344. *The Reactions of Hydrazones and Related Compounds with Strong Bases. Part I. A Modified Wolff–Kishner Procedure.*

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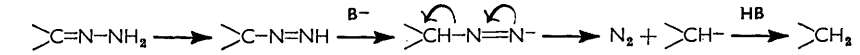
A new Wolff–Kishner procedure, involving potassium t-butoxide in toluene, has been used to reduce benzophenone and also two compounds [cholest-4-en-3-one and the α-amino-ketone (I)] that give abnormal products under conventional conditions.

The Wolff–Kishner reaction of hydrazones and semicarbazones is a popular method for reducing aldehydes and ketones to hydrocarbons, but there are numerous reports of the formation of unexpected products. For example, reduction of the carbonyl groups of αβ-unsaturated aldehydes and ketones is frequently accompanied by a shift in the position of the double bond.[1] In the Wolff–Kishner reaction of many α-amino-ketones and related compounds, an elimination competes with the normal reduction, and in some instances is the predominant reaction.[2,3] Typical procedures for the Wolff–Kishner reaction involve the use of metal alkoxides at 180—220° or the use of potassium hydroxide in ethylene glycol at 200°, and these rather vigorous conditions may be responsible for some of the anomalous reactions. The Wolff–Kishner reaction is usually considered [3,4] to occur by the following mechanism:



The first two stages of this process involve the abstraction of protons by base, and the use of a strong base in an anhydrous medium should enable the reaction to be conducted at a temperature lower than is usually employed. We have found this to be the case and have shown further that potassium t-butoxide in toluene or dimethyl sulphoxide promotes the normal Wolff–Kishner reaction in certain compounds that were previously reported to give abnormal products.

The new procedure was first applied to benzophenone. When a solution of benzophenone hydrazone and potassium t-butoxide in toluene was refluxed for 4 hr., diphenylmethane was obtained in 85% yield. This reaction and those described below were conveniently followed by measuring the volume of nitrogen produced; in most cases heating was continued until gas evolution ceased. Other conditions for the reaction were tried, but were less effective. Thus, with dimethyl sulphoxide as solvent either at 40° or at 100° diphenylmethane was formed in lower yield after a longer reaction time (Table, reactions 2 and 3), and when the hydrazone was prepared *in situ* from benzophenone and anhydrous hydrazine a mixture of benzophenone azine and diphenylmethane was isolated (Table, reaction 4). In a recent report, Cram, Sahyun, and Knox [5] have also described a Wolff–Kishner reaction employing potassium t-butoxide in dimethyl sulphoxide.

Wolff–Kishner reduction of cholest-4-en-3-one gives a mixture of alcohols and hydrocarbons but the isolation of cholest-4-ene was described on several occasions.[6] However, the cholestene was not characterised adequately, and Lardelli and Jeger [1] showed subsequently that isomerisation of the double bond also occurs, to give cholest-3-ene in about 25% yield, and they found no cholest-4-ene. We have investigated the reaction of the hydrazone and the semicarbazone of cholest-4-en-3-one with potassium t-butoxide. Cholest-4-en-3-one with hydrazine in ethanol or in ethanol containing triethylamine [7]

[1] Lardelli and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1817.
[2] Leonard and Gelfand, *J. Amer. Chem. Soc.*, 1955, **77**, 3269.
[3] Leonard and Gelfand, *J. Amer. Chem. Soc.*, 1955, **77**, 3272.
[4] Seibert, *Ber.*, 1947, **80**, 494.
[5] Cram, Sahyun, and Knox, *J. Amer. Chem. Soc.*, 1962, **84**, 1734.
[6] Lettré, *Z. physiol. Chem.*, 1933, **221**, 73; Dutcher and Wintersteiner, *J. Amer. Chem. Soc.*, 1939, **61**, 1992; Huang-Minlon, *ibid.*, 1949, **71**, 3301.
[7] Barton, O'Brien, and Sternhell, *J.*, 1962, 470.

