557. *Reductions with Aluminium Alkoxides. Part II. Modified Procedure.*

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When the Meerwein–Ponndorf reduction is modified by dropping the carbonyl compound in slowly during the reaction, so that its concentration is always low, improved yields of alcohols are obtained from aldehydes and unstable ketones. Reasons for this are discussed.

Reductions by aluminium alkoxides without solvent may be conveniently employed in certain cases.

The usual method of carrying out Meerwein–Ponndorf reductions (cf. Wilds, "Organic Reactions," Vol. II, Wiley & Sons, New York, 1944, p. 178) involves addition of all the carbonyl compound to the solution of aluminium *iso*propoxide at the beginning of the reaction, and slow removal of acetone until reduction is complete. Only one departure from this has been noted. Rouvé and Stoll (*Helv. Chim. Acta*, 1947, **30**, 2216), carrying out a large-scale reduction of mesityl oxide which required 54 hours, added the ketone during 4½ hours and obtained a yield of 73%, much better than the 18% recorded by Kenyon and Young (*J.*, 1940, 1547; misquoted as 63% by Wilds). For reasons discussed below, it seemed desirable that in the reduction of any highly reactive carbonyl compounds their concentration should be kept low, and this conclusion has been tested on a number of substances.

The table shows the improved yields obtained when the carbonyl compound was added dropwise during several hours.

Results of modified Meerwein–Ponndorf reduction.

	Yield, %.			Yield, %.	
Compound reduced.	Found.	Recorded.	Compound reduced.	Found.	Recorded.
m-Nitrobenzaldehyde ...	92	75 (*a*)	Benzylideneacetone ...	96	28 (*a*)
Cinnamaldehyde	80	68 (*b*); 75 (*a*)	Cinnamylideneacetone	70—80	—
(−)-Phellandral	87	65 (*c*)	*ψ*-Ionone *	95	—
Mesityl oxide	80	73 (*d*); 18 (*e*); 23 (*a*)	*cyclo*Pentanone	74	33 (*f*)
			(−)-Piperitone *	85	6 (*g*)

* Products were mixed stereoisomers.

(*a*) Ferrier, *Compt. rend.*, 1945, **220**, 460 (aluminium *sec.*-butoxide). (*b*) Young, Hartung, and Crossley, *J. Amer. Chem. Soc.*, 1936, **58**, 100. (*c*) Human, Macbeth, and Rodda, this vol., p. 350. (*d*) Rouvé and Stoll, *loc. cit.* (*e*) Kenyon and Young, *loc. cit.* (*f*) Lund, *Ber.*, 1937, **70**, 1520. (*g*) Read and Walker, *J.*, 1934, 308.

Four reactions of carbonyl compounds, catalysed by aluminium alkoxides, may give rise to by-products in the Meerwein–Ponndorf reduction. First, aldehydes may undergo the Tischtschenko reaction, giving esters at a rate which probably depends on the square of the concentration of aldehyde (cf. the Cannizzaro reaction; Geib, *Z. physikal. Chem.*, **1934**, *A*, **169**, 41); this side-reaction should then be suppressed by keeping the concentration of aldehyde low.

Secondly, the carbonyl compound may undergo an acid-catalysed aldol condensation with itself, if of suitable structure, giving rise to unsaturated compounds of the mesityl oxide type. Thirdly, it may undergo the same type of condensation with acetone produced during the reaction. A detailed kinetic study of these reactions does not appear to be available, but their mechanism (Watson, *Trans. Faraday Soc.*, **1941**, **37**, **707**) is such that they should also be suppressed by keeping the concentration of carbonyl compound low—the concentration of acetone is then necessarily low.

In some reductions of reactive ketones such as alkyl*cyclo*hexanones by the conventional method, it was noted that the temperature of the distillate fell very quickly, sometimes as low as 65°, which indicated the rapid development of a high concentration of acetone. This formation of acetone more quickly than it can be removed increases the risk of side reactions by slowing the main reaction (which is reversible). Volatile products may be contaminated with the reduction products of mesityl oxide. It has been observed that some reductions, notably that of phellandral, require no longer by the modified procedure than by the conventional procedure, and that in the conventional method the reduction is initially quite rapid and then becomes very slow. This effect is probably due to the formation of highly unsaturated conjugated carbonyl compounds by the second and third side-reactions, because this type of compound is known to be rather difficult to reduce. A considerable part of the high-boiling by-products in the reduction of phellandral by the usual method appears to be alcoholic in nature.

In the products from reductions by the modified procedure high-boiling residue was negligible, except in the case of *cyclo*pentanone, which was added more quickly than the other substances. The modified procedure should be particularly useful for substances of high molecular weight, where the products cannot be purified by distillation.

A fourth possible side-reaction is the racemisation of optically active ketones, or isomerisation such as the inversion of menthone. Apparently (see preceding paper) the inversion of menthone is not suppressed by using the modified procedure.

