The Reduction of Some Carbonyl Compounds with Sodium Borohydride.

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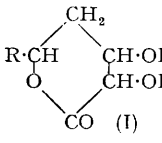
Six carbonyl compounds have been reduced by use of sodium borohydride. Generally it was necessary to use the method of inverse addition in order to obtain reasonable yields of the corresponding alcohols. The latter formed very stable complexes with boron, and were isolated in the pure state after removal of the boron as methyl borate.

The primary purpose in carrying out the reduction of a series of carbonyl compounds with sodium borohydride was to explore the possibility of utilizing this reaction in a projected synthesis of racemic auxin-a lactone (I; R = 3 : 5-di-*sec.*-butyl*cyclo*pent-1-enyl) (Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181). The literature records

only two syntheses of compounds structurally related to auxin-a. In the first of these, which furnished a model containing the appropriate side chain attached to the unsubstituted *cyclo*pentene ring (Kögl and Ultee, *Rec. Trav. chim.*, 1950, **69**, 1576), the cyclic double bond was incorporated *via* exhaustive methylation. In the second instance (English, Gregory, and Trowbridge, *J. Amer. Chem. Soc.*, 1951, **73**, 615), which resulted in the unsubstituted *cyclo*pentane derivative, the 1 : 2-glycol system was prepared *via* direct hydroxylation of an ethylenic bond. Neither of these approaches is capable of furnishing, in an unambiguous manner, racemic auxin-a lactone.



(I)

A possible approach to the problem would be through selective reduction of the 1 : 2-diketo-lactone corresponding to auxin-a lactone, provided the reaction could be carried out in such a way as to leave untouched both the cyclic double bond and the lactone (or carboxyl) grouping. This specificity was apparently obtained in the use of sodium borohydride by Chaiken and Brown (*ibid.*, 1949, **71**, 122). These authors, however, in describing the use of this reagent in reductions, reported unsuccessful attempts to isolate the reduction products of both glucose and pyruvic acid because of the very stable complexes formed by boron with the polyhydric alcohol and the α-hydroxy-acid, respectively. In dealing with carbohydrates it has since been found possible to eliminate the boron from its complexes by several methods (Abdel-Akher, Hamilton, and Smith, *ibid.*, 1951, **73**, 4691), one of which we have adopted with fair success. This consists in removing the boron as the very volatile methyl borate, by heating the complex with an acidic methanol solution. Under these conditions the α-hydroxy-acids were readily esterified, and this necessitated an additional hydrolysis step. Ester interchange was also found to occur readily.

The application of these procedures to pyruvic acid, glyoxal, mesoxalic acid (in the form of its sodium salt), and phenylglyoxylic acid resulted in satisfactory yields (50—75%) of the corresponding hydroxy-compounds. However, the yields of simple reduction products from both ethyl αβ-dioxobutyrate and ethyl α-acetoxy-β-oxobutyrate were far from satisfactory, *i.e.*, 15—25%.

In dealing with alkali-sensitive compounds (all of the above except mesoxalic acid), it was found necessary to use the method of inverse addition (Bachmann and Dreiding, *ibid.*, 1949, **71**, 3222), in order to minimize undesirable condensations or rearrangements. A typical case was pyruvic acid, affording lactic acid in 61% yield on inverse addition of reductant. On the other hand, when the sodium borohydride solution was added to the pyruvic acid, no lactic acid could be isolated. Instead, a thick syrup was obtained which failed to give tests either for a 1 : 2-glycol or for a ketone, although it did give a positive test for an α-hydroxy-acid when treated with lead dioxide (Baeyer and Liebig, *Ber.*, 1898, **31**, 2106). The substance therefore was not dimethyltartaric acid, earlier obtained by bimolecular reduction of pyruvic acid (Böttinger, *Annalen*, 1877, **188**, 318). It is possible that the reduction product was γ-carboxy-α-hydroxy-γ-valerolactone, formed from para-pyruvic acid (or its lactone) which is known to be formed spontaneously from salts of pyruvic acid (Wolff, *ibid.*, 1899, **305**, 154).

