that at *p*H 3.0, for example, the radius of the equivalent sphere is not more than 28% greater than its value at the isoelectric point. The estimated changes are smaller than those calculated by Tanford[8] from his titration data; he found a radial "swelling" of approximately 50% at *p*H 3.0.

Although unequivocal correlations cannot be made as yet between the calorimetric and sedimentation behavior of BSA in acid solutions, the endothermic reaction of BSA has been tentatively associated with the reversible configurational changes. The correlation between the exothermic reaction and the aggregation phenomenon is under investigation.

CONTRIBUTION NO. 1297
STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

The Conversion of Androstane-3,17-dione to Androsterone[1]

BY CARL DJERASSI, A. J. MANSON AND MARVIN GORMAN

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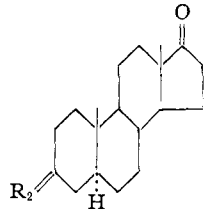
In spite of the fact that androsterone (II) was the first male sex hormone to be isolated and possesses a relatively simple structure, no short synthesis has been available for this steroid.[2] This in turn has prevented extensive clinical experiments with this substance, which many endocrinologists feel merits more attention. In connection with Raney nickel desulfurization experiments under way in this Laboratory, we have made certain ancillary observations which indicate that a facile synthesis of androsterone should be possible and these are being reported in the present note.

The only complicating feature of any androsterone synthesis is the formation of a 3α-alcohol of the 5α-series, which usually requires conditions (*e.g.*, platinum-catalyzed hydrogenation in an acid medium)[3] which also would reduce the 17-keto group unless protected.[2] It now has been observed that while androstane-3,17-dione (I) is reduced to a mixture of diols when refluxed with fresh W-2 Raney nickel[4] in ethanol solution, the 17-keto group is not affected by non-pyrophoric (old) Raney nickel catalyst. This same non-pyrophoric catalyst, however, was quite effective in reducing a saturated 3-keto function as demonstrated by the conversion of cholestan-3-one to a 2:1 mixture of cholestan-3α-ol and cholestan-3β-ol. A noteworthy feature of this reduction is the relatively high proportion of 3α-epimer formed, which suggested that a one-step conversion of androstane-3,17-dione (I), a commercial intermediate in the manufacture of estrone, to androsterone (II) should be feasible.

Indeed, when androstane-3,17-dione (I) was refluxed with non-pyrophoric Raney nickel catalyst, *i.e.*, W-2 catalyst which had been stored for a period of one to three months, nearly 50% of androsterone (II) was formed, together with 34% of the epimeric epiandrosterone (III). The two isomers could, of course, be separated quantitatively by means of digitonin, but chromatographic separation also proved feasible. No attempt was made to determine the optimum conditions for the synthesis of androsterone, but it was noted that "hydrogen-free" Raney nickel catalyst[5] was equally effective. In view of the fact that cholestan-3-one is not reducible[6] by *fresh* W-2 Raney nickel in benzene or acetone solution and yields chiefly cholestan-3β-ol when heated in ethanol solution, it appears that the formation of large amounts of the 3α-epimer with non-pyrophoric or hydrogen-free catalyst in ethanol must proceed by a different mechanism. A possible explanation is that the latter reduction involves a hydrogen transfer from ethanol to the ketone, in spite of the fact that this does not appear to be operative[7] in Raney nickel desulfurizations.



I, R_2 = O

II, R_2 = 

III, R_2 = 

Experimental[8]

Reduction of Cholestan-3-one with Non-pyrophoric W-2 Raney Nickel.—A solution of 600 mg. of cholestan-3-one in 75 cc. of absolute ethanol was refluxed with *ca.* 6 g. of W-2 Raney nickel[4] (1 month old) for 5 hours. After filtering and evaporating to dryness, 588 mg. of colorless solid was obtained, which by infrared spectroscopy (no infrared carbonyl band) was shown to consist of a mixture of the epimeric cholestan-3-ols. Chromatography on 24 g. of alumina and elution with benzene–ether (4:1) yielded 390 mg. of cholestan-3α-ol; after recrystallization from ethyl acetate, it exhibited m.p. 185–186°, $[\alpha]^{20}D$ +26° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 10.0 μ; **acetate**, m.p. 94–96°, $[\alpha]^{20}D$ +42° (EtOH). Further elution with the same solvent furnished 200 mg. of cholestan-3β-ol, m.p. 140–141°, $\lambda_{max}^{CHCl_3}$ 9.68 μ. Identity was established in each case by mixture melting point and infrared comparison with authentic samples.

When the reaction was repeated with fresh (one day old) W-2 catalyst, 83% of cholestan-3β-ol was formed.

