651. *Olefinic Acids. Part V. γ-Methoxycrotonic Acid.*

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The synthesis of *γ-methoxycrotonic acid* has been investigated, and a suitable process devised for its preparation. It is very sensitive towards alkali, and readily undergoes prototropic change into the *βγ*-unsaturated isomer; this conversion has been studied under various conditions. *β*-Methoxycrotonic acid, also, undergoes prototropic change, whereas the *α*-methoxy-acid is stable towards alkali. These results can be attributed to the powerful $+M$ effect of the methoxy-group, and can also be reconciled with hyperconjugation influences. *γ*-Methoxycrotonic acid undergoes addition reactions with toluene-*ω*-thiol, thiolacetic acid, and diazomethane.

Some attempts to synthesise other analogues of *γ*-methoxycrotonic acid are described. Methoxyacetone undergoes the Reformatsky reaction and yields, with ethyl bromoacetate, *ethyl β-hydroxy-γ-methoxy*isovalerate, but dehydration of this product takes place in the *βγ*-direction. Condensation of dimethoxyacetone with ethyl cyanoacetate gives *ethyl α-cyano-γ-methoxy-β-(methoxymethyl)crotonate*.

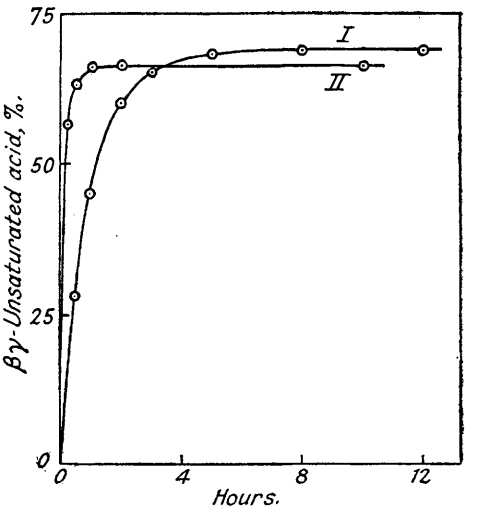
In Part IV (preceding paper) it was shown that α-methoxy- and α-ethoxy-β-methylenebutyric acids readily underwent prototropic change in the presence of alkali and that the equilibrium mixtures consisted largely of the α-alkoxy-ββ-dimethylacrylic acids. In order to determine the effect of alkoxy-substituents in the *γ*-position of αβ-unsaturated acids, the preparation of *γ*-methoxycrotonic acid has been studied.

Ethyl *γ*-bromocrotonate is a highly reactive substance, and is known to give the *γ*-hydroxy- and *γ*-acetoxy-esters when treated with moist silver oxide and with sodium acetate, respectively (Rambaud, *Bull. Soc. chim.*, 1934, [v], **1**, 1206, 1317). However, it is reported to give, with alcoholic sodium ethoxide, mainly ethyl 2-ethoxy*cyclo*propane-1-carboxylate (*idem*, *ibid.*, 1938, [v], **5**, 1552). It is possible that a similar reaction occurs with sodium methoxide, since we have failed to isolate any ethyl *γ*-methoxycrotonate by treatment of the bromo-ester with

that reagent, either under the mildest conditions in methanol or in benzene suspension. It was thought, however, that γ-bromocrotonic acid might more readily undergo nucleophilic replacement of bromine, since it should be less susceptible towards addition than the ester. This proved to be so, and with methanolic sodium methoxide it gave *γ-methoxycrotonic acid* in good yield. Unfortunately, the γ-bromo-acid is not readily prepared in large quantity, and the method was therefore unsuitable. It may be noted that, although the replacement reaction occurs in an anionotropic system, no rearrangement was observed, the conditions being essentially bimolecular (cf. Part IV, *loc. cit.*); had rearrangement occurred, the formation (by subsequent prototropic change) of α-methoxycrotonic acid would have taken place.

γ-Ethoxycrotonic acid was synthesised by Lespieau (*Bull. Soc. chim.*, 1906, [iii], **33**, 467) from epichlorohydrin, but the yields and exact conditions were not specified. It has now been found possible to prepare γ-methoxycrotonic acid by this route, but the later stages required detailed investigation in order to obtain satisfactory results.

The isomerisation of γ-methoxycrotonic acid with aqueous alkali at 100°.



I, N-NaOH. II, 4·8N-NaOH.

