

302. *Reformatsky Reactions with Methyl γ -Bromocrotonate.*

By E. R. H. JONES, D. G. O'SULLIVAN, and M. C. WHITING.

Reformatsky reactions between methyl γ -bromocrotonate and various carbonyl compounds have been investigated. A detailed study of the reaction with benzaldehyde has revealed that distillation of the crude product at very low pressures and hydrolysis in very dilute alkaline solutions are essential in order to obtain reasonable yields of the expected δ -hydroxy-acid.

A by-product, identified as the methyl ester of β -hydroxy- β -phenyl- α -vinylpropionic acid, and methyl crotonate, which have been isolated in addition to the normal product, probably arise from different modes of reaction of the resonating anion of the initially formed zinc complex with benzaldehyde.

IN view of the appearance of a paper by English and Gregory (*J. Amer. Chem. Soc.*, 1947, **69**, 2123) describing Reformatsky reactions between ethyl γ -bromocrotonate and various aldehydes, an account of some work along similar lines carried out in these laboratories seemed desirable. We have been interested in this reaction for various reasons—its application to the synthesis of vitamin A acid and related substances (Arens and van Dorp, *Rec. Trav. chim.*, 1946, **65**, 338; Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866; Heilbron, *J.*, 1948, 386), the possibility of employing it for the synthesis of $\alpha\beta$ -unsaturated δ -lactones (Haynes and Jones, *J.*, 1946, 954), and as a possible approach to the synthesis of auxin-a (Kögl and Erxleben, *Z. physiol. Chem.*, 1934, **227**, 51) and analogues.

The crude *methyl* ester of 4-phenylbut-1-en-4-ol-1-carboxylic acid (I) obtained from a Reformatsky reaction between benzaldehyde and methyl γ -bromocrotonate underwent appreciable dehydration on distillation at 0.1 mm. to cinnamylideneacetic ester (cf. English and Gregory, *loc. cit.*), the content of the latter increasing from 7% to 20%, as measured by the intensity of light absorption at 3050 μ . Distillation in a short-path still at 10^{-4} mm. effectively prevented dehydration. The resulting ester was hydrolysed with a 1% solution of potassium hydroxide in aqueous methanol to the crystalline hydroxy-acid, m. p. 115°, the yield from benzaldehyde being 25%. It was shown spectrographically that in more concentrated solutions extensive dehydration occurred, cinnamylideneacetic acid being the only isolable product.

The low yields of analytically pure ester and of crystalline acid obtained by English and

Gregory (*loc. cit.*) (22%, and 7% of impure material, respectively, from benzaldehyde) are in accordance with our observations on the instability of these substances towards high temperatures and strongly basic reagents.

Ziegler *et al.* (*Annalen*, 1942, 551, 80) stated that when benzaldehyde was condensed with methyl γ -bromocrotonate and the crude product was distilled at 12 mm. (b. p. 160—180°) it gave "4-phenylbut-1-en-4-ol-1-carboxylic ester" in 70% yield. In our experience the yield is only of the order of 40—45% even when the crude product is distilled at 10^{-4} mm., falling to about 25% when a pressure of 0.1 mm. is used, much dehydration then taking place. Ziegler *et al.* recorded no physical constants other than boiling point, and no analysis other than a methoxyl determination not very near to the calculated value for the hydroxy-ester.

A small quantity of a by-product, m. p. 83°, was isolated on one occasion from the distilled ester; it analysed as $C_{12}H_{14}O_3$, *i.e.*, it was isomeric with the normal hydroxy-ester, it showed no high-intensity light absorption above 2200 μ ., and in a Zerewitinoff determination it evolved methane corresponding to the presence of one active hydrogen atom. Hydrogenation with a palladium catalyst gave an ester, m. p. 40—41°, hydrolysed by cold dilute potassium hydroxide solution to an acid, $C_{11}H_{14}O_3$, m. p. 115—116°, which proved to be β -hydroxy- β -phenyl- α -ethylpropionic acid; the literature m. p.s of 110—112° and 111.5—112.5° for the latter probably refer to mixtures of stereoisomerides. The methyl ester of the authentic acid had m. p. 42° and did not depress the m. p. of the hydrogenation product. Ozonolysis of the original ester, m. p. 83°, gave a 34% yield of formaldehyde; it is therefore *methyl β -hydroxy- β -phenyl- α -vinylpropionate* (II).