Our work with ethyl αβ-dioxobutyrate met with several unexpected difficulties. For the preparation of this ester in quantity it was found necessary first to form the α-hydroxy-imino-derivative of ethyl acetoacetate according to a revised procedure (E. Coolidge, Diss., The Johns Hopkins Univ., 1949), and to oxidise this derivative with oxides of nitrogen (*Org. Synth.*, John Wiley and Sons, Inc., New York, 1941, Coll. Vol. I, 266). However, the orange-yellow diketone thus obtained formed a colourless crystalline hydrate of m. p. 96—98°. This value, although midway between the m. p.s reported for the hydrates of the methyl and the *iso*propyl ester (80° and 115°, respectively) (Denis, *Amer. Chem. J.*, 1907, **38**, 563), does not agree with either of the values reported for the ethyl ester, *viz.*, 140° (Denis, *loc. cit.*) and 148° (Müller, *Ber.*, 1933, **66**, 1668). It was therefore necessary to prove that our material was authentic diketo-ester, and all the evidence at hand indicates that this is the case. For instance, our product gave the known benzilic acid type of rearrangement to yield *iso*malic acid (Denis, *loc. cit.*); both the hydrate and the free diketo-ester furnished the same dianil, of correct m. p. (Bouveault, *Bull. Soc. chim.*, 1905, **33**, 481); and reduction of both ester and hydrate afforded αβ-dihydroxybutyric

esters. A further unexpected feature was the fact that, even with the method of inverse addition, it was necessary to use massive quantities of reagent to effect complete reduction of the two keto-groups, and this led to much high-boiling product, apparently produced by condensation. Nevertheless, reduction of the ethyl ester gave, after removal of methyl borate, methyl αβ-dihydroxybutyrate in low yield. The same ester was obtained, also in poor yield, by starting with methyl αβ-dioxobutyrate and using sodium borohydride, or in good yield with Raney nickel by the technique of Mozingo, Spencer, and Folkers (*J. Amer. Chem. Soc.*, 1944, **66**, 1859). It is noteworthy that, while Raney nickel was quite efficient, Adams's catalyst with hydrogen under about 3 atm. pressure was without effect on the dicarbonyl system.

The reduction of either ethyl or methyl α-acetoxy-β-oxobutyrate with sodium borohydride also formed considerable high-boiling material, along with the desired α-acetoxy-β-hydroxy-derivative. As with the αβ-diketo-esters, Adams's catalyst and hydrogen were without action, but Mozingo's technique was quite effective. As a further check on the identity of our reduction products, methyl α-acetoxy-β-hydroxybutyrate, produced *via* Raney nickel reduction, was hydrolysed to the dihydroxy-acid and the latter was esterified, yielding the same methyl dihydroxy-ester as that furnished by sodium borohydride reduction of both the diketo- and the α-acetoxy-β-keto-esters.

Several unsuccessful attempts were made to isolate in crystalline form αβ-dihydroxybutyric acid and its phenylhydrazide. The reason for this lack of success appears to lie in the fact that, although the pure optical forms have been obtained in the solid state, no method has succeeded in separating the two racemic acids, or their derivatives (Braun, *ibid.*, 1929, **51**, 231). It seems safe, therefore, to conclude that sodium borohydride reductions are in no sense stereospecific, and that the product consists of a mixture of the DL-*threo*- and the DL-*erythro*-form.

Experimental

Reduction of Pyruvic Acid.—Freshly prepared pyruvic acid (*Org. Synth.*, Coll. Vol. I, 1941, p. 475) (15·0 g.) was dissolved in water (100 ml.), cooled to 0° and carefully neutralised (final pH 5) with a cold solution of sodium hydroxide (6·85 g.) in water (20 ml.). Portions of this salt solution were then added dropwise (30 min.) to a mechanically stirred solution of sodium borohydride (3·3 g.) in water (35 ml.), the temperature being kept at 10—15°. After storage at 0° for 2½ hr., the mixture was reduced to half-volume under water-pump vacuum, acidified with hydrobromic acid, and again evaporated (reduced pressure) until a thick syrup formed. Excess of 4% methanolic hydrogen bromide (from dry gas) was added to the residue, and methyl borate was removed by gentle warming under reduced pressure (at atmospheric pressure considerable esterification occurred). The crude syrup, freed from sodium bromide, weighed 11·5 g., and gave a negative sodium nitroprusside test for pyruvic acid (Simon, *Compt. rend.*, 1897, **125**, 534).

