Reduction of Steroid Ketones and other Carbonyl Compounds by Modified Wolff–Kishner Method

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According to Dutcher and Wintersteiner[2] the reduction of C_3-steroid ketones by the Wolff–Kishner method under usual conditions gives mainly the corresponding C_3-epimeric carbinols with small amounts of the expected C_3-methylenic products. In the case of the α,β-unsaturated ketone, cholestenone, the reduction follows a still more complex course. In addition to the epimeric unsaturated carbinols and a small amount of the normal product, Δ^4-cholestene, the saturated carbinols, α-coprosterol and β-cholestanol have also been isolated. The authors stated that the abnormal reduction can be explained by the assumption that the hydrazone or semicarbazone is partially hydrolyzed to free ketone, which is then reduced by sodium alcoholate to give the secondary alcohol. These possibilities are, however, eliminated by the modified Wolff–Kishner reduction,[3,4] in which the water is evaporated during the heating period. Moreover, the excess of hydrazine hydrate used in this reaction should keep the concentration of the regenerated ketone at a low level.[2] In fact all the C_3-steroid ketones so far investigated gave the normal C_3-methylenic compounds by the modified Wolff–Kishner reduction. The formation of carbinols has never been observed. This reaction proceeds also normally on keto groups at other positions, C_7, C_{12}, C_{17} and C_{20}, except at C_{11}, which remains unattacked. Thus, 3-hydroxy-11-keto-etiocholanic acid is unreduced. 3,α-Acetoxy-11,-

20-diketopregnane (I) gave a reduced product melting at 152–153° in which one of the two keto groups is unattacked. In view of the fact that the 20-keto compounds, such as Δ^5-pregnen-3(β)-ol-20-one (IV) and its hydrogenation product, allopregnan-3(β)-ol-20-one (VI) can be transferred to Δ^5-pregnan-3(β)-ol (V) and 3,β-hydroxyallo-pregnane (VII), respectively, the reduced product from I may be formulated as 3,α-hydroxy-11-ketopregnane (III). Δ^5-Pregnen-3(β)-ol (V), which has not previously been reported, is transferred to the known compound, allopregnan-3(β)-ol (VII) by catalytic hydrogenation. From the reaction products of 3,α-acetoxy-11,20-diketo-12-bromopregnane (II) two isomeric compounds could be isolated, one of which melts at 152–153° and is identical with III and the other melts at 109°. Both give the same analytical result, but the latter is more dextrorotatory and its structure is under investigation.
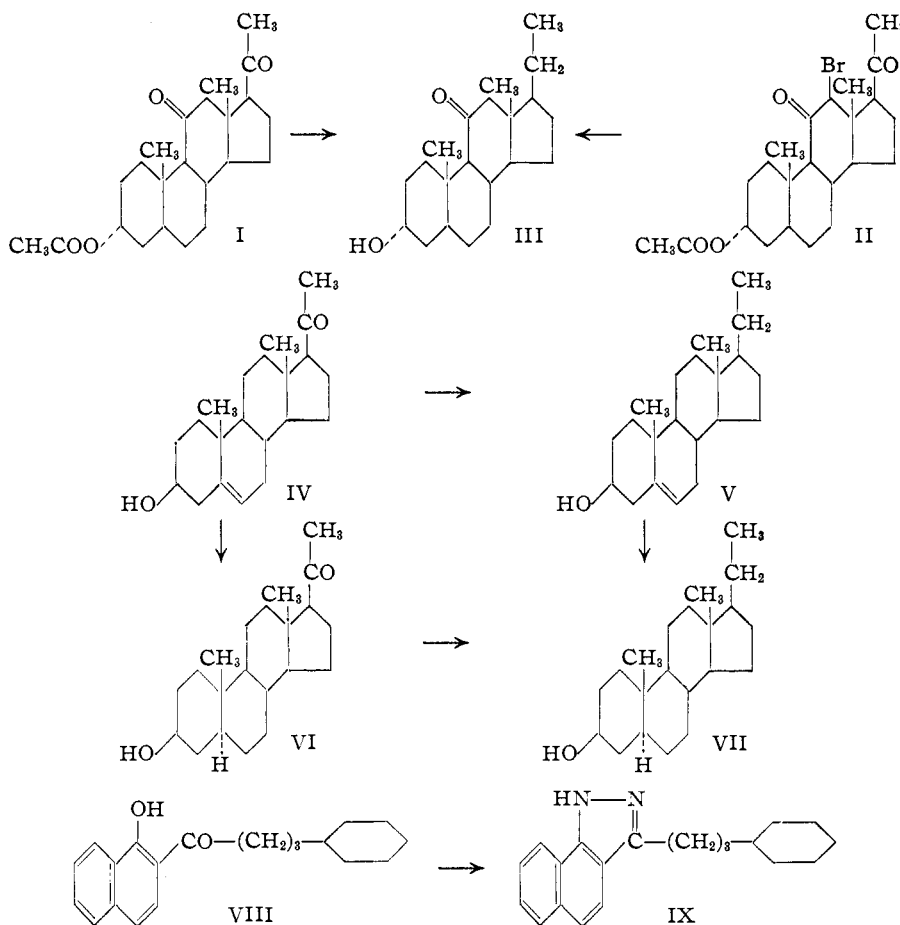
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(2) Dutcher and Wintersteiner, THIS JOURNAL, 61, 1992 (1939).