There are two possible explanations for the formation of this product. It might be formed by a Reformatsky reaction between benzaldehyde and methyl α -bromo- α -vinylacetate, the latter being present as an impurity in the methyl bromocrotonate used (it could be formed by an allylic rearrangement of the latter). This possibility is extremely unlikely in view of the fact that the bromocrotonic ester employed was carefully fractionated before use (it had b. p. 98.5—100°/24 mm., n_D^{25} 1.4983—1.5003). Alternatively, the by-product might be formed from γ -bromocrotonic ester in the manner described below.

Under the same conditions crotonaldehyde gave a crude product which on distillation at 13 mm. gave the methyl ester of hepta-1 : 3 : 5-triene-1-carboxylic acid, m. p. 75—76° (Kuhn and Hoffer, *Ber.*, 1930, 63, 2164). Fractionation of the crude ester at 1 mm., however, gave a homogeneous product in 22% yield which, according to analytical and spectrographic data, is *methyl hepta-1 : 5-dien-4-ol-1-carboxylate*.

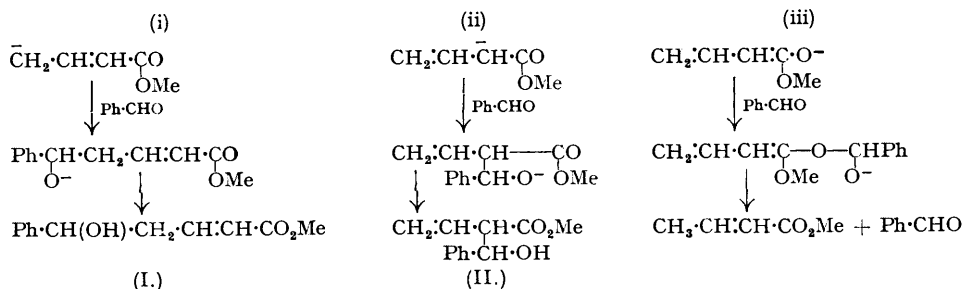
With simpler carbonyl compounds, including acetone, butaldehyde, and diisopropyl ketone, the results were less satisfactory. Small yields of inhomogeneous materials were obtained, and much self-condensation of the carbonyl compound appeared to take place; mesityl oxide and 2-ethylhexenal respectively were isolated, as 2 : 4-dinitrophenylhydrazones, from the low-boiling fractions in the first two cases.

The reactions with acetophenone and cyclohexanone were also studied, in connection with polyene syntheses, the interest centering on the dehydrated products rather than the hydroxy-esters. In both cases the hydroxy-ester was the primary product, as shown by the absorption spectrum. The crude 4-phenylpent-1-en-4-ol-1-carboxylic ester (from acetophenone) underwent dehydration on distillation (b. p. 125—130°/10⁻² mm.), and alkaline hydrolysis gave crystalline *δ -phenylsorbic acid* (20% yield from acetophenone).

The crude hydroxy-ester from cyclohexanone was partially dehydrated with potassium hydrogen sulphate, and hydrolysis then yielded a mixture of the *hydroxy-acid* and *cyclohexylidenecrotonic acid*, separable by chromatography (yields from cyclohexanone 1.2% and 2.5%, respectively). The hydroxy-ester underwent some fission on hydrolysis with hot methanolic potassium hydroxide solution into cyclohexanone and crotonic acid; the former was isolated as its 2 : 4-dinitrophenylhydrazone, in 50% yield; this fact, and the difficulties of separation, account for the low yields.