Epichlorohydrin was converted into 2-hydroxy-3-methoxy-*n*-propyl chloride and thence into β-hydroxy-γ-methoxybutyronitrile (I) by Koelsch's method (*J. Amer. Chem. Soc.*, 1943, **65**, 2461). The formation of γ-methoxycrotonic acid from this nitrile, involving hydrolysis and dehydration, was attempted in several ways. (i) The nitrile was dehydrated over potassium carbonate to give γ-methoxycrotononitrile (Koelsch, *loc. cit.*); hydrolysis of the latter with either 25% sulphuric acid or 10% aqueous sodium hydroxide did not give any appreciable quantity of the solid methoxy-acid. In retrospect, the failure of the alkaline hydrolysis was probably caused by the very easy isomerisation into the βγ-unsaturated methoxy-acid, which was established later. (ii) Hydrolysis of the nitrile (I) with aqueous alkali gave β-hydroxy-γ-methoxybutyric acid (p-*phenylphenacyl* ester), but dehydration of the acid gave only poor yields of oil. (iii) The nitrile (I) was converted into *methyl β-hydroxy-γ-methoxybutyrate*; dehydration of this with phosphoric oxide was unsuccessful, but by distillation over anhydrous potassium carbonate some dehydration was effected. (iv) *Ethyl β-hydroxy-γ-methoxybutyrate* (II) was also prepared from the nitrile (I) and acetylated to give *ethyl β-acetoxy-γ-methoxybutyrate* (III), distillation of which in portions over anhydrous potassium carbonate gave *ethyl γ-methoxycrotonate* (IV). The latter was rapidly hydrolysed by *brief* treatment with hot N-alkali to give γ-methoxycrotonic acid (V) in good yield :

$$\underset{\text{(I.)}}{MeO\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CN} \xrightarrow{71\%} \underset{\text{(II.)}}{MeO\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CO_2Et} \xrightarrow{90\%} \underset{\text{(III.)}}{MeO\cdot CH_2\cdot CH(OAc)\cdot CH_2\cdot CO_2Et}$$

$$\xrightarrow{83\%} \underset{\text{(IV.)}}{MeO\cdot CH_2\cdot CH{:}CH\cdot CO_2Et} \xrightarrow{74\%} \underset{\text{(V.)}}{MeO\cdot CH_2\cdot CH{:}CH\cdot CO_2H}$$

Hydrogenation of γ-methoxycrotonic acid in aqueous solution, over a palladium–charcoal catalyst, gave γ-methoxybutyric acid (p-*phenylphenacyl* ester) with only a trace of butyric acid. The hydrogenolysis of (V) thus occurs much less readily than that of the corresponding γ-hydroxy-acid (see Part IV, *loc. cit.*).

γ-Methoxycrotonic acid is very readily converted into the βγ-unsaturated isomer by the action of alkali, and for this reason the hydrolysis of its ester (see above) must be carried out rapidly. The isomerisation of the acid was followed in a roughly quantitative manner by heating it with excess of aqueous alkai (N. and 4·8N.), the β-methoxymethylenepropionic acid (VI) formed being determined by acidification of test portions and precipitation of the 2 : 4-dinitrophenylhydrazone of succinsemialdehyde (VII). It was found (see figure) that the equilibrium mixture contained *ca.* 70% of (VI); as would be expected, equilibration is faster with the higher concentration of alkali, since the mobility will then be greater, but the composition of

the final product is, within experimental error, independent of the alkali concentration. It was also observed that slow isomerisation occurred when (V) was set aside at ordinary temperature with excess of 5N-alkali, but that the sodium salt of (V) was unchanged by heating it in aqueous solution at 100°. In a larger-scale experiment, γ-methoxycrotonic acid was heated with 5N-alkali at 100° for 2 hours (cf. figure), and β-*methoxymethylenepropionic acid* (VI) was isolated from the product; it exhibited lactonic properties and probably existed partly in the form (VIII).

$MeO\cdot CH{:}CH\cdot CH_2\cdot CO_2H$ (VI.) $\quad CHO\cdot CH_2\cdot CH_2\cdot CO_2H$ (VII.) $\quad MeO\cdot CH(O)\cdot CH_2\cdot CH_2\cdot CO$ (VIII.)

Since in crotonic acid the equilibrium lies entirely on the αβ-side, it is evident that the methoxy-group in the γ-position exercises a profound effect. It was already known that in the α-position a methoxy-group favoured the αβ-form (cf. Part IV, *loc. cit.*), and the opportunity was therefore taken to examine under comparable conditions the αβ–βγ change for α-, β-, and γ-methoxycrotonic acid, all of which were now available. Equilibration was brought about by heating the acids with ethanolic sodium ethoxide, and the amount of αβ-acid was then determined from the absorption spectra, by the technique described in Part IV. α-Methoxycrotonic acid, as expected, was practically unaffected by this treatment (confirmed on a larger scale by isolation of the unchanged acid), whereas with β- and γ-methoxycrotonic acids *ca.* 60% and 70%, respectively, of βγ-forms were present; the figure for the γ-methoxy-acid was thus approximately the same as that determined, by different means, in the solutions equilibrated with aqueous alkali. On the earlier theories of tautomeric change, the favouring of the αβ-unsaturated form by α-substitution, and, of the βγ-form by β- and γ-substitution, is the result which would have been expected if the substituent group in each case had $(+I, -T)$ characteristics (cf. Baker, " Tautomerism," Routledge, 1934, p. 56). That the methoxy-group $(-I, +T)$ behaves in this way must be attributed, as pointed out in Part IV, to the powerful mesomeric $(+M)$ effect, which overshadows the weak inductive $(-I)$ property. In the light of more modern concepts, the problem may be considered from the point of view of the energy contributions resulting from the hyperconjugation of the methoxy-group with ethylenic linkages in the appropriate positions. With the α-methoxy-acid, such hyperconjugation can apply only to the αβ-unsaturated structure (IX), whilst with the γ-methoxy-acid it only comes into play