(3) Huang-Minlon, ibid., 68, 2487 (1946).

(4) Huang-Minlon, ibid., 70, 2802 (1948).

TABLE I

Compound	Product	M. p., °C.	Recryst. from	Yield, %	$[\alpha]^{25}D$	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Estrone	3-Hydroxy-1,3,5-estratriene[a]	134–134.5	Dil. alc.	79.2	+89 (in alc.)	$C_{18}H_{24}O$	84.31	84.50	9.46	9.44
Dehydroepian-drosterone	Δ^5-Androsten-3(β)-ol[b]	132–133	Ethyl acetate	71.5	−47° (alc.)	$C_{19}H_{30}O$	83.13	83.28	11.01	11.07
Δ^5-Pregnen-3(β)-ol-20-one	Δ^5-Pregnen-3(β)-ol	133–134	Methanol	79.5	−46° (alc.)	$C_{21}H_{34}O$	83.39	83.52	11.33	11.02
	Acetyl derivative	147–148	Methanol			$C_{23}H_{36}O_2$	80.18	80.28	10.53	10.45
Allopregnan-3(β)-ol-20-one[c]	Allopregnan-3(β)-ol[d]	136–137	Methanol	84.7	+18 (CHCl₃)	$C_{21}H_{36}O$	82.83	82.82	11.92	11.79
	Acetyl derivative	115–116	Acetone		−61° (CHCl₃)					
Androstandione	Androstane[e]	48–49	Dil. acetone	83.3	+1° (CHCl₃)	$C_{19}H_{32}$	87.75	87.83	12.25	12.28
Testosterone	Δ^4-Androsten-17-ol (Desoxytestosterone)[f]	152–153	Petroleum ether	55.2	+47° (alc.)	$C_{19}H_{30}O$	83.13	83.16	11.01	11.03
	Acetyl derivative	98–100	Dil. methanol							
Cholestanone	Cholestane[g]	79–80	Ether–alc.	83.4	+24.8° (CHCl₃)					
Cholestenone	4-Cholestene	77–78	Acetone–alc.	61.4	+64.0° (CHCl₃)	$C_{27}H_{46}$	87.47	87.28	12.53	12.69
3α-Acetoxy-11,20-diketo-pregnane	3α-Hydroxy-11-ketopregnane	153–153.5	Dil. CH₃OH	70.5	+79.6° (CHCl₃)	$C_{21}H_{34}O_2$	79.20	79.53	10.73	10.95
3α-Acetoxy-11,20-diketo-12-bromopregnane	3α-Hydroxy-11-ketopregnane	152–153	Dil. CH₃OH	40.0	+79.9° (CHCl₃)	$C_{21}H_{34}O_2$	79.20	79.48	10.73	10.41
	And its isomer	109[h]	Ether–methanol	2.4	+107.5° (CHCl₃)	$C_{21}H_{34}O_2$	79.20	79.66	10.73	10.44
Dehydrocholic acid	Cholanic acid	165–166[g]	Acetone	91.6						
Methyl 3-benz-oxy-12-ketocholanate	Lithocholic acid[i]	188–189[g]	Acetone	99.3	+34° (alc.)					
Ethyl 3,12-di-hydroxy-7-ketocholanate	Acetic choleic acid[j]	138–141[g]		62.3						
Vanillin	3,4-Dimethoxy-1-methylben-zene[k]	B. p. 133–135 (50 mm.)		77.3	$n^{25}D$ 1.5257					
Veratraldehyde	3,4-Dimethoxy-1-methylben-zene	B. p. 122–124 (27 mm.)		81	$n^{25}D$ 1.5259					
9-Anthraalde-hyde[l]	9-Methylanthra-cene[m]	80–81	CH₃OH	88		$C_{15}H_{12}$	93.74	93.81	6.25	6.16
α-Naphthalde-hyde semi-carbazone	1-Methylnaph-thalene	B. p. 125 (24 mm.)		71	($n^{25}D$ 1.6153) (picrate m. p. 141–142)					
Cinnamic alde-hyde	Propenylbenzene	B. p. 176–178 (755 mm.)		70	($n^{25}D$ 1.5464)					
Friedeline[n]	Friedelane[n]	244–245	CHCl₃ (alc.)	83	+42.5 (CHCl₃)	$C_{30}H_{52}$	87.30	87.25	12.70	12.80
Cerine[o]	Friedelane	243–244	CHCl₃ (alc.)	75.4	+42.0 (CHCl₃)	$C_{30}H_{52}$				
2-(γ-Cyclohexyl-butyro)-α-naphthol	3-(γ-cyclohexyl-propyl)-6,7-benzoindazole)	129–130	Alcohol	75		$C_{26}H_{34}N_2$	82.13	82.35	8.27	8.19

