

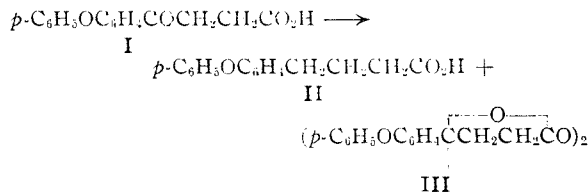
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A Simple Modification of the Wolff-Kishner Reduction

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Recently Soffer, Soffer and Sherk² and Herr, Whitmore and Schiessler³ have independently reported modifications in the Wolff-Kishner reduction consisting in the use of diethylene or triethylene glycol in combination with metallic sodium or sodium methoxide in order to obviate the requirement of pressure equipment. Of the two procedures, that of Soffer has the advantage that it proceeds in one step and gives higher yields, but it still has some shortcomings as applied to large-scale operations: expensive 100% hydrazine hydrate is required, as well as large amounts of solvent and sodium, and the reaction time is very long (fifty to one hundred hours).

A further improvement that eliminates these disadvantages was discovered in the course of the preparation of a large quantity of γ -(*p*-phenoxyphenyl)-butyric acid (II) by the reduction of β -(*p*-phenoxybenzoyl)-propionic acid⁴ (I). Clemmensen reduction by the Martin procedure⁵ as improved by Sherman⁶ was tried several times, both by the author and by Dr. E. Berliner but the



best yield was 54% and a high-melting by-product was isolated having the composition of the pinacol dilactone III. Initial trials of the Wolff-Kishner reduction by the Soffer procedure were more promising, and it was then found that the process can be greatly simplified by merely adjusting the reaction temperature to 190–200° by distilling off some of the water and excess hydrazine hydrate after the formation of the hydrazone is judged complete. When this is done, it is no longer necessary to use a large volume of solvent and a large excess of sodium in order to maintain a low water content and so attain a high reaction temperature, and cheap 85% hydrazine hydrate can be used in place of 100% reagent. Thus the keto acid I was refluxed in a moderate volume of diethylene-glycol with 85% hydrazine hydrate and three equivalents of sodium (one-tenth that used by Soffer) for one hour and the flask was then left open until the inside temperature had reached 195–200°; after refluxing at this temperature for

three hours longer the reaction was complete and the yield of once-crystallized product was 91%. In a run conducted with 100% hydrazine hydrate and more sodium for a longer period, but without opening the flask to allow distillation, the yield was only 48%. Finally, it was found that metallic sodium can be replaced by either sodium or potassium hydroxide, and by this simple and economical procedure the keto acid I was reduced in 500-g. batches in yields over 90%.

The same procedure was applied to three other keto acids and one ketone with good results, and in two instances the yields were distinctly higher than Martin⁵ obtained by his improved Clemmensen procedure. In the application of the method to the preparation of substances boiling below 190°, it is only necessary to provide the flask with a take-off adapter and to remove aqueous liquor intermittently from the trap until a suitable reaction temperature has been reached. Thus propiophenone and cyclohexanone were reduced satisfactorily in yields of 80% and better.

The application of this modified procedure to the reduction of steroid ketones⁷ and other carbonyl compounds will be investigated further in association with Professor L. F. Fieser, who has made this work possible and aided the author in its prosecution.

Experimental

β -(*p*-Phenoxybenzoyl)-propionic Acid.^{4,8}—To a mixture of 680 g. (4 moles) of diphenyl ether, 400 g. (4 moles) of powdered succinic anhydride and 2 kg. of thiophene-free benzene in a 12-liter flask there was added at intervals four 270-g. portions of anhydrous aluminum chloride; each time the flask was swirled gently until the reaction subsided. The mixture was then refluxed for two hours, allowed to cool overnight, and poured carefully onto 6 liters of crushed ice and 500 cc. of concentrated hydrochloric acid. The resulting mixture was poured back into the flask and steam distilled to remove the benzene, and the oil-water residue was poured into large beakers and cooled with stirring to prevent caking. The solidified product was collected and dissolved in 4 liters of water containing 424 g. (4 moles) of sodium carbonate and, in order to coagulate the alumina, the turbid solution was either warmed on the steam-bath for several hours or boiled with Norite; Cellite was added and the solution filtered and poured slowly into 1.6 liters of water and 400 cc. of concentrated hydrochloric acid. The precipitated white solid when dried to constant weight weighed 1000 g. (93%). The melting point varied from 116–118° to 118–119° but in any case the material was suitable for direct use in the Wolff-Kishner reduction provided it had been fully dried. With a large batch, time is saved by dissolving the partially dried acid in 4 liters of hot benzene, filtering, distilling off the bulk of the benzene, and stirring in 2 liters of 90–120° ligroin. The crystalline product

(1) On leave of absence from the National Research Institute of Chemistry, Academia Sinica.

