TABLE I

PEROXIDE INFLUENCED REACTION OF AMINES WITH CARBONYL SULFIDE[a]

Amine Used	Peroxide Used	Solvent Used	Time (hours)	Temp., °C.	Product	Yield, %
Aniline	H_2O_2	H_2O	24	25	1,3-Diphenylurea	70
	CH[b]	CH_3OH	72	5		80[c]
	DPB[d]	CH_3OH	24	25		0
p-Methoxyaniline	H_2O_2	H_2O	72	25	1,3-Di-*p*-methoxyphenylurea	88
p-Chloroaniline	H_2O_2	H_2O	72	25	1,3-Di-*p*-chlorophenylurea	14
p-Nitroaniline	H_2O_2	H_2O	72	25	No product	0
	H_2O_2	CH_3OH	120	25		0
	CH[b]	CH_3OH	120	25		0
Benzylamine	CH[b]	CH_3OH	96	5	1,3-Dibenzylurea	89
	H_2O_2	H_2O	24	25		75
n-Hexylamine	H_2O_2	H_2O	48	25[f]	1,3-Di-*n*-hexylurea	66
n-Decylamine	H_2O_2	H_2O/CH_3OH	48	5	1,3-Di-*n*-decylurea	76
2-Aminoethanol	CH[b]	CH_3OH	96	25	2-Oxazolidinone	23
Ethylenediamine	H_2O_2	H_2O	120	25	2-Imidazolidinone	6
1,2-Propanediamine	H_2O_2	H_2O	120	25	4-Methyl-2-imidazolidinone	94
p-Aminophenol	H_2O_2	CH_3OH	24	5	1,3-Di-*p*-hydroxyphenylurea	32
2,4,6-Trichloroaniline	H_2O_2	CH_3OH	96	25	No product	0
o-Phenylenediamine[e]	H_2O_2	CH_3OH	96	25	2-Benzimidazolol	82
2-Aminodiphenyl	H_2O_2	CH_3OH	96	25	No product	0
1-Naphthylamine	CH[b]	CH_3OH	96	25	1,3-Di-1-naphthylurea	42
2-Naphthylamine	H_2O_2	H_2O	96	25	1,3-Di-2-naphthylurea	17
	CH[b]	CH_3OH	96	25		92
o-Aminophenol	CH[b]	CH_3OH	96	25	2-Benzoxazolol	89

[a] All these reactions were run essentially as described for the formation of 1,3-diphenylurea for the aromatic amines and 1,3-dibenzylurea for the aliphatic amines. The products were identified by comparison with separately synthesized authentic specimens. [b] Cumene hydroperoxide. [c] Yield in this case based on the addition of a sodium methoxide in a molar equivalent quantity to the amine. Without the sodium methoxide, the yield after 96 hours was only 46%. [d] Dibenzoyl peroxide. [e] Reference 1 reports a 29% yield of benzimidazolone-2 by heating *o*-phenylenediamine with carbonyl sulfide at 225° for 11 hours. [f] When this reaction was run at 5° the yield of 1,3-di-*n*-hexylurea was only 43%.

peroxide, or oxygen at 150° a 27–30% yield, based on the aniline used, of methyl phenylcarbamate was isolated. Magnesium peroxide failed to induce reaction. If the urethan arises from methanolysis of 1,3-diphenylurea, then the yields are good. However, this same reaction in benzene, using di-*tert*-butyl peroxide, afforded only a 33% yield of 1,3-diphenylurea.

EXPERIMENTAL

1,3-Diphenylurea. A suspension of 9.3 g. of aniline in 150 ml. of water containing 10 ml. of 30% hydrogen peroxide was prepared in a 2-l. heavy walled suction flask. The flask was evacuated and carbonyl sulfide then was introduced until a reading of 5 lbs. was retained on the cylinder gauge; a snug fitting rubber stopper was sufficient to hold this pressure. The inlet tube was clamped and the reaction mixture permitted to stand for 24 hours at room temperature. The solid material which deposited was collected and dried; yield 9.0 g.; m.p. 231–232°.

To remove the accompanying sulfur, the product was suspended for two minutes in a boiling solution prepared from 7 g. of sodium sulfide and 7 g. of sodium hydroxide in 50 ml. of H_2O. After cooling and filtering, the product was washed with 100 ml. of cold water; yield 7.5 g. (70%); m.p. 235–236° alone and when mixed with an authentic analytical sample. After concentration and oxidation of the original filtrate, there was obtained another 0.1 g. of sulfur in the form of sulfate.

