142. *Reactions of Carbinols in the Presence of Alkali. Part I. The Reduction of Ketones by Primary Alcohols.*

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The reduction is described of several aliphatic ketones to the corresponding secondary alcohols by the action of simple aliphatic primary alcohols in the presence of concentrated aqueous alkali at 240°. The mechanism of the reaction is discussed.

THE literature contains several references to the reduction of ketones by primary alcohols in the presence of alkali. Zagoumenny (*Annalen*, 1877, **184**, 174) obtained benzhydrol by heating benzophenone with alcoholic potassium hydroxide, and Montagne (*Rec. Trav. chim.*, 1908, **27**, 327; 1912, **31**, 298; 1916, **35**, 258; 1920, **39**, 339; 1922, **41**, 703; *Ber.*, 1916, **49**, 2243) showed that the ease of reduction of many substituted benzophenones depended upon the nature of the substituents. Palfray and Sabetay (*Compt. rend.*, 1932, **194**, 79; 1934, **198**, 1513; 1936, **203**, 1523) and Mastagli (*ibid.*, 1937, **204**, 1656; **205**, 802; *Ann. Chim.*, 1938, **10**, 281) reduced aromatic ketones, and a number of aromatic and higher aliphatic aldehydes, to the corresponding secondary and primary alcohols by boiling with potassium benzyloxide in benzyl alcohol, a process evidently analogous to that under discussion. Rubin (*J. Amer. Chem. Soc.*, 1944, **66**, 2075) has reported the reduction of 3-anisylhexan-4-one to the carbinol by alcoholic potassium hydroxide. The method has also been applied in the porphyrin field (Fischer and Zeile, *Annalen*, 1929, **468**, 98) and for the reduction of alicyclic bridged-ring ketones (Allen, Jones, and VanAllan, *J. Org. Chem.*, 1946, **11**, 268).

Few examples are known, however, of the reduction of aliphatic ketones by this method. The classical instance of the reduction of methylheptenone to methylheptenol was recorded by Tiemann (*Ber.*, 1898, **31**, 2991) and confirmed by Doeuvre (*Bull. Soc. chim.* 1929, **45**, 351), and Schicht (G.P. 327,510) described a process whereby the higher aliphatic ketones, such as behenone, were reduced by the action of primary alcohols in the presence of aqueous alkali. No systematic study appears to have been made of the reduction of simple aliphatic ketones under such conditions, and for reasons concerned with the subject matter of Parts II and III (following papers) it was necessary to establish the generality of the reaction.

For this purpose, di*iso*propyl ketone was treated with equimolecular quantities of methyl, ethyl, and *n*-propyl alcohols in the presence of a concentrated aqueous solution of either sodium or potassium hydroxide at 240° in a rocking autoclave. Hydrogen was liberated and, with one exception (methanol with potassium hydroxide), reduction to di*iso*propylcarbinol occurred in all experiments, better results being obtained throughout by the use of sodium hydroxide. Formic acid could not be isolated from the experiments in which methanol was used, but acetic and propionic acids were obtained when ethyl and *n*-propyl alcohol, respectively, were the reducing agents, the yield of carbinol then being *ca.* 55%. In connection with the scission

experiments to be described in Part III, the reduction of methyl *n*-butyl ketone by ethanol and potassium hydroxide was proved to give methyl-*n*-butylcarbinol and acetic acid, whilst *n*-propyl *n*-butyl ketone and *n*-butanol gave *n*-propyl-*n*-butylcarbinol and *n*-butyric acid. It was also shown that methyl *n*-hexyl ketone was reduced to the carbinol by butanol and aqueous sodium hydroxide. In all these experiments, considerable amounts of high-boiling materials, probably unsaturated ethers, were obtained; clearly, the yield of carbinol is likely to be adversely affected by the necessity of carrying out the reductions in a closed system, with consequent facilitation of secondary reactions.

Two experiments were also performed with acetophenone, which was reduced by methanol and by *n*-amyl alcohol, in the presence of aqueous sodium hydroxide, to give a small yield of phenylmethylcarbinol, accompanied by much resin, probably a styrene polymer.

Since the boiling points of the aliphatic ketones were not widely different from those of the corresponding carbinols, the quantitative separation of the ketone–carbinol mixtures was impracticable, and their ketone content was estimated by precipitation of the 2 : 4-dinitrophenyl-hydrazone, which was purified by chromatographic adsorption on alumina. Control experiments, on artificial ketone–carbinol mixtures, showed the yield of purified derivative to be at least 90%.