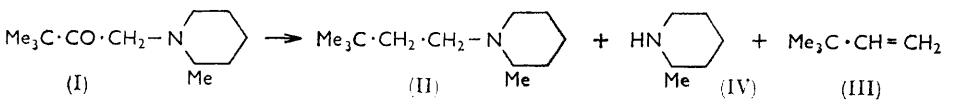
afforded the crude hydrazone. The infrared spectrum indicated the presence of unchanged ketone, but attempts to crystallise the hydrazone gave cholest-4-en-3-one azine; similar transformations of hydrazones into azines have been observed previously.[7] Reaction of the crude hydrazone with potassium t-butoxide in toluene furnished the normal Wolff–Kishner product, cholest-4-ene, in 65% yield. The constitution of the product was confirmed by its infrared absorption at 815 cm.$^{-1}$ (–CH=C<) and by its conversion in high yield into 4,5-dibromocholestane. Low-intensity infrared absorption at 775 cm.$^{-1}$ (*cis*–CH=CH–) indicated that the hydrocarbon contained some cholest-3-ene, but the amount was less than 10%. Cholest-4-ene was obtained in lower yield by reduction in dimethyl sulphoxide (Table, reaction 6).

Wolff–Kishner reactions with potassium t-butoxide.

Reaction no.	Reactants	Solvent	Reaction temp.	Reaction time (hr.)	Yield (%) of product
1	$Ph_2C{=}N{\cdot}NH_2$	PhMe	110°	4	85
2	$Ph_2C{=}N{\cdot}NH_2$	Me_2SO	100	8	60
3	$Ph_2C{=}N{\cdot}NH_2$	Me_2SO	40	48	35
4	$Ph_2CO + NH_2{\cdot}NH_2$	PhMe	110	12	55 *
5	Cholest-4-en-3-one hydrazone	PhMe	110	6	65
6	Cholest-4-en-3-one hydrazone	Me_2SO	100	24	30
7	Cholest-4-en-3-one semicarbazone	PhMe	110	60	81
8	Hydrazone of (I)	PhMe	110	36	83

* Benzophenone azine (30%) was also isolated.

The semicarbazone of cholest-4-en-3-one reacted with potassium t-butoxide more slowly than the hydrazone, but almost pure cholest-4-ene was isolated in higher yield (81%). This reaction provides a new route to cholest-4-ene, more convenient than procedures involving thioketals of cholest-4-en-3-one [8,9] and comparable in yield and purity of product with the reduction of cholest-4-en-3-one by lithium aluminium hydride and aluminium chloride.[10] The new Wolff–Kishner procedure may be applicable to other αβ-unsaturated ketones; it could be the method of choice when other groups attacked by the hydride reagent are also present.



Leonard and Gelfand [3] showed that under Wolff–Kishner conditions certain α-substituted pinacolones, $Me_3C{\cdot}CO{\cdot}CH_2R$, readily undergo elimination reactions *via* the hydrazones to give 3,3-dimethylbut-1-ene. 3,3-Dimethyl-1-2′-methylpiperidinobutan-2-one (I), for example, afforded a mixture of the reduction product (II) (44%), 2-methylpiperidine (IV), and 3,3-dimethylbut-1-ene (III) (38%). We find that when the hydrazone of this amino-ketone (I) reacts with potassium t-butoxide in toluene, normal Wolff–Kishner reduction occurs to give the amine (II) in 83% yield; only a trace of the elimination product, 2-methylpiperidine, was detected. This is a striking example of the effect of conducting the Wolff–Kishner reaction in anhydrous medium; the reaction temperature was slightly lower than that used by Leonard and Gelfand,[3] but this difference cannot alone account for the change in the course of the reaction.

Experimental

Potassium t-butoxide was sublimed at 150°/0·05 mm.; dimethyl sulphoxide was distilled from barium oxide; and toluene was dried over sodium.