The *p*-bromophenacyl ester (Rather and Reid, *J. Amer. Chem. Soc.*, 1919, **41**, 75), recrystallised from acetone–water, had m. p. 111—113°, not depressed on admixture with authentic material. For the calculation of yield, the sparingly soluble 1-hydroxyethylbenziminazole was prepared (Phillips, *J.*, 1928, 2393) and crystallised from water; it had m. p. 178—180°, not depressed on admixture with authentic substance. On this basis the yield of lactic acid was 61%.

When the reduction was carried out by addition of reductant *to* pyruvic acid, and the product worked up as above, a thick syrup resulted. On attempted purification by distillation obvious decomposition resulted and a thick red-brown fluorescent oil, b. p. *ca.* 175°/15 mm., was obtained. Tests were therefore conducted on the crude product. This was not ketonic, and contained at least one hydroxyl group as shown by a positive test with ceric nitrate reagent (Shriner and Fuson, " Identification of Organic Compounds," John Wiley and Sons, New York, 3rd Edn.), but would form neither a dinitrobenzoate nor a *p*-bromophenacyl ester. On pyrolysis it showed the typical behaviour of an α-hydroxy-acid (Le Sueur, *J.*, 1905, **87**, 1888). The possibility that the compound contained a glycol grouping was eliminated by its negative test with periodic acid (Shriner and Fuson, *loc. cit.*). With lead acetate the compound readily formed a lead salt, but on regeneration from this salt, a solid was obtained that melted over a wide range. After treatment of the syrup with base, followed by acidification, the solution was oxidised with lead dioxide (Baeyer and Liebig, *loc. cit.*), liberating much carbon dioxide. Removal of lead by filtration gave a solution showing a positive iodoform test, and furnishing a very small amount

of a 2 : 4-dinitrophenylhydrazone, m. p. 85—110°. No semicarbazone could be prepared, and no evidence of 1 : 3 : 5-triacetylbenzene (the expected product) could be obtained.

Reduction of Phenylglyoxylic Acid.—The freshly prepared acid (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 244, footnote 11, 1941) (5 g.) in water (35 ml.) was neutralised with dilute sodium hydroxide, cooled, and added dropwise (½ hr.) to a vigorously stirred solution of 0·4 g. of sodium borohydride in 10 ml. of water, the temperature of the mixture being kept at 10—18°. On acidification with hydrochloric acid, hydrogen was evolved (from excess of borohydride), and a white solid boron complex (1·2 g.) was precipitated. The filtrate was extracted five times with ether, and the ether was evaporated, leaving 2·2 g. of an organic–boron mixture. Dissolution of the combined solids in benzene–acetone (9 : 1) removed a small amount of mandelic acid, m. p. 118—120°. The insoluble boron-containing residue, m. p. 212—213°, was boiled with 4% methanolic·hydrogen chloride until free from boron. The residue was methyl mandelate, m. p. 48—53°. For the isolation of pure mandelic acid it was found best to evaporate the reduction product to dryness under reduced pressure without prior addition of acid. The dry residue was then neutralised with concentrated hydrochloric acid–methanol, excess of 4% methanolic hydrogen chloride added, and the methyl borate removed under reduced pressure until a portion of the solution, when ignited, burned with a pale blue flame. The remainder of the methanol was evaporated, and the residue refluxed with excess of 10% aqueous sodium hydroxide for 1 hr. After acidification the solution was extracted six times with ether (use of a continuous-extraction apparatus occasioned no improvement in yield). Evaporation furnished mandelic acid in 76% yield.