[a] Butenandt and Westphal, Z. physiol. Chem., **223**, 147 (1934).   [b] Butenandt and Suranyi, Ber., **75**, 591 (1942).   [c] Prepared from Δ^5-pregnenolone according to Plattner, Heusser and Angliker, Helv. Chim. Acta, **29**, 468 (1946).   [d] Ruzicka, Meister and Prelog, prepared from dehydroepiandrosterone, ibid., **30**, 867 (1947).   [e] Butenandt and Tschering, Z. physiol. Chem., **229**, 185 (1934); Prelog, Ruzicka and Wieland, Helv. Chim. Acta, **27**, 66 (1944).   [f] Marker, Wittle and Tullar prepared from Δ^5-cholestene, THIS JOURNAL, **62**, 223 (1940).   [g] Not depressed by admixture with authentic sample.   [h] The residue of the methanolic mother liquor of (a) was dissolved in a mixture of benzine (30–60°) and benzene (4-1) and eluted with the same mixed solvents (3:1, 2:1, 1:1) and finally with pure benzene.   This low melting isomer is isolated from the first crystalline fractions.   [i] After acidifying with dil. HCl the crude product was washed with hot water to remove benzoic acid liberated from the starting material.   [j] One sample is transferred to desoxycholic acid m. p. 170–171° not depressed by mixture with authentic sample.   [k] On methylation of the crude reduced product with dimethyl sulfate.   [l] Prepared according to "Org. Syntheses," **20**, 11 (1940).   [m] Fieser and Hartwell obtained this product melting at 77–78° in lower yield from the same starting material by usual Wolff–Kishner reduction, THIS JOURNAL, **60**, 2555 (1938).   [n] Ruzicka, Jeger and Ringnes [Helv. Chim. Acta, **27**, 932 (1944)] reduced this compound by usual Wolff–Kishner procedure, but the yield of friedelane is not given.   [o] Drake and Jacobsen [THIS JOURNAL, **57**, 1570 (1935)] also obtained same reduced product, friedelane, from friedeline and cerine by Clemmensen reduction.

Similar smooth reduction of the carbonyl group in other compounds apart from the steroids, was also noted (see Experimental). One case, however, needs to be specially mentioned for its abnormal behavior. Thus the carbonyl compound (VIII) did not give the corresponding methylene compound by the modified Wolff–Kishner reduction but gave the indazole derivative (IX) in good yield. This, however, is not surprising since α-aceto-β-naphthol is known to react with hydrazine yielding indazole derivative.[5]

(5) Witt and Braun, Ber., **47**, 3216 (1914);   Fries and Schimmel-schmidt, Ber., **58**, 2835 (1925).

Experimental[6]

The reduction has been carried out by procedures similar to those described in previous papers.[3,4] Thus a mixture of the starting material, diethylene or triethylene glycol (Note 1), alkali hydroxide and 85% hydrazine hydrate (Notes 2 and 3) was refluxed for about half an hour and the condenser was then removed to allow the aqueous liquor to evaporate and the temperature of the reaction mixture to rise to about 200°. In cases where either the starting material or the reduced product is volatile a take-off adapter was used instead of removing the condenser to evaporate aqueous liquor. After refluxing at this temperature for about two hours the reaction mixture was cooled, diluted with water (Note 4) and the separated reaction product was filtered or extracted with ether (Note 5). The results are summarized in Table I (Notes 6 and 7).