$Me\cdot CH{=}C(OMe)\cdot CO_2H$ (IX.) $\quad CH{=}CH\cdot CH_2\cdot CO_2H$ (OMe) (X.) $\quad Me\cdot C{=}CH\cdot CO_2H$ (OMe) (XI.) $\quad CH_2{=}C(OMe)\cdot CH_2\cdot CO_2H$ (XII.)

in the βγ-unsaturated form (X). With the β-methoxy-acid both the αβ- (XI) and the βγ-form (XII) offer the possibility of hyperconjugation, but, whereas in (XI) the effect is in competition with the hyperconjugation of the methyl group with the ethylenic linkage, this does not arise in (XII); the latter structure may therefore be considered to be the more stable. The mobility of the γ-methoxy-acid, in its original αβ-unsaturated form, must be increased by the $-I$ effect of the methoxy-group, since the $+M$ effect (which would decrease mobility) cannot operate until the βγ-structure is established.

The readiness with which γ-methoxycrotonic acid undergoes addition reactions was shown in several instances. An aqueous solution of sodium γ-methoxycrotonate reacted smoothly on heating with toluene-ω-thiol to give, in good yield, β-*benzylthio-γ-methoxybutyric acid* (XIII), characterised by oxidation to β-*benzylsulphonyl-γ-methoxybutyric acid*; a comparative experiment, with sodium crotonate, gave a smaller yield of β-benzylthiobutyric acid. γ-Methoxycrotonic acid gave quantitative yields of the expected addition products when treated with (*a*) thiolacetic acid, and (*b*) diazomethane. From the former, β-*acetylthio-γ-methoxybutyric acid* (XIV) was obtained, which on being heated in sodium carbonate solution with benzyl chloride was converted into (XIII). The diazomethane reaction gave *methyl* 4-*methoxymethylpyrazoline*-3-*carboxylate* (XV). The addition of bromine to γ-methoxycrotonic acid is described in Part VI (following paper).

$MeO\cdot CH_2\cdot CH(S\cdot CH_2Ph)\cdot CH_2\cdot CO_2H$ (XIII.) $\quad MeO\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot CO_2H$ (XIV.) $\quad MeO\cdot CH_2\cdot CH{-}CH\cdot CO_2Me$ (CH_2 N=N) (XV.)

From the foregoing experiments it appeared that nucleophilic addition to the β-carbon atom took place rather more readily with γ-methoxycrotonic acid than with crotonic acid itself, but, since the differentiation was more striking when the corresponding α-bromo-acids were investigated, discussion of the additive reactivity is deferred to Part VI (following paper).

Some attempts were made to synthesise other analogues of γ-methoxycrotonic acid, including γ-methoxy-β-methylcrotonic acid and ββ-bismethoxymethylacrylic acid, and although these were unsuccessful some interesting points emerged.

Few methoxy-ketones have been subjected to the Reformatsky reaction (cf. Rubin, Paist, and Elderfield, *J. Org. Chem.*, 1941, **6**, 260; Shriner, "Organic Reactions," 1942, Vol. I, 1), but methoxyacetone was found to react with ethyl bromoacetate to give *ethyl β-hydroxy-γ-methoxyisovalerate* (XVI), hydrolysis of which gave the corresponding *hydroxy-acid*. Distillation of the hydroxy-ester over potassium carbonate gave a mixture of products, in which only methoxyacetone was identified (2 : 4-*dinitrophenylhydrazone*); this ready thermal scission is, in effect, a reversed Claisen reaction. When the hydroxy-acid was heated with acetic anhydride the product was mainly β-formylbutyric acid (XVII) (2 : 4-*dinitrophenylhydrazone*), indicating that although dehydration had been effected it had occurred in the βγ-direction; this is in accord with the observations of Rubin *et al.* (*loc. cit.*), who found that the dehydration of somewhat similar compounds, under acidic conditions, proceeded in this way and gave aldehydes. The *acetoxy*-ester was largely recovered unchanged after distillation over sodium acetate.

$MeO{\cdot}CH_2{\cdot}CMe(OH){\cdot}CH_2{\cdot}CO_2Et$ (XVI.) $\quad CHO{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (XVII.) $\quad (MeO{\cdot}CH_2)_2C{:}C(CN){\cdot}CO_2Et$ (XVIII.)