Reduction of Glyoxal.—Commerical 30% glyoxal solution (16·7 g., *i.e.*, 5 g. of glyoxal) was diluted with water (35 ml.), cooled to 0°, and neutralised with dilute sodium hydroxide (final pH 8). This cold solution was then added slowly to a rapidly stirred solution of sodium borohydride (1·7 g.) in water (10 ml.) at such a rate that the internal temperature did not rise above 60°. After acidification, evaporation, and removal of methyl borate as described above, the concentrated mixture was filtered. The sodium chloride was washed with absolute methanol, and the filtrate and washings were combined, neutralised, and distilled, yielding 3·58 g. (72%) of ethylene glycol, b. p. 107—108°/24 mm. The dibenzoate had m. p. 71—73°, undepressed on admixture with authentic material.

Sodium Mesoxalate.—Since in our hands the preparation of crystalline mesoxalic acid (Curtiss, *Amer. Chem. J.*, 1906, **35**, 477) was without success, our reduction experiments were carried out with sodium mesoxalate, prepared as follows. Dibromomalonic acid (Conrad and Reinbach, *Ber.*, 1902, **35**, 1817) (26 g., 0·1 mol.) was refluxed for 3 hr. with sodium hydroxide (18 g., 0·45 equiv.) in water (50 ml.). The sodium mesoxalate was slowly precipitated in 86·4% yield. The dianilino-derivative slowly formed from a concentrated aqueous solution of sodium mesoxalate (0·9 g.) when mixed with concentrated hydrochloric acid (0·6 g.) and aniline (1·8 g.); it (1·9 g.) was washed with alcohol, and had m. p. 118—119·5°. Conrad and Reinbach (*loc. cit.*) report 120°.

Reduction of Sodium Mesoxalate.—To the salt (8 g., 0·054 mol.), dissolved in water (500 ml.) at 60°, was added sodium borohydride (0·55 g., 0·014 mol.) in water (20 ml.), and the solution was rapidly stirred for ½ hr. after mixing was complete. The water was removed (water-pump vacuum), the residue neutralised, and excess of 4% methanolic hydrochloric acid added. After removal of methyl borate, the solution was neutralised, and the remainder of the methanol removed by distillation. Sodium hydroxide was added until the solution contained 10% thereof, the whole refluxed for 2 hr., cooled, and neutralised. Addition of barium chloride (11 g., 0·045 equiv.) in water (25 ml.) precipitated barium tartronate (9 g.). This was washed several times with water, and then shaken for ½ hr. with the stoicheiometric amount of sulphuric acid in fifteen times its volume of water. Evaporation yielded the free tartronic acid in 52·5% yield.

Since the m. p. of tartronic acid is dependent upon the rate of heating (Balk, *Annalen*, 1939, **537**, 286), the diamide was prepared from barium tartronate. The salt (1·06 g.) was mixed with absolute ethanol to a pasty mass, and dry hydrogen chloride was passed through the mixture for 30 min. After standing for 1 hr., the precipitate was removed, and excess of aqueous ammonia was added to the filtrate. The basic filtrate was evaporated the following day, and the residue triturated with 4 ml. of water. The insoluble portion was collected and recrystallised from 2 ml. of hot water containing 0·5 ml. of ethanol. The diamide formed small needles, m. p. 195—196°, undepressed on admixture with authentic tartrondiamide, prepared similarly from barium tartronate, the latter obtained by basic hydrolysis of ethyl monobromomalonate (*Org. Synth.*, Coll. Vol. I, 1941, p. 245).

Ethyl αβ-Dioxobutyrate.—This was best prepared as follows. Ethyl acetoacetate (130 g.,

1 mol.) was mixed with glacial acetic acid (132 ml.) and cooled, and sodium nitrite (74·8 g., 1·08 mol.) in water (180 ml.) was slowly added to the rapidly stirred solution, with the temperature being kept below 10°. The solution was then set aside at room temperature for ½ hr., then extracted several times with ether. The extracts were carefully neutralised with saturated sodium hydrogen carbonate solution, washed with water, dried (Na_2SO_4), and kept cold.