In all the Reformatsky reactions methyl crotonate was formed and much of the carbonyl compound was recovered, although most of the zinc reacted. The same effect has been noted previously (Newman, *J. Amer. Chem. Soc.*, 1942, 64, 2131) in conventional Reformatsky reactions and ascribed to enolisation of the carbonyl compound (cf. Arens and Van Dorp, *loc. cit.*; Newman, *loc. cit.*); in the case of benzaldehyde enolisation is impossible, yet methyl crotonate was formed and, despite the difficulty of separation, more benzaldehyde was recovered on one occasion than corresponded to the amount of unreacted zinc. The following alternative explanation seems plausible. The anion of the initially formed zinc complex can be supposed to react with benzaldehyde in three different ways, in accordance with the three major resonance

structures, giving, after acidification, (i) the normal product, (ii) the by-product, β -hydroxy- β -phenyl- α -vinylpropionic ester, and (iii) methyl crotonate and benzaldehyde from a readily-



hydrolysed intermediate. This hypothesis accounts convincingly for the three products isolated from the reaction between benzaldehyde and methyl γ -bromocrotonate. It gains support from the well-known behaviour of crotyl and methylvinyl carbinyl halides in Grignard reactions (*inter alia*, Young and Roberts, *J. Amer. Chem. Soc.*, 1945, **67**, 319) and the predominance of the third mode of reaction may well account for the non-isolation of any normal products from attempted Reformatsky reactions with ϵ -bromosorbic ester (Heilbron, Jones, and O'Sullivan, *loc. cit.*). It may also be noted that Arens and Van Dorp (*loc. cit.*) mention the isolation of isomeric by-products in Reformatsky reactions between β -ionone and methyl γ -bromocrotonate.

Several unsuccessful attempts were made to convert the 4-phenylbut-1-en-4-ol-1-carboxylic acid into the corresponding lactone. Distillation at 10^{-4} mm. and at 10 mm. did not effect any change, and treatment with acids gave cinnamylideneacetic acid. Attempts were made to isomerise this presumably *trans*-acid to the *cis*-compound by irradiation with light from a mercury-vapour lamp, and also sunlight, with and without the addition of iodine, but in all cases the original acid was recovered unchanged. Dodge's method (*J. Amer. Chem. Soc.*, 1916, **38**, 450) was also employed; a sodium hydrogen sulphite addition compound was obtained without difficulty, but attempts to convert it into the lactone failed.

The conversion of the δ -substituted δ -hydroxy- $\alpha\beta$ -ethylenic acids into analogues of auxin-a is being studied, as also are other routes directed towards the same end. A brief account of the present work and of our future aims was given in the discussion following a paper read by the senior author at the International Congress of Pure and Applied Chemistry in London in July 1947.

EXPERIMENTAL.

Reformatsky Reactions.—A solution of the carbonyl compound and methyl γ -bromocrotonate (1 molecular equiv. of each) in an equal volume of dry benzene was added to the stirred suspension of activated zinc at such a rate that the benzene refluxed gently without external heating. The mixture was then heated under reflux for a further 15 minutes after the end of the spontaneous reaction. The cooled solution was worked up in the usual manner; evaporation of the benzene gave an oil containing methyl crotonate, recovered carbonyl compound, the required product, and usually an appreciable non-volatile residue.

4-Phenylbut-1-en-4-ol-1-carboxylic Acid.—The crude ester, obtained as described from benzaldehyde (21.2 g.), methyl γ -bromocrotonate (35.8 g.), and zinc (13.0 g.; 1.8 g. recovered) was heated at $100^\circ/10^{-2}$ mm. to remove benzaldehyde, and distilled at $100\text{--}110^\circ$ (bath temp.)/ 10^{-4} mm. The distillate (17.5 g.) solidified partly; after the addition of ether and light petroleum (b. p. $40\text{--}60^\circ$) the by-product (*methyl β -hydroxy- β -phenyl- α -vinylpropionate*) (0.9 g.) was separated as needles, m. p. 81° , which after crystallisation from light petroleum (b. p. $40\text{--}60^\circ$) had m. p. 83° (Found: C, 69.75; H, 6.7. $C_{12}H_{14}O_3$ requires C, 69.85; H, 6.85%). Light absorption in alcohol: Maximum, 2580 \AA .; $\epsilon = 140$; inflexion, 2640 \AA .; $\epsilon = 130$.