Although it has long been known (Dumas and Stas, *Annalen*, 1840, **35**, 129; Hell, *ibid.*, 1884, **223**, 269; Nef, *ibid.*, 1904, **335**, 302; Carroll, *J. Physical Chem.*, 1918, **22**, 128; Weizmann and Garrard, *J.*, 1920, **117**, 324; Fry *et al.*, *J. Amer. Chem. Soc.*, 1924, **46**, 2268; 1926, **48**, 958; 1928, **50**, 1122, 1130; Reid, Worthington, and Larcher, *ibid.*, 1939, **61**, 99) that primary alcohols, when heated alone with aqueous alkali, undergo dehydrogenation to give the corresponding acid, with liberation of two mols. of hydrogen : $R \cdot CH_2 \cdot OH \longrightarrow R \cdot CO_2H + 2H_2$, it is unlikely that this reaction is directly concerned in the reduction of ketones, since di*iso*propyl ketone was not reduced when heated with hydrogen and aqueous sodium hydroxide under the appropriate conditions. It may, of course, be postulated that the reduction occurs by " nascent " hydrogen, but a more likely explanation would appear to be that the reaction is of the Meerwein–Ponndorf–Verley type (cf. Rubin, *loc. cit.*; Wilds, " Organic Reactions," 1944, **2**, 178) and may be represented as $R \cdot CH_2 \cdot OH + R' \cdot CO \cdot R'' \rightleftharpoons R \cdot CHO + R' \cdot CH(OH) \cdot R''$. Under the strongly alkaline conditions, however, the equilibrium represented by the above equation will not be maintained, owing to a further reaction undergone by the aldehyde, *viz.*, conversion into the corresponding acid, with evolution of one mol. of hydrogen. Although it might appear that, in the case of a simple aliphatic aldehyde, condensation to an aldol or resin would supervene, it has been established by Fry and Schulze (*J. Amer. Chem. Soc.*, 1926, **48**, 958) that the introduction of acetaldehyde vapour into a mixture of sodium and potassium hydroxides at 250° results in a 90% yield of acetic acid, with the liberation of hydrogen; furthermore, the conversion of sebacic semialdehyde into sebacic acid with concentrated aqueous alkali has now been observed (Part II, following paper). In the reductions by benzyl alcohol, recorded by Palfray and Sabetay (*loc. cit.*) and by Mastagli (*loc. cit.*), the formation of benzoic acid from the intermediate benzaldehyde could clearly occur through a Cannizzaro reaction.

The overall reaction is, therefore, $R \cdot CH_2 \cdot OH + R' \cdot CO \cdot R'' \longrightarrow R \cdot CO_2H + R' \cdot CH(OH) \cdot R'' + H_2$, but it is evident that the direct dehydrogenation of the primary alcohol may occur simultaneously; this would be reflected in a yield of hydrogen greater than that of carbinol, and also, unless an excess of primary alcohol is used, in the presence of unchanged ketone in the reaction products. Both of these features were observed in the majority of the present experiments, and the formation of the high-boiling by-products indicates also that further secondary reactions occur under the vigorous conditions employed (cf. Guerbet, *Compt. rend.*, 1901, **133**, 1220; 1902, **134**, 467; 1908, **146**, 298, 1405).

<div align="center">Experimental.</div>

<div align="center">(Light petroleum refers to the fraction of b. p. 40—60°.)</div>

*Methyl-*n-*butylcarbinol.*—This was prepared in 60% yield by the method of Grignard and Fluchaire (*Ann. Chim.*, 1928, **9**, 15); b. p. 139—140°, $n_D^{19°}$ 1·4147.

Methyl n-*Butyl Ketone.*—Oxidation of the carbinol (20 g.) with the calculated amount of chromic acid (cf. *idem, ibid.*) gave a 50% yield of ketone, b. p. 128—130°, $n_D^{16°}$ 1·4041. For larger-scale work (100-g. batch) it was preferable to prepare the ketone directly by condensation of acetic anhydride and -butylmagnesium bromide at − 70°, according to the method of Newman and Booth (*J. Amer. Chem. Soc.*, 1945, **67**, 154).

n-*Propyl-*n-*butylcarbinol.*—This was obtained in 65% yield by the method of Bouveault and Locquin (*Bull. Soc. chim.*, 1906, **35**, 644); b. p. 77—78°/15 mm., $n_D^{17°}$ 1·4257. The α-*naphthylurethane* crystallised

from light petroleum in fluffy needles, m. p. 61—62° (Found : N, 4·85. $C_{19}H_{25}O_2N$ requires N, 4·7%).

n-*Propyl* n-*Butyl Ketone.*—Oxidation of the carbinol in acetone solution with chromic acid gave the ketone (80%), b. p. 167—169°, n_D^{14} 1·4173 (cf. Bouvealt and Locquin, *loc. cit.*). The 2 : 4-*dinitrophenyl-hydrazone* crystallised from light petroleum in orange needles, m. p. 41° (Found : N, 18·4. $C_{14}H_{20}O_4N_4$ requires N, 18·2%).

Estimation of Ketones in Ketone–Carbinol Mixtures.—A portion of the mixture (*ca.* 1 g., accurately weighed) in ethanol (5 c.c.) was shaken for 2 minutes with an excess of aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate, the solution diluted with water (100 c.c.), allowed to stand for ½ hour, and then extracted five times with 50-c.c. portions of benzene (light petroleum can be used if the derivative is sufficiently soluble in it). The combined extracts were chromatographed on a column of alumina (60 × 2·5 cm.), and the main band cut out as soon as it had separated. The derivative was recovered by elution with ether, the solvent removed, and the residue dried and weighed; the m. p. was usually only a few degrees below that of a recrystallised sample.