Reduction of Benzophenone Hydrazone.—(*a*) A mixture of benzophenone hydrazone [11] (10 g.), toluene (200 c.c.), and potassium t-butoxide (5 g.) was heated under reflux in an apparatus

[8] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.
[9] Barton and Rosenfelder, *J.*, 1951, 1048.
[10] Broome, Brown, Roberts, and White, *J.*, 1960, 1406.
[11] Curtius and Rauterberg, *J. prakt. Chem.*, 1891, **44**, 192.

protected from moisture and attached to a gas-burette. After nitrogen evolution had ceased (4 hr.), water was added, and the toluene solution was separated. The aqueous solution was extracted with ether, and the combined ether and toluene solutions were evaporated. Distillation of the residue gave diphenylmethane (7·5 g., 85%), b. p. 68°/0·05 mm., identical (infrared) with an authentic sample. Vapour-phase chromatography (Silicone; 140°) gave a single peak with the retention time of diphenylmethane.

(*b*) A mixture of benzophenone hydrazone (1 g.), potassium t-butoxide (0·5 g.), and dimethyl sulphoxide (20 c.c.) was heated at 100° until gas evolution ceased (8 hr.), added to dilute hydrochloric acid, and extracted with ether. After evaporation of the ether, the residue was chromatographed in light petroleum (b. p. 40—60°) on alumina. Elution with the same solvent and evaporation gave diphenylmethane (0·55 g., 60%), identified by its infrared spectrum and by vapour-phase chromatography.

When the experiment was carried out at 40° for 48 hr., diphenylmethane (0·32 g., 35%) was obtained.

(*c*) Anhydrous hydrazine [12] (10 c.c.) was added to benzophenone (10 g.) in toluene (200 c.c.) containing potassium t-butoxide (5 g.), and the solution was refluxed until gas evolution ceased (12 hr.). The crude product, obtained as described in (*a*), was triturated with light petroleum (b. p. 60—80°). Crystallisation of the residue from ethanol furnished benzophenone azine as needles (2·9 g., 30%), m. p. 163° (lit.,[11] m. p. 162°) (Found: C, 86·6; H, 5·8. Calc. for $C_{26}H_{20}N_2$: C, 86·7; H, 5·6%). After the removal of the azine, the light petroleum solution was evaporated and the residue was distilled to give diphenylmethane (4·9 g., 55%), b. p. 130°/13 mm.

Reaction of Cholest-4-en-3-one with Hydrazine.—A solution of cholest-4-en-3-one (11 g.) in ethanol (220 c.c.) and hydrazine hydrate (11 g.) was refluxed for 24 hr. Evaporation gave the crude hydrazone, m. p. *ca.* 80°, $\nu_{max.}$ 1670 cm.$^{-1}$ (>C=O of cholest-4-en-3-one), which was used in reduction experiments (see below). Attempts to crystallise the hydrazone resulted in the formation of cholest-4-en-3-one azine, separating from light petroleum (b. p. 60—80°) in colourless needles, m. p. 225—228° (lit.,[13] m. p. 230—231°) (Found: C, 84·7; H, 11·6. Calc. for $C_{54}H_{88}N_2$: C, 84·2; H, 11·8%).

Heating cholest-4-en-3-one in ethanol with hydrazine hydrate and triethylamine for 1 hr. gave a hydrazone of similar composition (infrared).