(2) Soffer, Soffer and Sherk, *THIS JOURNAL*, **67**, 1435 (1945).

(3) Herr, Whitmore and Schiessler, *ibid.*, **67**, 2061 (1945).

(4) Kipper, *Ber.*, **38**, 2190 (1905).

(5) Martin, *ibid.*, **58**, 1438 (1936).

(6) Private communication from C. S. Sherman.

(7) Datcher and Wintersteiner, *THIS JOURNAL*, **61**, 1992 (1939).

(8) Kipper (ref. 4) conducted the reaction in carbon disulfide, but E. Berliner found benzene to be preferable. The procedure given is based upon the experiences of several runs conducted by E. Berliner, by D. Curtin, by C. Moser and M. Paulshock, and by the author.

weighed 922 g. (85.5%), m. p. 118–119°. A recrystallized sample formed fine, white, feathery, crystals, m. p. 119–120°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.21; H, 5.31.

γ -(*p*-Phenoxyphenyl)-butyric Acid (II). (a) **Clemmensen Reduction.**—In a typical experiment a 270-g. batch of β -(*p*-phenoxybenzoyl)-propionic acid was reduced by the Martin procedure with added acetic acid⁶ and with the use of freshly poured zinc and stirring.⁶ The recovered total product, a yellowish oil (238 g.) on distillation afforded 146 g. (54%) of the acid II, b. p. 213–216° at 0.6 mm. The distillate crystallized readily to a solid melting at 68–70°; recrystallization from ligroin–benzene gave pointed, thick prisms, m. p. 71–72°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.99; H, 6.29. Found: C, 75.27; H, 6.66.

The pinacol dilactone III was isolated by digestion of the distillation residue with benzene; 11.5 g. of a white crystalline product separated (m. p. 228–230°), and on recrystallization from benzene melted at 231–232° (insoluble in cold alkali, sparingly soluble in ether).

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 75.87; H, 5.17. Found: C, 76.17; H, 5.25.

(b) **Wolff-Kishner Reduction Using Sodium.**—To a solution of 2.5 g. of sodium in 70 cc. of diethylene glycol there was added 10 g. of the keto acid I and 5 cc. of 85% hydrazine hydrate. After refluxing for one hour the condenser was removed until the temperature of the solution had reached 195–200°, when refluxing was continued for about three hours. The mixture was cooled, acidified, extracted with benzene; the washed and dried solution deposited 9.2 g. (97%) of crystalline acid, m. p. 66–68°. Recrystallization from benzene–ligroin (1:5) gave 8.63 g. (91.3%) of pure product, m. p. 69–70°.

A reduction made with 2.7 g. of keto acid, 5 g. of 100% hydrazine hydrate, 4 g. of sodium, and 80 cc. of diethylene glycol conducted under total reflux for seventy hours gave only 1.2 g. (48%) of pure reduced acid.

(c) **Use of Sodium Hydroxide.**—A mixture of 10 g. of I, 5 g. of sodium hydroxide, 80 cc. of diethylene glycol (or triethylene glycol), and 5 cc. of 85% hydrazine hydrate was refluxed for one hour and treated further as described in (b). The yield was 9.1 g. (96%) of product, m. p. 67–68°, and 8.62 g. (90.9%) of once-crystallized material (no depression in m. p.; found: C, 75.31; H, 6.37).

(d) **Use of Potassium Hydroxide.**—With use of this alkali it was possible to reduce still further the amount of solvent; a suitable charge was: 500 g. (1.85 moles) of keto acid I, 350 g. (6.25 moles) of potassium hydroxide, 250 cc. of 85% hydrazine hydrate, and 2500 cc. of triethylene (or diethylene) glycol. After refluxing for one and one-half hours the water was drained from the condenser and the temperature allowed to rise to 195°, when refluxing was continued for four hours longer. The cooled solution was diluted with 2.5 liters of water and poured slowly into 1.5 liters of 6 *N* hydrochloric acid and the light cream-colored solid dried: average yield 451 g. (95%), m. p. 64–66°.

