. Goodman and P. H. Wise, *ibid.*, **73**, 850 (1951).

[3] G. Egloff, "Physical Constants of Hydrocarbons," Vol. II, Reinhold Publishing Corp., New York, N. Y., 1940.

[4] G. Egloff, *ibid.*, Vol. III, 1946.