The Meerwein–Ponndorf reduction has also been carried out successfully in the absence of solvent. Reduction may be carried out with aluminium *iso*propoxide in hydrocarbon solvents (cf. Wilds, *op. cit.*) without any alcohol, and it has been found that heating fluorenone or benzophenone with an excess of alkoxide gives satisfactory results. There was no ready means of detecting the end of the reaction; but by working under reduced pressure the acetone could be removed as formed. The method may be useful for the rapid reduction of some ketones in circumstances where a high yield is not required; small-scale reductions require only a few minutes. Aluminium *sec.*-butoxide, which is liquid at room temperature, is more convenient than aluminium *iso*propoxide. The method failed with highly reactive carbonyl compounds; *o*-nitrobenzaldehyde and dibenzylideneacetone gave only resins.

After this work was completed, two papers were noted containing relevant data. Schintz, Lauchenauer, Jeger, and Rüegg (*Helv. Chim. Acta*, **1948**, **31**, **2235**) have carried out a modified Oppenauer oxidation with satisfactory yield by heating an aluminium alkoxide with *p*-methoxybenzaldehyde in the absence of solvent. Chaikin and Brown (*J. Amer. Chem. Soc.*, **1949**, **71**,

122) reduced carbonyl compounds (*e.g.*, cinnamaldehyde, mesityl oxide, and *cyclo*pentanone) to the corresponding alcohols with sodium borohydride, in yields equal to those obtainable by the modified Meerwein–Ponndorf reduction.

EXPERIMENTAL.

Aluminium iso*Propoxide*.—This was prepared by the standard method (Wilds, *op. cit.*), purified by distillation, and stored as 0·75M-solution in *iso*propyl alcohol. Several batches showed behaviour not previously recorded. The crude alkoxide, freshly made from carefully distilled *iso*propyl alcohol and pure aluminium foil, always boiled over a considerable range, approx. 115—130°/1 mm., and only partly solidified immediately after distillation, giving a mixture of fine white needles and clear viscous syrup. The bulk of the crystals came from the first portion of the distillate. The mixture dissolved readily in warm *iso*propyl alcohol, and the cooled solution deposited the characteristic large clear crystals. When the distilled alkoxide was kept at room temperature in a closed evacuated flask, the syrup solidified in 1—2 days. About a week later, the m. p. of the solid was still ill-defined—above 100°, but below 125° (Ulich and Nespital, *Z. physikal. Chem.*, 1933, **165**, *A*, 298) or 118° (Robinson and Peak, *J. Physical Chem.*, 1935, **39**, 1125). After 3 months the waxy solid had changed, with considerable increase in volume, to a porous mass which readily crumbled to a white crystalline powder with sharp m. p. 142—143°. This powder, when melted and cooled, gave a waxy solid. The powder had a fairly sharp b. p., 136—138°/6 mm., and dissolved readily in *iso*propyl alcohol, the solution depositing crystals similar to those from the freshly-made alkoxide. Since aluminium *iso*propoxide is associated (Robinson and Peak, *loc. cit.*), this behaviour may indicate changes in the degree of association.

General Procedure.—The reduction of benzylideneacetone illustrates the method. The apparatus used is described in the preceding paper. The combination of reflux-ratio head and column of moderate fractionating efficiency and rather high hold-up was very suitable, as acetone was removed quickly from the site of reaction without the use of a high rate of take-off. Benzylideneacetone (20 g.) was dissolved in dry *iso*propyl alcohol (100 ml.), and the solution was added dropwise to the refluxing solution of 0·75M-aluminium *iso*propoxide (200 ml., 1 mole) during 4·25 hours, distillate being collected at the same rate. The temperature at the still-head never fell below 80°. 70 Minutes after the benzylideneacetone had been added the b. p. was 82° and the test for acetone was negative.

The bulk of the *iso*propyl alcohol was removed under reduced pressure (bath at 90°), the residue was treated with crushed ice and an aqueous solution of sodium hydroxide (20 g.), and the mixture was extracted 3 times with benzene (total, 125 ml.). The combined extracts were washed with water and dried, the solvent was removed, and the product (19·7 g.) distilled; b. p. 124—125°/3 mm. The 1-phenylbut-1-en-3-ol was colourless, readily solidified, and had m. p. 32·5—33·5° (Kenyon, Partridge, and Phillips, *J.*, 1936, 85, cited 33°).

Cinnamylideneacetone.—The benzene extracts of the reduction product, when evaporated, left a cream-coloured solid (14—16 g. from 20 g.), m. p. 55—60°, evidently impure 1-*phenylhexa*-1 : 3-*dien*-5-*ol*. Distillation in bulk led to decomposition, and purification by recrystallisation failed to raise the m. p. above 62°, apparently because of the presence of small amounts of sparingly soluble gum. The analytical sample, fine white needles, m. p. 65—66°, was obtained by short-path distillation at 100°/0·5 mm., followed by a quick recrystallisation from light petroleum (Found : C, 82·6, H, 8·2. $C_{12}H_{14}O$ requires C, 82·8; H, 8·1%).