For the proposed synthesis of ββ-bismethoxymethylacrylic acid, αα′-dimethoxyacetone was required. Grimaux and Le Fèvre (*Bull. Soc. chim.*, 1889, [iii], **1**, 11) and also Henze and Rogers (*J. Amer. Chem. Soc.*, 1939, **61**, 433) obtained only resinous products in attempts to prepare diethoxyacetone from αα′-dichloroacetone and sodium ethoxide. We observed similar results, even under the mildest conditions, with sodium methoxide, and also by treatment with methanol and silver carbonate. In order to reduce this high reactivity of the halogen atoms, αα′-dichloroacetone was converted into its dimethyl ketal, but this compound was remarkably stable. It was practically unaffected by prolonged heating with methanolic sodium methoxide under a variety of conditions.

Attempts were made to prepare dimethoxyacetone by the oxidation of 1 : 3-dimethoxypropan-2-ol, either by the general method of Henze and Rogers (*loc. cit.*) (sodium dichromate and aqueous sulphuric acid) or by the procedure devised by Bowden, Heilbron, Jones, and Weedon (*J.*, 1946, 39) for the oxidation of acetylenic carbinols (chromic anhydride–aqueous acetic acid–acetone). It proved to be impracticable to separate any large quantity of the ketone from unchanged alcohol, and the use of a greater proportion of oxidant merely resulted in diminished yield; nevertheless, an alcohol–ketone mixture was successfully condensed with ethyl cyanoacetate (cf. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452), to give *ethyl α-cyano-γ-methoxy-β-methoxymethylcrotonate* (XVIII). All efforts to hydrolyse and decarboxylate this compound failed. As was to be expected, in the presence of alkali the compound exhibited high mobility and was rapidly converted into the βγ-unsaturated form, as indicated by the formation of a carbonyl compound on subsequent acidification. Attempted hydrolysis by acid led to extensive decomposition.

Experimental.

(Light petroleum, unless stated otherwise, was the fraction of b. p. 40—60°. Light-absorption measurements were made in alcoholic solution.)

Methyl γ-Bromocrotonate.—Methyl crotonate (200 g.), *N*-bromosuccinimide (250 g.), and benzoyl peroxide (0·15 g.) were heated under reflux for 21 hours. The cooled solution was filtered and concentrated. Fractionation of the residue gave methyl γ-bromocrotonate (162 g.), b. p. 78—82°/8 mm., n_D^{20} 1·5021 (cf. Ziegler, *Annalen*, 1942, **552**, 80; Karrer and Schmidt, *Helv. Chim. Acta*, 1946, **29**, 573).

γ-Bromocrotonic Acid.—The methyl ester (40 g.) in 25% aqueous ethanol (500 c.c.) was hydrolysed with barium hydroxide (32 g.) by the method of Braun (*J. Amer. Chem. Soc.*, 1930, **52**, 3173). Yield, 8 g.; m. p. 69—71°.

Action of Sodium Methoxide on Methyl γ-Bromocrotonate.—Sodium methoxide (1·7 g.) was suspended in dry benzene (10 c.c.) and cooled to 0°. Methyl γ-bromocrotonate (5·5 g.) was added gradually, with vigorous stirring, a dark brown colour being developed. After 3 hours at 0° water was added, and the benzene layer was separated, dried (Na_2SO_4), and evaporated to an oil. A small amount of solid gradually formed; this was removed and crystallised from carbon tetrachloride in colourless prisms, m. p. 168—169°. It was possibly *methyl* cyclo*propenecarboxylate* (Found: C, 61·0; H, 6·1. $C_5H_6O_2$ requires C, 61·2; H, 6·2%). Light absorption: Max., 3030 A.; $E^1_{1\%}$ 2600. On attempted distillation, the residual oil resinified.

Action of Sodium Methoxide on γ-Bromocrotonic Acid.—The bromo-acid (3·35 g.) was dissolved in methanol and titrated (phenolphthalein) with 1·35N-methanolic sodium methoxide (14·5 c.c.). The sodium salt separated out during the neutralisation. The heterogeneous mixture was heated under reflux for 1 hour, then made homogeneous by addition of more methanol (10 c.c.), and heated for a further hour. The solvent was then removed under reduced pressure, and the residue was dissolved in dilute sulphuric acid and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to a solid, which was pressed on porous tile and crystallised from light petroleum in flattened needles of *γ-methoxycrotonic acid* (1·9 g.), m. p. 66—67° (Found: C, 51·5; H, 6·8. $C_5H_8O_3$ requires C, 51·6; H, 6·9%). Light absorption: Max., 2210 A.; $\varepsilon = 6030$.

*α-Hydroxy-β-methoxy-*n*-propyl Chloride.*—Prepared by the method of Koelsch (*loc. cit.*) this had b. p. 64—66°/9 mm., n_D^{18} 1·4456.

β-Hydroxy-γ-methoxybutyronitrile.—This was obtained from the above chloride (Koelsch, *loc. cit.*) and had b. p. 120—129°/17 mm., n_D^{18} 1·4386.

γ-Methoxycrotononitrile.—The hydroxy-nitrile was dehydrated over potassium carbonate (Koelsch, *loc. cit.*). The product had b. p. 183—185°, n_D^{18} 1·4364. When γ-methoxycrotononitrile (1·1 g.) was heated on the steam-bath with 25% sulphuric acid (10 c.c.) for 3½ hours, and then cooled and extracted with ether, only a trace of a dark oil was obtained; a similar result was observed when the hydrolysis was performed with 10% aqueous sodium hydroxide.