The filtrate was evaporated, the residue (n_D^{20} 1.552) dissolved in methanol (300 c.c.), and a solution of potassium hydroxide (6 g.) in water (350 c.c.) added. After standing overnight the crude acid was isolated in quantitative yield as a gum, which was dissolved in warm benzene. From the cold solution the hydroxy-acid (9.2 g.) separated as a powder, m. p. $113\text{--}114^\circ$; after crystallisation from benzene or water, it formed leaflets, m. p. 115° (English and Gregory, *loc. cit.*, give m. p. $115\text{--}116^\circ$) (Found: C, 68.75; H, 6.3. Calc. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.3%). Light absorption in alcohol: Maxima 2170 and 2640 \AA .; $\epsilon = 18,000$ and 270, respectively. The *methyl* ester, prepared by treating the sodium salt with methyl sulphate, had b. p. $149^\circ/10^{-1}$ mm., n_D^{20} 1.5410 (Found: C, 69.95; H, 6.75. $C_{12}H_{14}O_3$ requires C, 69.85; H, 6.85%). Light absorption in alcohol: Maximum, 2180 \AA .; $\epsilon = 17,000$.

β -Hydroxy- β -phenyl- α -ethylpropionic Ester and Acid.—(a) The by-product ester, m. p. 83° (134 mg.), was dissolved in methanol (3 c.c.) and shaken in hydrogen together with a palladium-barium sulphate catalyst (15 mg.; 5%) until absorption was complete. After filtration and evaporation of the solvent,

the residue solidified, m. p. 40—41°; a small sample (*ca.* 20 mg.) was removed and the remainder was treated with a solution of potassium hydroxide (150 mg.) in aqueous methanol (14 c.c.) for 24 hours at 20°. Acidification and isolation with ether in the usual way yielded a syrup which solidified on standing; crystallisation from cyclohexene gave the hydroxy-acid (75 mg.) as fine needles, m. p. 115—116° (Found: C, 67.85; H, 7.2. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.25%).

(b) The crude ester resulting from a Reformatsky reaction between benzaldehyde (10.6 g.), zinc (6.5 g.), and methyl α -bromo-*n*-butyrate (15 g.) was hydrolysed without preliminary distillation by treatment with a solution of potassium hydroxide (4 g.) in water (250 c.c.) and methanol (150 c.c.) at 20°. The acid fraction solidified and was crystallised from benzene to give the hydroxy-acid (6 g.). After a further crystallisation from benzene it had m. p. 110—112°; it was then recrystallised from aqueous methanol and finally from cyclohexene, giving fine needles, m. p. 115—116° undepressed on admixture with a specimen prepared by method (a) (Perkin and Stenhouse, *J.*, 1891, **59**, 1009, give m. p. 110—112°; Andres, *J. Russ. Phys. Chem. Soc.*, 1896, **28**, 668, gives m. p. 111.5—112.5°).

The methyl ester was prepared by allowing a solution of the hydroxy-acid (1 g.) [obtained by method (b)] in methanol (10 c.c.) containing sulphuric acid (0.05 g.) to stand at 20° for 72 hours. After isolation the neutral fraction solidified, and recrystallisation from light petroleum (b. p. 40—60°) gave the ester as stout needles, m. p. 42°, undepressed on admixture with the specimen prepared by hydrogenation of the by-product [method (a)] (Found: C, 69.5; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%).