1,3-Dibenzylurea. A solution of 10.7 g. of benzylamine in 150 ml. of methanol, containing 15.2 g. of cumene hydroperoxide in a 2-l. flask was charged with 5 lb. of carbonyl sulfide as described above and maintained at 5° for 96 hours. Upon collecting and recrystallizing from benzene there was obtained 10.7 g. (89%) of 1,3-dibenzylurea; m.p. 170–171° alone and mixed with an authentic specimen.

Methyl phenylcarbamate. A 1-l. Magne Dash Autoclave was charged with 9.3 g. of aniline, 15 g. of zinc peroxide, 150 ml. of methanol, and 25 lbs. of carbonyl sulfide. The mixture was stirred and heated to 150° for five hours. The reaction mixture was cooled and filtered, the filtrate evaporated to an oily residue, and the residue taken up in benzene. The benzene layer was first extracted twice with dilute aqueous hydrochloric acid, then treated with Norit and filtered, and finally evaporated to dryness; yield 5.1 g. (33%); m.p. 49–50°. Recrystallization from Skelly B provided white needles, m.p. 50–51° alone and when mixed with the authentic material.

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The Direct Conversion of Steroidal Δ^5-3β-Alcohols to Δ^5- and Δ^4-3-Ketones

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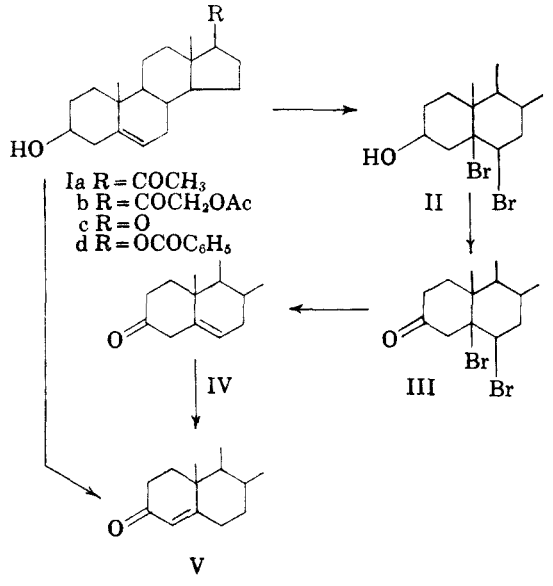
The conversion of a Δ^5-3β-alcohol (I) to the corresponding Δ^4-3-ketone (V) is an extremely important reaction in steroid chemistry and represents

the last step in the commercial synthesis of a variety of hormones.[1] Originally,[1] this was carried out by a three-step sequence involving protection of the double bond by bromination (II), chromium trioxide oxidation to the dibromo ketone III, and finally debromination with zinc in acetic acid. That this reaction proceeded *via* the Δ^5-3-ketone (IV) was demonstrated by the actual isolation[2] of this intermediate when the debromination of III was conducted in a neutral medium. The method of choice, both in the laboratory and on an industrial scale, for the elaboration of the Δ^4-3-keto grouping has been the Oppenauer oxidation[3] which yields the α,β-unsaturated ketone V in one step although the reaction presumably also involves the initial formation of the β,γ-unsaturated ketone IV which is isomerized immediately in the basic medium.



We have recently been interested for biological reasons in the synthesis of various steroidal Δ^5-3-ketones (IV) and it seemed of interest to examine whether such compounds could not be prepared by direct oxidation of Δ^5-3-alcohols (I) without protection of the double bond by bromination. The feasibility of such an approach was indicated by the observation of Fieser[4] that Δ^5-cholesten-3-one could be isolated in poor yield by sodium dichromate oxidation of cholesterol.

Our attention centered on an oxidation procedure which was originally developed by Jones and collaborators[5] for the oxidation of acetylenic carbinols and which has subsequently been employed by the Manchester group for the oxidation of a variety of unsaturated steroidal[6] and triterpenoid[7] alcohols. The procedure involves titration of the alcohol in acetone solution with a standard chromium trioxide–sulfuric acid reagent and the novel feature is represented by the acetone solvent which affects markedly the properties of this oxidation reagent. The reaction is nearly instantaneous and the yields are high. In all of the steroids which had been investigated previously,[6] the double bond was far removed from the alcohol to be oxidized and it remained to be determined whether this procedure was also applicable to alcohols with the unusually reactive 5–6 double bond.