β-Hydroxy-γ-methoxybutyric Acid.—β-Hydroxy-γ-methoxybutyronitrile (11·7 g.) was heated under reflux with 20% aqueous potassium hydroxide (60 c.c.) for 10 hours, whereafter no more ammonia was evolved. The solution was acidified and continuously extracted with ether for 24 hours. Evaporation of the dried (Na_2SO_4) extracts gave β-hydroxy-γ-methoxybutyric acid (11 g.), b. p. 110—114°/0·003 mm., n_D^{19} 1·4464. The p-*phenylphenacyl* ester crystallised from alcohol in plates, m. p. 96° (Found: C, 69·2; H, 6·3. $C_{19}H_{20}O_5$ requires C, 69·45; H, 6·15%). Dehydration of the acid by treatment in ether with phosphoric oxide or by distillation at 0·01 mm. over potassium hydrogen sulphate gave only poor yields of unsaturated liquid acids.

Methyl β-Hydroxy-γ-methoxybutyrate.—A solution of β-hydroxy-γ-methoxybutyronitrile (22·7 g.) in methanol (195 c.c.) and water (5 c.c.) was saturated with dry hydrogen chloride at 0° and subsequently heated under reflux in an oil-bath at 140° for 3 hours. Ammonium chloride was removed by filtration, and the filtrate was neutralised with sodium hydrogen carbonate, again filtered, and concentrated under reduced pressure. Fractionation of the residue gave *methyl β-hydroxy-γ-methoxybutyrate* (13 g.), b. p. 102—104°/17 mm., n_D^{22} 1·4311 (Found: C, 47·9; H, 8·15. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%). When this ester was distilled slowly at ordinary pressure over potassium carbonate it gave an unsaturated product, which appeared to contain some αβ-unsaturated ester (light absorption: Max., <2150 A.; $\varepsilon = 4300$ at 2180 A.) but could not be purified.

Ethyl β-Hydroxy-γ-methoxybutyrate.—A solution of β-hydroxy-γ-methoxybutyronitrile (450 g.) in ethanol (2500 c.c.) and water (60 c.c.) was treated with a stream of dry hydrogen chloride at 0° for 6 hours and then heated under reflux in an oil-bath at 125—130° for 3½ hours. After working up as for the methyl ester, *ethyl β-hydroxy-γ-methoxybutyrate* (442 g.), b. p. 119—122°/23 mm., n_D^{22} 1·4274, was obtained (Found: C, 51·6; H, 8·4. $C_7H_{14}O_4$ requires C, 51·8; H, 8·7%).

Ethyl β-Acetoxy-γ-methoxybutyrate.—The hydroxy-ester (468 g.) was heated under reflux with acetic anhydride (335 g.) for 1 hour in an oil-bath at 160—170°. On fractional distillation the *acetoxy*-ester (532 g.) was obtained, b. p. 104—110°/1·3 mm., n_D^{21} 1·4236 (Found: C, 52·6; H, 8·1. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9%).

Ethyl γ-Methoxycrotonate.—The acetoxy-ester was distilled, in 100-g. portions, over anhydrous potassium acetate, from a 250-c.c. flask heated with a Bunsen flame. The distillate was collected up to b. p. 195° and then fractionated to remove acetic acid. *Ethyl γ-methoxycrotonate* had b. p. 78—79°/15 mm., n_D^{28} 1·4330 (Found: C, 58·1; H, 8·2. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%). Yield, 312 g. from 531 g. of acetoxy-ester. Light absorption: Max., <2150 A.; $\varepsilon = 7200$ at 2160 A.

γ-Methoxycrotonic Acid.—The ethyl ester (75 g.) was added, all at once, to N-sodium hydroxide (1000 c.c.) at 80—90° with vigorous stirring. A homogeneous solution was obtained in 1 minute, and after a total of 3 minutes it was quickly acidified by the addition of 4N-sulphuric acid, cooled as rapidly as possible, saturated with ammonium chloride, and extracted with ether (2 × 100; 3 × 50 c.c.). The combined extracts from 4 such experiments were dried ($CaCl_2$) and evaporated to a solid (170 g.); continuous ether extraction of the combined aqueous residues gave a further quantity (79 g.) of less pure material, containing some oil. Crystallisation from light petroleum gave colourless needles of γ-methoxycrotonic acid (179 g.), m. p. 66—67°, undepressed on admixture with the acid, obtained above, from γ-bromocrotonic acid. The p-*phenylphenacyl* ester crystallised from ethanol in needles, m. p. 109·5° (Found: C, 73·2; H, 6·0. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·85%). The *methyl* ester, prepared by reaction in dry ether with the calculated amount of ethereal diazomethane, had b. p. 88°/31 mm., n_D^{21} 1·4383 (Found: C, 55·5; H, 8·0. $C_6H_{10}O_3$ requires C, 55·4; H, 7·75%). Hydrogenation of the acid (1·5 g.) in water (10 c.c.) in the presence of 10% palladium–charcoal (0·4 g.) was complete in ½ hour; continuous ether extraction of the filtered solution gave γ-methoxybutyric acid (0·9 g.), b. p. 130—138°/30 mm., n_D^{19} 1·4244, together with 0·15 g. of lower-boiling material which contained a little butyric acid. p-*Phenylphenacyl γ-methoxybutyrate* crystallised from ethanol in needles, m. p. 81° (Found: C, 72·75; H, 6·35. $C_{19}H_{20}O_4$ requires C, 73·0; H, 6·45%).