Ozonolysis of Methyl β -Hydroxy- β -phenyl- α -vinylpropionate.—The ester (74.5 mg.) was dissolved in glacial acetic acid (3 c.c.) and treated with ozonised oxygen for $\frac{1}{2}$ hour. Decomposition of the ozonide with zinc dust and water, followed by distillation of the aqueous solution gave 13 c.c. of liquid. Half of this was treated with a solution of "dimedone" (*ca.* 70 mg.) in cold water (15 c.c.). After standing overnight at 0°, the separated derivative (16 mg.), m. p. 160—180°, was collected. Following crystallisation from aqueous methanol it had m. p. 187°, undepressed on admixture with an authentic specimen of the formaldehyde derivative.

Methyl Hepta-1:5-dien-4-ol-1-carboxylate.—A Reformatsky reaction was effected between crotonaldehyde (7 g.) and methyl γ -bromocrotonate (18 g.) with zinc (6.6 g.) in benzene (25 c.c.). Fractional distillation of the product gave the methyl ester (3 g.), b. p. 65°/1 mm., n_D^{25} 1.4672 (Found: C, 62.9; H, 8.0. $C_9H_{14}O_3$ requires C, 63.55; H, 8.3%).

δ -Phenylsorbic Acid.—The crude ester from acetophenone (20 g.), methyl γ -bromocrotonate (30 g.) and zinc (13 g., 3.5 g. recovered) weighed 25 g. after removal of acetophenone by distillation at 1 mm. A portion (15 g.) was fractionally distilled at 10⁻² mm.; the fraction, b. p. 125—130° (11 g.), was hydrolysed with cold 10% methanolic potassium hydroxide solution for 24 hours. Treatment of the acid fraction (5 g.) with light petroleum (b. p. 40—60°) gave the acid (3.5 g.) as plates, m. p. 141°, unchanged on recrystallisation (Found: C, 76.6; H, 6.45. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.45%). Light absorption in alcohol: Maxima, 2280 and 3050 Å.; $\epsilon = 10,500$ and 30,000 respectively. The methyl ester (2.3 g.), prepared in the usual way from the acid (3 g.), methanol (25 c.c.), and sulphuric acid (0.5 g.), had b. p. 130°/10⁻² mm., n_D^{27} 1.6225 (Found: C, 76.9; H, 6.95. $C_{13}H_{14}O_3$ requires C, 77.2; H, 7.0%).

cyclohexylidenecrotonic Acid and γ -1-Hydroxycyclohexylcrotonic Acid.—The crude ester from cyclohexanone (20 g.), methyl γ -bromocrotonate (35 g.), and zinc (13 g.; 1.5 g. recovered) was heated in nitrogen with fused potassium hydrogen sulphate (9 g.) for two hours at 160° and then for one hour at 180°. The mixture was cooled, water added, and the ester extracted with ether and washed with sodium hydrogen carbonate solution. Evaporation of the dried extract and distillation at 0.1 mm. gave the mixed esters, b. p. 90—125° (17.7 g.), which were hydrolysed with a slight excess of cold 10% methanolic potassium hydroxide for 24 hours. In this way a red solid (7.1 g.) was obtained which was sublimed at 10⁻⁴ mm. and crystallised from pentane to give a colourless product (5.5 g.), m. p. 58—60°. Analytical and light-absorption data indicated that this was a mixture; it was therefore chromatographed on silica gel, and two fractions were obtained: (i) m. p. 69° (1.6 g.); (ii) m. p. 58—60° (0.6 g.). On crystallisation from pentane these gave respectively cyclohexylidenecrotonic acid (0.8 g.) (A) as prisms, m. p. 75° (Found: C, 71.9; H, 8.45. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%), and γ -1-hydroxycyclohexylcrotonic acid (0.4 g.) (B), as needles, m. p. 64° (Found: C, 65.0; H, 8.65. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%). Light absorption of (A) in alcohol: Maximum, 2680 Å.; $\epsilon = 20,000$. The methyl ester of (A), prepared in the usual way from the acid (2 g.), methanol (20 c.c.), and sulphuric acid (0.2 g.), had b. p. 100°/10⁻¹ mm., n_D^{22} 1.5096 (Found: C, 73.1; H, 8.9. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7.

THE UNIVERSITY, MANCHESTER, 13.

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