Reduction of Androstane-3,17-dione with Non-pyrophoric W-2 Raney Nickel.—A solution of 500 mg. of androstane-3,17-dione was refluxed in 50 cc. of absolute ethanol with 5.0 g. of W-2 Raney nickel (identical results were obtained with catalyst of 1 and 3 months age) and the total reduction product passed through 18 g. of alumina. The bulk was eluted with benzene–ether (9:1) while 57 mg., representing a diol mixture ($\lambda_{max}^{CHCl_3}$ 2.8–3.0, 9.62 and 10.0 μ) was eluted with ether–methanol (9:1). The pooled benzene–ether eluates consisted of a mixture of androsterone (II) and epiandrosterone (III) as demonstrated by infrared examination ($\lambda_{max}^{CHCl_3}$ 5.76 (17-ketone), 9.62 (epiandrosterone) and 10.0 μ (androsterone)). Separation was achieved by means of digitonin,[9] the material being dissolved in 60 cc. of 90% ethanol and added to a solution of 2.28 g. of digitonin in 140 cc. of 90% ethanol. After 2 hours, the precipitate was filtered, washed with ethanol and ether and the

(1) We are indebted to the American Cancer Society on recommendation of the Committee on Growth of the National Research Council for a research grant.

(2) For the most recent synthesis and leading references see J. Iriarte, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955).

(3) *Cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, 3rd ed., p. 99.

(4) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

(5) H. Hauptmann and B. Wladislaw, THIS JOURNAL, **72**, 707 (1950).

(6) C. Djerassi, M. Gorman and J. A. Henry, *ibid.*, **77**, 4647 (1955).

(7) W. A. Bonner, *ibid.*, **74**, 1033 (1952); *cf.* M. L. Wolfrom and J. V. Karabinos, *ibid.*, **66**, 909 (1944).

(8) All melting points were determined on the Kofler block.

precipitate was decomposed by the pyridine procedure.[9] The digitonin precipitable fraction, **epiandrosterone** (III), weighed 168 mg., m.p. 169–175°, raised to 174–175° after one recrystallization from acetone, $\lambda_{max}^{CHCl_3}$ 5.76 and 9.62 μ. From the original digitonin filtrate after evaporation to dryness, there was isolated 240 mg. of **androsterone** (II), which after one recrystallization from acetone exhibited m.p. 184–186°, undepressed upon admixture with authentic androsterone (m.p. 184–185°, $[\alpha]_D$ +94.5° (EtOH)), $[\alpha]^{20}D$ +97° (EtOH), $\lambda_{max}^{CHCl_3}$ 5.76 and 10.0 μ. **Androsterone acetate** showed m.p. 165–166°, $[\alpha]^{20}D$ +87° (EtOH).

Hydrogen-free W-2 Raney nickel catalyst[5] gave essentially the same proportion of epiandrosterone (III) (34%) and androsterone (II) (42%). Androstan-17-one was not reduced by non-pyrophoric Raney nickel, but when androstane-3,17-dione (I) was treated under the above conditions with fresh (pyrophoric) W-2 Raney nickel catalyst, infrared examination demonstrated that both carbonyl groups had been reduced completely.

(9) *Cf.* G. C. Butler and G. F. Marrian, *J. Biol. Chem.*, **124**, 237 (1938).

DEPARTMENT OF CHEMISTRY
WAYNE UNIVERSITY
DETROIT, MICHIGAN

The Course of the Acylation of 2,6-Lutidine in the Presence of Phenyllithium

BY NEWTON N. GOLDBERG AND ROBERT LEVINE

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In earlier reports from other[1] and these laboratories[2,3] the following scheme has been suggested for the base-effected acylation of the methylated tar bases, 2-picoline, 4-picoline, quinaldine and 2,6-lutidine, with esters.

$$CH_3Z + MR \longrightarrow RH + MCH_2Z \quad (1)$$

$$MCH_2Z + RCO_2R' \longrightarrow R'OM + RCOCH_2Z \quad (2)$$

$$RCOCH_2Z + MCH_2Z \longrightarrow (RCOCHZ)^-M^+ + CH_3Z \quad (3)$$

or

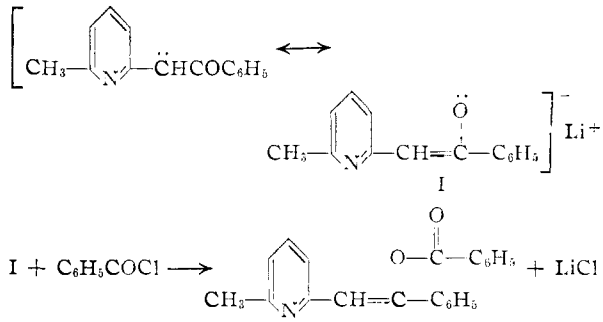
$$RCOCH_2Z + MR \longrightarrow (RCOCHZ)^-M^+ + RH \quad (4)$$

Z = 2-pyridyl, 4-pyridyl, 2-quinolyl or 6-methyl-2-pyridyl radical

MR = $NaNH_2$, KNH_2 or C_6H_5Li

In support of this scheme it has been shown[2] that the interaction of molar equivalents of phenyllithium, 2-picoline and ethyl benzoate gave a 58% yield of 2-phenacylpyridine (based on the assumption that the third step indicated above occurs). When this reaction was repeated except that a 2:2:1 molar ratio of reactants was used, the yield of ketone was increased to 80%.