Dry nitrous oxide (*Org. Synth., loc. cit.*) was passed through the dry ethereal solution (ice temperature) for about 5 hr. After several hours at 0°, the mixture was allowed to warm to room temperature and was kept thus for 2 days. The ether was removed under reduced pressure, and the residue cautiously distilled, yielding a fraction, b. p. 79—140°/30 mm. This was dissolved in an equal weight of water, shaken in the cold with excess of calcium carbonate, and extracted fifteen times with ether. The dried extracts ($CaCl_2$) were distilled, yielding 42 g. (30%) of ethyl αβ-dioxobutyrate, b. p. 72—80°/22 mm. The amounts given above are optimum, the yield being severely decreased if larger or smaller amounts of reagents are used.

On exposure to air the product formed the hydrate, m. p. 96—98°. Recorded m. p.s are 140° (Denis, *loc. cit.*) and 148° (Müller, *loc. cit.*). The identity of our product was proved in two ways. The ester hydrate (0·2 g.) was kept in a solution of sodium hydroxide (1·25 g.) in water (5 ml.) for 2 days. After acidification and evaporation under reduced pressure, the residue was extracted with ether. Evaporation of the ether left colourless crystals of *iso*malic acid, m. p. 142° (decomp.), in agreement with Denis (*loc. cit.*). Preparation of the dianil from both ethyl αβ-dioxobutyrate and its hydrate, according to Bouveault (*loc. cit.*), gave crystalline material, m. p. and mixed m. p. 117—118°, in agreement with the reported figure.

Reduction of Ethyl αβ-Dioxobutyrate.—The ester (5 g., 0·0345 mol.) was dissolved in methanol (35 ml.) and added to a rapidly stirred solution of sodium borohydride (4·7 g., 0·011 mol.) in methanol (50 ml.) at such a rate that the temperature was kept at 10—15°. After removal of the methyl borate, the solution was concentrated, refluxed with excess of methanolic hydrochloric acid for 6 additional hours, neutralised, and dried (Na_2SO_4). On distillation a fraction was taken, b. p. 109—112°/10 mm. (yield 18%). The same product was obtained in the same yield starting with the crystalline hydrate of methyl αβ-dioxobutyrate, m. p. 72—74°, obtained in the same manner as the ethyl ester. Reduction gave methyl αβ-dihydroxybutyrate, b. p. 109—112°/10 mm.; Glattfield and Straitiff (*J. Amer. Chem. Soc.*, 1938, **60**, 1385) give b. p. 109°/10 mm. Hydrolysis of the dihydroxy-ester yielded only a thick syrup that could not be induced to crystallise.

Hydrogenation of Methyl αβ-Dioxobutyrate.—A solution of the ester hydrate (9·5 g.) in 300 ml. of absolute ethanol was mixed with 100 g. of freshly prepared Raney nickel (Mozingo, Spencer, and Folkers, *loc. cit.*) and refluxed for 7 hr. After removal of the catalyst by centrifugation, methyl αβ-dihydroxybutyrate was isolated in 52·7% yield.

Reduction of Ethyl α-Acetoxy-β-oxobutyrate.—The acetoxy-ester (8 g., 0·0425 mol.), prepared by Dimroth and Schweizer's method (*Ber.*, 1923, **56**, 1380), was dissolved in methanol (30 ml.) and added with stirring to a solution of sodium borohydride (2·9 g., 0·0764 mol.) in methanol (25 ml.). The temperature of the reaction mixture rose to 55° and then dropped to 31° when the reduction was complete. After neutralisation with methanolic hydrogen chloride, filtration, and concentration, a pale yellow fragrant liquid remained. *Ethyl α-acetoxy-β-hydroxybutyrate* was obtained in about 25% yield, b. p. 98—100°/2 mm. (Found: OC_2H_5, 24·0. $C_8H_{14}O_5$ requires OC_2H_5, 23·7%). The hydroxy-ester gave negative tests for carbonyl groups, and a positive test for hydroxy-groups.

Hydrogenation of Ethyl α-Acetoxy-β-oxobutyrate.—The ester was reduced in 59% yield by the technique described above using Raney nickel. After separation of the catalyst, concentration under vacuum left a thick, green, gelatinous residue, which gave a positive test for nickel with dimethylglyoxime and left a white infusible mass upon ignition. After addition of water to the jelly, it was distilled, and yielded ethyl α-acetoxy-β-hydroxybutyrate without significant decomposition (Found: C, 50·7; H, 7·6. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4%).

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