As described in the experimental section, the reaction proceeded smoothly and in spite of the presence of acid in the reagent, it was possible to isolate in good yield the Δ^5-3-ketone (IV) uncontaminated by the Δ^4-3-ketone (V). There seems little doubt that the chromium trioxide–acetone oxidation of steroidal Δ^5-3-alcohols represents the method of choice for the synthesis of Δ^5-3-ketones (IV). If the α,β-unsaturated ketone V is desired, it is only necessary to subject IV to brief isomerization conditions (see experimental) whereupon the conjugated ketone can be obtained in 70–80% overall yield (based on I). Typical procedures for the synthesis of progesterone (Va), desoxycorticosterone acetate (Vb), and testosterone benzoate (Vd) are given in the experimental portion.

EXPERIMENTAL[8]

Δ^5-Pregnene-3,20-dione (IVa). To a cold (10–15°) solution of 3.0 g. of Δ^5-pregnen-3β-ol-20-one (Ia)[9] in 400 cc. of acetone (distilled from permanganate) was added rapidly with stirring from a burette 2.75 cc. of standard chromium trioxide reagent.[10] Nitrogen gas was bubbled[11] through all the solvents, reagents and reaction solution before and during the oxidation. After 2–5 minutes, the reaction mixture was diluted with 2 l. of water and the precipitate was filtered and washed well with water; yield, 2.67 g., m.p. 138–147°,

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

(2) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936). *Cf.* L. F. Fieser, *Org. Syntheses*, **35**, 43 (1955).

(3) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937). For a review see C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

(4) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4377 (1953).

(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(6) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, 2402 (1951).

(7) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); T. G. Halsall, R. Hodges, and E. R. H. Jones, *J. Chem. Soc.*, 3019 (1953).

(8) Melting points were determined on a Fisher-Johns apparatus. All rotations were measured in chloroform solution. We are grateful to Mrs. Dolores Phillips for the ultraviolet (95% ethanol solution) and infrared measurements and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses.

(9) We are indebted to Syntex, S. A., Mexico City for a gift of this material.

(10) A solution of 26.72 g. of chromium trioxide in 23 cc. of conc'd sulfuric acid diluted with water to a volume of 100 cc. was used throughout. Reduction of the sulfuric acid concentration to 5 or 10% led to inferior yields.

(11) This was done to prevent any atmospheric oxidation since it has been reported that Δ^5-3-ketones can yield hydroperoxides [L. F. Fieser, T. W. Greene, F. Bischoff, G. Lopez, and J. J. Rupp, *J. Am. Chem. Soc.*, **77**, 3928 (1955)].

$[\alpha]_D^{22}$ +68°, λ_{max}^{CHCl} 5.85 μ (no bands in the hydroxyl or 6 μ region), log ϵ 2.67 at 240 mμ, developing to a maximum at 240 mμ, log ϵ 4.2 after the addition of one drop of 10% potassium hydroxide solution. The physical constants[12] were changed only slightly after recrystallization from ethyl acetate (slight warming in nitrogen atmosphere and rapid cooling in Dry Ice): m.p. 139–148°, log ϵ 2.57 at 240 mμ, $[\alpha]_D^{23}$ +60°.

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.75; H, 9.67.

Progesterone (Va). The oxidation of 3.0 g. of Δ^5-pregnen-3β-ol-20-one (Ia) was repeated as described above but the total, crude oxidation product was dissolved in warm methanol, 3 drops of 10% potassium hydroxide was added, and the solution was heated on the steam-bath for 5 minutes and then neutralized with acetic acid. The crude product, m.p. 113–131°, $[\alpha]_D$ +182° had an infrared spectrum nearly indistinguishable from that of progesterone, but it still contained a small amount of pregnenolone. This was removed by chromatography whereupon 2.31 g. of progesterone, m.p. 121–123°, was obtained after recrystallization from methanol. The later eluates furnished 280 mg. of impure starting alcohol (m.p. 175–185°), raised to 183–186° after several recrystallizations.