More convincing evidence for the existence of an anion in step three would be available if it were possible to isolate a diacylated tar base by adding an extremely reactive acylating agent, *e.g.*, an acid chloride, to a mixture of the tar base, phenyllithium and ester which had been allowed to react for the customary reaction time. Therefore, benzoyl chloride was added to a mixture of phenyllithium, 2,6-lutidine and methyl benzoate. From this reaction there was isolated a mixture of 2-phenacyl-6-methylpyridine (67%), the lithium salt of 2-phenacyl-6-methylpyridine (18%) and the enol benzoate of 2-phenacyl-6-methylpyridine (11%). The isolation of both the lithium salt of 2-phenacyl-6-methylpyridine and the enol ester of 2-phenacyl-6-methylpyridine indicates that 2-phenacyl-6-methylpyridine exists as an anion in the reaction mixture.



It is interesting to note that when the last reaction was effected in the absence of benzoyl chloride a 94.5% yield of 2-phenacyl-6-methylpyridine[3] and none of the enol benzoate were obtained. It should be noted also that Wibaut and co-workers[4,5] have treated 2,6-lutidyllithium (prepared from 2,6-lutidine and phenyllithium) with benzoic anhydride and obtained only the enol benzoate. These results indicate that the anion of 2-phenacyl-6-methylpyridine is a stronger base than the chloride and benzoate ions but a weaker base than methoxide ion.

It was also of interest to determine whether the reaction of phenyllithium with 2-phenacyl-6-methylpyridine would give the corresponding tertiary alcohol. However, carbinol formation did not occur. Instead, because of the apparent high acidity of the ketone, an acid–base reaction occurred in preference to addition to the carbonyl group to give the lithium derivative of the ketone, which on treatment with benzoyl chloride gave a mixture of 2-phenacyl-6-methylpyridine (5–6%), the lithium salt of 2-phenacyl-6-methylpyridine (46–46.5%) and the enol benzoate of 2-phenacyl-6-methylpyridine (45–47%).

Experimental

Reaction of 2,6-Lutidine with Phenyllithium and Methyl Benzoate Followed by the Addition of Benzoyl Chloride.—2,6-Lutidine (21.4 g., 0.2 mole) was added to an ether solution of phenyllithium (0.2 mole) and this was followed by the addition of methyl benzoate (0.1 mole, 13.6 g.). The mixture was refluxed for 30 minutes. Then benzoyl chloride (14.1 g., 0.1 mole), dissolved in 50 ml. of anhydrous ether, was added and the mixture refluxed for two hours and then processed as described in the following experiment to give 14.1 g. (66.8%) of 2-phenacyl-6-methylpyridine, b.p. 143–145° at 1.0 mm.; picrate,[3] m.p. 180–181°; 3.4 g. (10.8%) of the enol benzoate of 2-phenacyl-6-methylpyridine, m.p. 137–138°, and 3.9 g. (18.0%) of the lithium salt of 2-phenacyl-6-methylpyridine.

When the reaction was repeated except that the mixture was refluxed for 16 hours after the benzoyl chloride was added, there were obtained 5.3–6.8 g. (25.1–32.8%) of 2-phenacyl-6-methylpyridine, 11.8–12.8 g. (37.5–40.6%) of the enol benzoate and 3.4–4.6 g. (13.8–21.2%) of the lithium salt.

Reaction of 2-Phenacyl-6-methylpyridine, Phenyllithium and Benzoyl Chloride.—2-Phenacyl-6-methylpyridine (21.1 g., 0.1 mole), dissolved in 50 ml. of anhydrous ether, was added to an ether solution of phenyllithium (0.1 mole) prepared as described earlier.[2] Then benzoyl chloride (14.1 g., 0.1 mole), dissolved in 50 ml. of anhydrous ether, was added dropwise. The mixture was refluxed for two hours and then poured onto 300 g. of crushed ice and 100 ml. of water. A yellow solid precipitated from the basic solution and was

(1) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2023 (1949).

(2) N. N. Goldberg, L. B. Barkley and R. Levine, *ibid.*, **73**, 4301 (1951).

(3) N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

(4) C. C. Kloppenburg and J. P. Wibaut, *Rec. trav. chim.*, **65**, 393 (1946).

(5) J. I. de Jong and J. P. Wibaut, *ibid.*, **70**, 962 (1951).