Catalytic reduction of Δ^5-pregnen-3(β)-ol (V) to allopregnan-3(β)-ol (VII): 0.2 g. of Δ^5-pregnen-3(β)-ol in 30 cc. of alcohol containing 3 drops of hydrobromic acid (48%) was shaken with hydrogen in the presence of 0.05 g. of Adams catalyst until the calculated amount of hydrogen was absorbed. The reaction mixture was filtered and the filtrate was concentrated in vacuum to a small volume. On dilution with water allopregnan-3(β)-ol (VII) separated in plates. It was recrystallized from methanol, m. p. 136–137, not depressed by admixture with the Wolff–Kishner reduction product from VI; yield 0.18 g.

Note 1.—The amount of diethylene glycol or triethylene glycol used can be varied according to the solubility of the carbonyl compound or its hydrazone formed during the reaction so that a clear or nearly clear reaction mixture is obtained during the heating period. Sometimes it is advisable to dissolve the carbonyl compound in alcohol before addition of glycol and other reagents, e.g., in the case of cholestanone and cholestenone.

Note 2.—The amount of alkali hydroxide used is about 10% to the volume of the glycol used and the amount of

85% hydrazine hydrate used is always in excess (3 moles or more).

Note 3.—In reduction of alkali-sensitive compounds such as aldehydes, α,β-unsaturated ketones and those carbonyl compounds in which the carbonyl group is adjacent to an asymmetric center it is advisable to reflux the glycol solution of starting material with hydrazine hydrate for about half an hour and then add a concentrated aqueous solution of alkali hydroxide slowly as described previously.[4]

Note 4.—If the reduced product is acidic, it is obtained by acidifying the cooled reaction mixture with dilute hydrochloric acid.

Note 5.—In cases where the starting material contains methoxy group the crude reduced product was remethylated with dimethyl sulfate.

Note 6.—Most of the technical steroid ketones[7] were recrystallized before reduction, since otherwise the yield is sometimes unsatisfactory. The yields of reduced products given in Table I are on the basis of pure products for which the melting points are given.

Note 7.—In cases where the carbonyl compound is unstable and difficult to purify such as α-naphthaldehyde the hydrazone or semicarbazone can be taken as starting material for reduction.

Summary

1. The modified Wolff–Kishner method has been applied to the reduction of a number of steroid ketones and a few other carbonyl compounds giving excellent or comparatively good yields.

2. In the case of the steroids the reduction proceeds normally on the keto groups at positions C_3, C_7, C_{12}, C_{17} and C_{20}, but the C_{11} keto group remains unattacked.

(6) The microanalyses were carried out by Shirley Katz of this Laboratory.

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Drugs Effecting Muscular Paralysis. Some Substituted Dioxolanes and Related Compounds[1]

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The drugs which effect muscular paralysis may be divided into two classes, depending on whether the predominant action is peripheral or central in nature.[3] The usual curariform agents, including most natural alkaloids and certain quaternary ammonium salts, belong to the former class. The first important compounds to be discovered having a central action were o-toloxy-1,2-propanediol (myanesin) and certain related α-glyceryl ethers.[4] Recently,[5] it was found that another class of compounds, the 2-substituted-4-hydroxymethyl-1,3-dioxolanes, possessed an action similar to that of the α-glyceryl ethers. In fact, the results of test-

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(3) Craig, Chem. Rev., 42, 285 (1948).

(4) Berger and Bradley, Brit. J. Pharmacol., 1, 265 (1946).

(5) Berger, Boekelheide and Tarbell, Science, 108, 561 (1948).

ing in mice indicate that the best compounds of the dioxolane series exceed those of the α-glyceryl ether series both in degree of activity and in margin of safety. In an attempt to find the scope of activity and the effect of changes of structure on activity in the dioxolane series, a number of substituted dioxolanes have been prepared. In the present paper the synthesis of these dioxolanes is described and evidence is presented establishing the structures of several of the most active members of this series.[6]

The synthesis of the substituted dioxolanes was accomplished, in general, by heating the appropriate carbonyl compound with glycerol or ethylene glycol and an acid catalyst in the presence of a hydrocarbon solvent and with continuous removal

(6) The results of the physiological testing of these compounds will be reported separately by F. M. Berger, M.D., School of Medicine and Dentistry, University of Rochester, Rochester, New York.