Reduction of Aliphatic Ketones.—The ketone (0·5 mol.), primary alcohol (0·5 mol.), alkali hydroxide (220 g.), water (150 c.c.), and an emulsifier (0·3 g. of palmitic acid) were shaken in an autoclave for 3 hours at 240°. After cooling, the gas was released and measured, and the contents of the autoclave were then diluted with water and extracted with ether to obtain the neutral products, which were fractionated. The main fraction, consisting of the ketone–carbinol mixture, was analysed for ketone content by the method described above; di*iso*propylcarbinol was identified as the phenylurethane, m. p. 96—99°; methyl-*n*-butyl-, *n*-propyl-*n*-butyl-, and methyl-*n*-hexyl-carbinols as the α-naphthylurethanes, m. ps. 61°, 61°, and 57—58°, respectively, not depressed on admixture with the authentic derivatives. High-boiling products were encountered in all experiments; *e.g.*, from the reduction of methyl *n*-hexyl ketone by butanol there was obtained a fraction (15 g.), b. p. 225—235°/20 mm., n_D^{22} 1·4772, which was unsaturated, but showed no ketonic or alcoholic properties. Acid products were isolated from the aqueous portion by acidification with sulphuric acid and ether extraction, acetic, propionic, and *n*-butyric acids being identified, after distillation, as the *p*-bromophenacyl esters, m. ps. 85°, 61°, and 63° respectively. The results are summarised in the table.

Ketone–carbinol mixture.

Ketone.	Alcohol.	Alkali.	H_2 (l.).	Acid (g.).	G.	B.p.	n_D^{18}.	Ketone (g.).	Carbinol (g.).	Yield of carbinol (%).
$COPr^\beta_2$	MeOH	NaOH	9	—	28	125—136°	1·4105	18	10	17
,,	,,	KOH	11	—	32	124—128	1·4034	32	0	0
,,	EtOH	NaOH	9	5	40	127—140	1·4178	10	30	52
,,	,,	KOH	10	3	34	127—137	1·4118	14	20	34
,,	*n*-PrOH	NaOH	5	9	40	122—140	1·4178	8	32	55
,,	,,	KOH	2·5	2	34	120—137	1·4094	27	7	12
$COMeBu^a$	EtOH	KOH	3	1	11·5	134—145	1·4141	0·5	11	22
$COPr^aBu^a$	*n*-BuOH	KOH	1·5	4	30	70—83 *	1·4223	10	20	31
$COMe·C_6H_{13}(n)$	*n*-BuOH	NaOH	2	5	13	171—184	1·4243	1 †	12	19

* At 18 mm.

† The 2 : 4-*dinitrophenylhydrazone*, a yellow microcrystalline powder, m. p. 78—79°, from aqueous ethanol, was not that of the expected methyl *n*-hexyl ketone, but appeared to be derived from a carbonyl compound $C_7H_{14}O$ (Found : C, 52·15; H, 6·0; N, 19·0. $C_{13}H_{18}O_4N_4$ requires C, 53·0; H, 6·15; N, 19·0%). The absorption spectrum in alcohol, kindly determined by Dr. E. A. Braude, showed $\lambda_{max.}$ 2250, 2560, and 3580 a. (log ϵ : 4·23, 4·02, and 4·36 respectively) consistent with its formulation as a derivative of an aldehyde $C_6H_{13}·CHO$ (cf. Braude and Jones, *J.*, 1945, 498). This is unlikely to be *n*-heptaldehyde (2 : 4-dinitrophenylhydrazone, m.p. 107°) and its identity is obscure.

Reduction of Acetophenone.—Acetophenone (60 g., 0·5 mol.), primary alcohol (0·5 mol.), sodium hydroxide (220 g.), water (150 c.c.), and palmitic acid (0·3 g.) were shaken in an autoclave at 240°, and the products isolated in the usual way. With methanol, heating being maintained for 5 hours, the hydrogen amounted to 12 l. The neutral products gave a main fraction (13 g.), b. p. 101—109°/18 mm., n_D^{18} 1·5233, from which was obtained the phenylurethane, m. p. 92—93°, of phenylmethylcarbinol. Much high-boiling material was present. The acid products contained benzoic acid, m. p. 122° (presumably a decomposition product), and a trace of formic acid, separated as the lead salt.

Reduction with *n*-amyl alcohol for 3 hours gave hydrogen (2 l.), *n*-valeric acid (5 g.), identified as the *p*-bromophenacyl ester, m. p. 63°, and a neutral fraction (4 g.), b. p. 104—109°/19 mm., n_D^{17} 1·5109, which gave the phenylurethane of phenylmethylcarbinol, m. p. 92—93°. A large amount of high-boiling material (45 g., b. p. 135—220°/1 mm.) was also formed.