When stored at room temperature, the alcohol, in solution or in the solid state, soon changed to a yellowish insoluble gum. The change was retarded by refrigeration or the addition of benzoquinone.

Piperitone.—Reduction was very slow. Addition of the ketone was spread over 10 hours, and an additional 9 hours' heating was required before the test for acetone became negative. To prevent the acid-catalysed dehydration of piperitol (Read and Walker, *loc. cit.*), a few drops of *NN*-dimethyl*cyclo*hexylamine were added to the product before working it up, and also placed in the receiver before distillation. The ketone reduced had α_D^{20} −49·4° (homogeneous); the main fraction of the product, b. p. 100—105°/5 mm., had α_D^{20} −38·2° (homogeneous) and appears to be a mixture (it is being further investigated). There was a small fore-run and practically no residue.

Other Carbonyl Compounds Reduced.—Mesityl oxide was completely reduced in 6·5 hours. Light petroleum (b. p. 20—40°) was used as extractant for the 2-methylpent-2-en-4-ol, which had b. p. 139—140° after two distillations, and gave a *p*-diphenylylurethane m. p. 95—97° (Kenyon and Young, *loc. cit.*, report 90—91°) (Found : C, 77·4; H, 7·5. Calc. for $C_{19}H_{21}O_2N$: C, 77·2; H, 7·2%), and a 3 : 5-*dinitrobenzoate*, fine pale yellow needles (from light petroleum), m. p. 82—84° (Found : C, 53·4; H, 5·1. $C_{13}H_{14}O_6N_2$ requires C, 53·1; H, 4·8%). The m. p. of the esters was constant, but not sharp, and each may still have contained some 2-methylpent-1-en-4-yl ester, which was shown by Kenyon and Young to be produced in small amount by reduction of mesityl oxide.

Phellandral, $\alpha_D^{17\cdot5}$ −143·1° (homogeneous), yielded phellandrol, α_D^{19} −88·8° (homogeneous). Conversion of the latter into its *p*-nitrobenzoate (90% yield) and recrystallisation from light petroleum and then from methyl alcohol gave the pure ester, m. p. 66—67° (Human, Macbeth and Rodda, *loc. cit.*).

*cyclo*Pentanone (20 g.) was reduced in >4 hours (addition in 3·2 hours). The *cyclo*pentanol was extracted with light petroleum and distilled twice (b. p. 138—140°) to free it from a small amount of high-boiling residue.

ψ-Ionone appeared to be reduced normally during 6 hours but the product boiled from 80° to 110° at 0·5 mm. There was negligible residue. The product, apparently alcoholic, is being examined to determine whether partial cyclisation has also occurred.

From the respective aldehydes, added during 4—5 hours and completely reduced in 6 hours, there were prepared cinnamyl, m. p. 30—31° (lit., 33°), and *m*-nitrobenzyl alcohol, m. p. 25° (lit., 27°).

Reductions Without Solvent.—Fluorenone (1·8 g.) and aluminium *sec.*-butoxide (5 g., 2 moles) were placed in a flask which was then evacuated at the water-pump and heated in a bath at 105—110°. The fluorenone melted and dissolved with vigorous frothing, and the yellow colour quickly faded to a pale straw (in a closed evacuated system, methyl ethyl ketone condensed in the cool parts). After 5 minutes, frothing had stopped and, after cooling, the mixture was partitioned between chloroform (20 ml.) and dilute sulphuric acid. The chloroform extract was washed with water, dried, diluted with an equal volume of light petroleum, and refrigerated. Fluorenol (1·2 g.) was obtained as colourless plates, m. p. 154·5—155·5°, and concentration of the solution yielded a second similar batch (0·45 g.) (Baker and Adkins, *J. Amer. Chem. Soc.*, 1940, **62**, 3302, give m. p. 155—156°).

Benzophenone (2·4 g.) was heated with fused aluminium *iso*propoxide (5·5 g.) under the same conditions; reduction was equally rapid. Benzhydrol, isolated by extraction with benzene and recrystallised from light petroleum, formed colourless needles (2·1 g.), m. p. 64—65° (lit., 68°). A second recrystallisation raised the m. p. to 67°.

When solid fluorenone and solid aluminium *iso*propoxide (m. p. 142—143°) were mixed, a temperature of 150° was needed to effect fusion in a reasonable time, and the fluorenol (70% yield) was contaminated with a trace of orange substance.

One of us (J. A. M.) expresses his thanks for financial support from the Commonwealth Research Fund.

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[*Received, July 4th,* 1949.]