Δ^5-Pregnene-3,20-dione-21-ol acetate (IVb). The oxidation of 3.0 g. of 21-acetoxypregnenolone (Ib)[9] was carried out as above to yield 2.69 g. of crude ketone, m.p. 115–126°. Recrystallization from acetone (solution with slight warming, concentration and allowing crystallization to proceed to 4° in an atmosphere of nitrogen) afforded 2.39 g. of long prisms of the acetone solvate showing m.p. 123–137°, $[\alpha]_D^{26}$ +66°, log ϵ 2.65 at 240 mμ (λ_{max} 240 mμ, log ϵ 4.2 after addition of KOH), no evidence of conjugated ketone by infrared examination. The physical constants were not changed by further recrystallization and the absence of any desoxycorticosterone acetate impurity (Vb) was also confirmed by biological assay.[13]

Anal. Calc'd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Calc'd for $C_{23}H_{32}O_4 \cdot C_3H_6O$: C, 72.52; H, 8.90. Found (after drying at room temperature): C, 72.49; H, 8.79; (after drying at 80° and 0.01 mm.), C, 74.01; H, 8.53.

The direct preparation of desoxycorticosterone acetate (Vb) was carried out as described above for progesterone (Va) except that the crude isomerization product was first reacetylated at C-21; yield, 75%, m.p. 156–157.5°, infrared spectrum identical with that of authentic material.

Δ^5-Androstene-3,17-dione (IVc). The oxidation of dehydroepiandrosterone (Ic)[9] proceeded in 76% yield and the resulting Δ^5-androstene-3,17-dione (IVc) (recrystallized from acetone) exhibited m.p. 119–125° (with softening at 115°; clear melt on heating above 125°), log ϵ 2.48 at 240 mμ (λ_{max} 240 mμ, log ϵ 4.15 after addition of KOH), $[\alpha]_D^{26}$ +42°, $\lambda_{max}^{CHCl_3}$ 5.72 and 5.82 μ.[14]

Anal. Calc'd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.35; H, 9.01.

Δ^5-Androsten-17β-ol-3-one benzoate (IVd). The oxidation of Δ^5-androstene-3β,17β-diol 17-monobenzoate (Id) furnished after recrystallization from acetone nearly 80% of IVd with m.p. 142–148°, $[\alpha]_D^{26}$ +41° (chloroform), $[\alpha]_D^{27}$ +27° (benzene),[15] no evidence for presence of testosterone benzoate (Vd) by either infrared examination or rotatory dispersion.[16]

Anal. Calc'd for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.21; H, 8.10

Testosterone benzoate (IVd). The crude oxidation product from 400 mg. of Δ^5-androstene-3β,17β-diol 17-benzoate (Id) was dissolved in hot methanol, 2 cc. of 10% sulfuric acid was added, and the solution was heated and concentrated over a period of 15 minutes. The product was extracted with ether, chromatographed on Merck acid-washed alumina, and recrystallized from ether whereupon 320 mg. of testosterone benzoate (Vd), m.p. 193–194.5° was obtained; identity was established in the usual manner by infrared means.

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(12) U. Westphal and J. Schmidt-Thomé, *Ber.*, **69**, 889 (1936) prepared this substance in 40% yield by the bromination sequence (Ia → IIa → IIIa → IVa) and report m.p. 158–160°, $[\alpha]_D$ +65.5° but give no spectral data. All of our melting points for Δ^5-3-ketones have been broader, even if the substance was prepared by this alternate scheme and this may be due to thermal rearrangement to the Δ^4-3-ketone. Westphal and Schmidt-Thomé observed an increased dextrorotation when their sample was heated and it has been our experience that the best criteria are the rotation (nearly 130° more negative) and the spectral properties.

(13) Results to be published by Dr. R. I. Dorfman, Worcester Foundation for Experimental Biology.

(14) A. Butenandt and J. Schmidt-Thomé (*Ber.*, 69, 882 (1936) report a 24% yield of product of m.p. 158° with sintering from 140°; no other physical constants are given. We have repeated their preparation and observed the following constants: m.p. 118–127° (with sintering from 112° resolidification at 130° and slow melting from 140–160°), $[\alpha]_D^{26}$ +50° log ϵ 2.85 at 240 mμ, infrared spectrum virtually identical with that of the specimen prepared by the chromium trioxide–acetone oxidation of Ic. It should be noted that wide melting point ranges have also been observed with other Δ^5-3-ketones of the androstane series [*cf.* ref. 15 and A. Butenandt and G. Hanisch, *Ber.*, 69, 2773 (1936)].

(15) L. Ruzicka, M. W. Goldberg and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937) report m.p. 170–180°, $[\alpha]_D$ +23° (benzene) for a sample prepared by the standard bromination-oxidation-debromination route.

(16) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).