γ -(*p*-Phenoxybenzoyl)-butyric acid was obtained by condensing diphenyl ether (54 g.) with glutaric anhydride in benzene with aluminum chloride under ice cooling. The acid precipitated from soda solution melted at 101–105° (50 g., 88%), and crystallization from benzene–ligroin gave 48 g. (84.5%) of prisms, m. p. 110–111°. The substance is readily soluble in alcohol or benzene, sparingly soluble in ligroin.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 72.16; H, 5.85.

δ -(*p*-Phenoxyphenyl)-valeric Acid.—Reduction of 10 g. of the keto acid by procedure (c) above gave 9.1 g. (95.8%)

of crude acid, m. p. 60–62°, or 8.1 g. (85.3%) of once-crystallized product (long white blades), m. p. 66–67°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.46; H, 6.99.

γ -(3-Acenaphthyl)-butyric Acid.—Reduction of 5.1 g. of β -(3-acenaphthoyl)-propionic acid in the presence of potassium hydroxide as in (d) above gave 4.81 g. (99.8%) of crude product, m. p. 140–143°; the recrystallized material (charcoal) amounted to 3.91 g. (81%) and melted at 147–148° (lit.,⁹ 147–148°).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.93; H, 6.71. Found: C, 80.16; H, 7.19.

Fieser and Peters⁹ could not reduce this keto acid at all by the early Clemmensen method and obtained a 40% yield on using the methyl ester. Martin,⁵ using added toluene, obtained yields of 50% from the acid and 60% from the methyl ester.

γ -(3-Methoxyphenyl)-butyric Acid.—On reduction of 2 g. of β -(3-methoxybenzoyl)-propionic acid by procedure (d) and remethylation of the product extracted by ether from the acidified reaction mixture there was obtained 1.67 g. (83.3%) of crude acid, m. p. 40–42°. Two crystallizations from ligroin gave 1.2 g. (64.5%), m. p. 46–47°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 68.12; H, 7.03.

Martin,⁵ who reviewed the earlier literature, obtained this acid by Clemmensen reduction in yields varying from 25 to 60% according to the size of the batch.

Diphenylmethane.—A mixture of 18.2 g. of benzophenone, 7 g. of sodium hydroxide, 100 cc. of triethylene glycol and 10 cc. of 85% hydrazine hydrate was treated as above, the ether residue on distillation over sodium gave 14.0 g. (83.3%) of pure hydrocarbon, b. p. 149° at 23 mm., n_D^{25} 1.5752.

***n*-Propylbenzene.**—A mixture of 40.2 g. of propiophenone, 40 g. of potassium hydroxide, 300 cc. of triethylene glycol and 30 cc. of 85% hydrazine hydrate was refluxed for one hour and then aqueous liquor was removed by means of a take-off adapter until the temperature of the liquid rose to 175–178°, when refluxing was continued for three hours. The reaction mixture and aqueous distillate were combined and extracted with ether and the neutral organic fraction was distilled over sodium. The yield of hydrocarbon was 29.6 g. (82.2%); b. p. 160–163°, n_D^{25} 1.4908, d_4^{25} 0.8593. Soffer and co-workers² used four times as much solvent, a large excess of sodium, and a reaction time of forty-nine hours.

Cyclohexane.—The reduction of cyclohexanone (39.2 g.) was conducted as in the preceding section, and at the end the product was distilled out of the reaction mixture and was then washed neutral, dried, and distilled over sodium to give 27.0 g. (89.4%) of cyclohexane, b. p. 80–81°, n_D^{25} 1.4245. The Whitmore group³ report a yield of 63%.

Summary

The improved procedure consists in refluxing the carbonyl compound in a moderate amount of diethylene or triethylene glycol with 85% hydrazine hydrate and about three equivalents of sodium hydroxide or potassium hydroxide for one hour, distilling enough water and excess hydrazine hydrate to raise the temperature to 180–200°, and refluxing the solution for three or four hours longer. The yields are excellent and the process is applicable on a large scale.

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(9) Fieser and Peters, *THIS JOURNAL*, **54**, 4374 (1932).