Action of Alkali on γ-Methoxycrotonic Acid.—(*a*) The acid (1·006 g.) was dissolved in N-sodium hydroxide (25 c.c.) and heated at 100°. At intervals, 2-c.c. portions of the cooled solution were withdrawn, acidified with 4N-sulphuric acid, and treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. After 1 hour, the precipitated derivative was collected, washed, dried *in vacuo* over calcium chloride, and weighed. A similar series of determinations was carried out in 4·8N-sodium hydroxide (25 c.c., with 1·001 g. of acid). The results are shown in the figure.

(*b*) When the acid (0·1 g.) was dissolved in excess of 4·8N-sodium hydroxide (1 c.c.), set aside for 24 hours, then acidified and treated with the 2 : 4-dinitrophenylhydrazine reagent, a small yield of derivative was obtained, corresponding to *ca.* 10% conversion into the βγ-form.

(*c*) When the acid was exactly neutralised with N-alkali and the solution thereafter heated at 100° for 2 hours, no appreciable amount of 2 : 4-dinitrophenylhydrazone was formed on addition of the reagent.

(*d*) γ-Methoxycrotonic acid (5·75 g.) was heated with 4·8N-sodium hydroxide (50 c.c.) for 2 hours at 100°, then cooled and treated with a slight deficiency (118 c.c.) of 2N-hydrochloric acid. The solution was immediately extracted with ether, and the dried ($CaCl_2$) extracts, on evaporation and fractionation of the residue, gave *β-methoxymethylenepropionic acid* (1·9 g.), b. p. 73—75°/3·5 mm., n_D^{20} 1·4330 (Found : C, 51·7; H, 7·2. $C_5H_8O_3$ requires C, 51·6; H, 6·9%). It showed no appreciable light absorption above 2150 A. It was not completely soluble in sodium carbonate solution and probably existed partly in the lactonic form.

Action of Sodium Ethoxide on α-, β-, and γ-Methoxycrotonic Acid.—The α- and β-methoxy-acids were prepared by the method of Owen (Part I; *J.*, 1945, 385).

(*a*) The acids (*ca.* 10 mg. each) were equilibrated by heating for 18 hours at 100° with 2·6N-ethanolic sodium ethoxide; the solutions were thereafter neutralised and diluted, according to the procedure described in Part IV (*loc. cit.*), for the determination of the absorption spectra :

Acid.	Initial absorption.		Final absorption.	
	$\lambda_{max.}$, A.	ε.	$\lambda_{max.}$, A.	ε.
α-Methoxycrotonic	2230	9,400	2220	9400
β- ,, ...	2340	13,700	2280	5300
γ- ,, ...	2210	6,000	<2200	1700 at 2200 A.

The decrease in the wave-length of maximum absorption (accompanying the reduction in concentration of the αβ-unsaturated acid) which is most marked when the β- and γ-methoxy-acids are treated with alkoxides, has been observed also in other instances of $\alpha\beta \longrightarrow \beta\gamma$ change encountered in the present investigations.

(*b*) α-Methoxycrotonic acid (5·8 g.) was heated with 5N-soduim methoxide (60 c.c.) in a sealed tube at 100° for 24 hours. The acid was recovered unchanged (4·8 g.), m. p. and mixed m. p. 58°.

Addition Reactions of γ-Methoxycrotonic Acid.—(a) *With toluene-ω-thiol.* The acid (1·18 g.) was dissolved in water (1 c.c.) and neutralised with 5N-sodium hydroxide (2·1 c.c.). Toluene-ω-thiol (2 g.) was added and the solution was heated under nitrogen for 18 hours at 100°. Excess of thiol was extracted with ether and the solution was then acidified with 4N-sulphuric acid. Ether extraction gave *β-benzylthio-γ-methoxybutyric acid* (2·13 g.; 87%) as a colourless viscous liquid, b. p. 140—160° (bath temp.)/0·0001 mm., n_D^{18} 1·5453 (Found : C, 59·9; H, 6·8; S, 13·1. $C_{12}H_{16}O_3S$ requires C, 60·0; H, 6·7; S, 13·4%).