Cholest-4-ene. (*a*) A mixture of cholest-4-en-3-one hydrazone (5 g.), toluene (50 c.c.), and potassium t-butoxide (2·5 g.) was refluxed until the evolution of nitrogen ceased (6 hr.), and then added to dilute hydrochloric acid. The toluene layer was separated, the aqueous solution was extracted with ether, and the combined toluene–ether solution was evaporated. The residue in light petroleum (b. p. 40—60°) was filtered through alumina. Evaporation gave cholest-4-ene, separating from acetone in needles (2·8 g., 65%), m. p. 74—75°, $[\alpha]_D$ +75° (*c* 0·9 in $CHCl_3$) {lit.,[8] m. p. 82—83·5°, $[\alpha]_D$ +76° (*c* 0·7 in $CHCl_3$)}. A sample (125 mg.) was converted into its dibromide. Trituration of the crude product with ethanol gave needles (133 mg., 75%), m. p. 110—115°. Crystallisation from benzene–ethanol raised the m. p. to 115—116° (lit.,[9] m. p. 116—117°), undepressed on admixture with an authentic sample, m. p. 115—116°. The infrared spectrum of the sample, m. p. 74—75°, showed a peak at 815 cm.$^{-1}$ and one of low intensity at 775 cm.$^{-1}$ (–CH=CH– of cholest-3-ene); comparison with the spectra of mixtures of cholest-3-ene and cholest-4-ene of known composition showed that the cholest-4-ene prepared in this experiment contained less than 10% of cholest-3-ene.

(*b*) Cholest-4-en-3-one hydrazone (5 g.), dimethyl sulphoxide (100 c.c.), and potassium t-butoxide (2 g.) were heated at 100° for 24 hr. Dilution with aqueous hydrochloric acid, extraction with ether, and purification of the product as described in (*a*) gave cholest-4-ene (1·3 g., 30%), m. p. 63—70°. The compound gave a dibromide, m. p. 115°, and was shown by infrared analysis to contain less than 10% of cholest-3-ene.

(*c*) Cholest-4-en-3-one semicarbazone [13] (1 g.) was heated with toluene and potassium t-butoxide as described for the hydrazone in (*a*) above. When evolution of nitrogen ceased (60 hr.), the crude product was obtained in the usual way. Filtration through an alumina column gave cholest-4-ene (0·68 g., 81%), m. p. 70—73°, $[\alpha]_D$ +72° (*c* 0·9 in $CHCl_3$), shown by infrared analysis to contain less than 10% of cholest-3-ene.

3,3-*Dimethyl*-1-2′-*methylpiperidinobutane* (II).—A solution of 3,3-dimethyl-1-2′-methylpiperidinobutan-2-one hydrazone [3] (5 g.) and potassium t-butoxide (4 g.) in toluene (30 c.c.)

[12] Cf. Barton, Ives, and Thomas, *J.*, 1955, 2056.

[13] Dannenburg, Scheurlen, and Simmer-Rühle, *Annalen*, 1956, **600**, 68.

was refluxed until gas evolution ceased (36 hr.). After the addition of toluene (30 c.c.), the solution was concentrated to small volume, and the distillate was retained for further investigation (see below). The residue was treated with water and then extracted with benzene. The benzene solution was shaken with aqueous hydrochloric acid, and the acid solution was made alkaline with aqueous sodium hydroxide and then extracted with ether. Evaporation of the ether gave 3,3-dimethyl-1-2′-methylpiperidinobutane as an almost colourless oil (3·4 g.). The infrared spectrum, which was unchanged after distillation of the compound at 90°/10 mm., was identical with that of an authentic sample prepared by the method of Leonard and Gelfand.[3] The picrate separated from ethanol in yellow needles, m. p. and mixed m. p. 148—151° (lit.,[3] m. p. 151—152°).

The toluene distillate was extracted with aqueous hydrochloric acid, and the acid solution was made alkaline with aqueous sodium hydroxide and extracted exhaustively with ether. After evaporation of the ether, the residue was distilled to give two fractions. The first fraction was obtained at atmospheric pressure as a colourless oil (0·1 g.), b. p. 85°, and was shown (infrared) to consist of t-butyl alcohol containing a small amount of 2-methylpiperidine. The second fraction (0·2 g.), b. p. 90°/10 mm., was 3,3-dimethyl-1-2′-methylpiperidinobutane (total yield, 3·6 g., 83%).

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