(b) *With thiolacetic acid.* γ-Methoxycrotonic acid (3·5 g.) was dissolved in thiolacetic acid (3·1 g.) by gentle warming. After a few hours, some unchanged methoxy-acid had separated; the mixture was therefore heated under nitrogen for 1 hour at 100° and then fractionated, to yield *β-acetylthio-γ-methoxybutyric acid* (5·1 g., 85%), b. p. 134°/0·2 mm., n_D^{18} 1·4910 (Found : C, 43·6; H, 6·2; S, 16·4. $C_7H_{12}O_4S$ requires C, 43·75; H, 6·3; S, 16·7%). Light absorption : Max., 2280 A.; ε = 8100.

(c) *With diazomethane.* γ-Methoxycrotonic acid (1 g.) in ether (10 c.c.) was treated with an excess of ethereal diazomethane (100 c.c.) in the dark for 4 days. Evaporation of the solvent then gave *methyl 4-methoxymethylpyrazoline-3-carboxylate* as a pale yellow oil (1·5 g.), b. p. 120°/0·01 mm., n_D^{16} 1·5124 (Found : C, 48·8; H, 7·1; N, 15·8. $C_7H_{12}O_3N_2$ requires C, 48·8; H, 7·0; N, 16·2%).

β-Benzylsulphonyl-γ-methoxybuyric Acid.—(*a*) β-Benzylthio-γ-methoxybutyric acid (0·6 g.) was dissolved in water (2 c.c.) containing sodium carbonate (0·2 g.). Potassium permanganate (1·05 g.) dissolved in water (30 c.c.) was added gradually, with cooling, the colour being rapidly discharged in the early stages, but persisting after the addition of the total quantity. The excess was removed with sulphur dioxide. The product, isolated by ether extraction, formed a viscous oil, from which *β-benzylsulphonyl-γ-methoxybutyric acid* gradually separated; it recrystallised from water in needles, m. p. 95° (Found : C, 53·2; H, 5·8; S, 11·1. $C_{12}H_{16}O_5S$ requires C, 52·9; H, 5·9; S, 11·8%).

(*b*) β-Acetylthio-γ-methoxybutyric acid (0·8 g.) and sodium carbonate (1 g.) were dissolved in water (15 c.c.). A solution of benzyl chloride (0·6 g.) in ethanol (10 c.c.) was added, and the mixture was heated on the steam-bath under nitrogen for 1 hour. The solution was cooled and extracted with ether to remove excess of benzyl chloride and benzyl alcohol, and then gradually treated with a solution of potassium permanganate (1 g.) in water (30 c.c.). After treatment with sulphur dioxide and extraction with ether, β-benzylsulphonyl-γ-methoxybutyric acid, m. p. and mixed m. p. 95°, was obtained.

Action of Toluene-ω-thiol on Crotonic Acid.—The acid (1·0 g.) was suspended in water (1 c.c.), and neutralised with 5N-sodium hydroxide (2·5 c.c.); toluene-ω-thiol (2 g.) was added and the mixture was heated at 100° for 18 hours under nitrogen. After being worked up in the same way as described for the addition to γ-methoxycrotonic acid, the crude product (2·0 g.) on distillation afforded β-benzylthiobutyric acid (1·8 g.; 74%) as a colourless viscous liquid, b. p. 100° (bath temp.)/0·0001 mm., n_D^{18} 1·5503, which was characterised by oxidation with potassium permanganate to β-benzylsulphonylbutyric acid, m. p. 132°.

Methoxyacetone.—Prepared by the reaction of methoxyacetonitrile (*Org. Synth.*, Coll. Vol. II, p. 387) with methylmagnesium iodide according to the method of Henze (*J. Amer. Chem. Soc.*, 1934, **56**, 1350), this had b. p. 112—114°, n_D^{14} 1·4016. The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in yellow needles, m. p. 163° (Found : C, 45·1; H, 4·7; N, 20·5. $C_{10}H_{12}O_5N_4$ requires C, 44·8; H, 4·5; N, 20·9%).

*Ethyl β-Hydroxy-γ-methoxy*isovalerate.—To a solution of methoxyacetone (23 g.) and ethyl bromoacetate (34 g.) in dry benzene (150 c.c.), zinc wool (13·5 g.) was added, followed by a trace of iodine. When the initial vigorous reaction had subsided, the temperature was raised to *ca.* 75° by warming the mixture on the steam-bath, and another small crystal of iodine was added. A further vigorous reaction occurred, and subsided after 15 minutes. The mixture was finally heated on the steam-bath under reflux

for 45 minutes and then cooled. The product was decomposed by the addition of ice and 4N-sulphuric acid, and the benzene layer was removed, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Fractionation of the residue gave *ethyl β-hydroxy-γ-methoxyisovalerate* (16·5 g.), b. p. 105°/21 mm., n_D^{22} 1·4293 (Found: C, 54·2; H, 9·0. $C_8H_{16}O_4$ requires C, 54·5; H, 9·2%). On slow distillation over potassium carbonate at ordinary pressure and refractionation of the distillate, a lower-boiling fraction, b. p. 75—78°/230 mm., n_D^{20} 1·3958, was obtained, which was shown to contain methoxyacetone by formation of the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 164—165°.

Dehydration of β-Hydroxy-γ-methoxyisovaleric Acid.—The acid was prepared by hydrolysis of the above ethyl ester (6·2 g.) with boiling 5N-methanolic potassium hydroxide for 18 hours; methanol was then evaporated under reduced pressure, and the solid residue was dissolved in water, extracted with benzene to remove a small amount of oil, acidified, and continuously extracted with ether for 36 hours. Evaporation of these dried ($CaCl_2$) extracts gave the crude hydroxy-acid (2·5 g.), b. p. 80—90°/0·001 mm. A portion (1·5 g.) was heated under reflux with acetic anhydride (6 c.c.) for 3 hours on a sand-bath. After removal of acetic acid and acetic anhydride by distillation, a main fraction, b. p. 49—55°/0·01 mm., was obtained; this reduced alkaline permanganate and on treatment with aqueous 2 : 4-dinitrophenylhydrazine sulphate gave *β-formylbutyric acid* 2 : 4-*dinitrophenylhydrazone*, which formed orange needles, m. p. 174—175°, from aqueous methanol (Found: C, 44·7; H, 4·0; N, 19·5. $C_{11}H_{12}O_6N_4$ requires C, 44·6; H, 4·1; N, 18·9%).

Ethyl β-Acetoxy-γ-methoxyisovalerate.—Ethyl β-hydroxy-γ-methoxy*iso*valerate (8·1 g.) was heated under reflux with acetic anhydride (11 c.c.) for 3 hours. Fractionation of the product gave the *acetoxy*-ester (7·4 g.), b. p. 47°/0·2 mm., n_D^{17} 1·4283 (Found: C, 54·7; H, 8·1. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%). On distillation of a portion at ordinary pressure over sodium acetate, a very small amount of a lower-boiling unsaturated liquid was obtained, b. p. 83—100°/15 mm., n_D^{21} 1·4322, but the bulk of the acetoxy-ester was recovered unchanged.

Reactions of αα′-Dichloroacetone.—(*a*) The ketone (2 g.) and silver carbonate (6 g.) in methanol (25 c.c.) were heated under reflux for 7 hours. The filtered solution on evaporation gave an oil, which resinified on attempted distillation at 10 mm.

(*b*) A solution of the ketone (6·35 g.) in methanol (100 c.c.) was cooled to −10°, and 2·35N-methanolic sodium methoxide (3·5 c.c.) was gradually added. The temperature was allowed to rise during 2 hours to 7°, the solution becoming neutral. A further quantity (17·5 c.c.) of the sodium methoxide was added, at 0—5°, during 7 hours; the solution became neutral after being kept at this temperature overnight. Sodium chloride was removed by filtration, and methanol by evaporation under reduced pressure; the residue was a brown resin.

Stability of αα′-Dichloroacetone Dimethyl Ketal.—The ketal, m. p. 81°, was prepared by the method of Prjanischnikow and Leontowitsch (*Ber.*, 1935, **68**, 1866). (*a*) This compound (1·7 g.) was heated under reflux with 1·18N-methanolic sodium methoxide (10 c.c.) for 60 hours. Water was added, the organic material was removed in ether, and the chloride ion in the aqueous portion was determined volumetrically; it corresponded to 1·5% of the theoretical for complete replacement.

(*b*) A similar experiment, in a sealed tube at 180° for 24 hours, in the presence of copper powder (0·06 g.), indicated *ca.* 5% liberation of chloride ion.

(*c*) A similar experiment, in a sealed tube at 180° for 68 hours, in the presence of sodium iodide (0·3 g.) and copper powder (0·06 g.), gave *ca.* 5% liberation of chloride ion.

Oxidation of 1 : 3-*Dimethoxypropan-2-ol.*—(*a*) To the alcohol (20 g.), prepared from glycerol αα′-dichlorohydrin by the method of Henze and Rogers (*loc. cit.*), and sodium dichromate (30 g.), a solution of sulphuric acid (14·2 c.c.) in water (104 c.c.) was added during 4 hours with vigorous stirring, the temperature being kept at 15—20° by external cooling. After being stirred for a further 16 hours the product was isolated by continuous ether extraction; it was acidic, and was therefore dissolved in aqueous sodium carbonate and again isolated by continuous extraction with ether. The material (15·2 g.), b. p. 63—65°/11 mm., n_D^{19} 1·4180, contained *ca.* 27% of ketone (estimated as the 2 : 4-dinitrophenylhydrazone).

(*b*) Dimethoxypropanol (24 g.) was dissolved in acetone (44 c.c.) and treated with a solution of chromic acid (14·9 g.) in dilute sulphuric acid (12 c.c. of concentrated acid in 44 c.c. of water), added during 2 hours, the temperature being maintained at 0°. After being stirred for a further 3 hours, the acetone was removed under reduced pressure, and the aqueous solution was continuously extracted with ether. The extracts were dried (K_2CO_3) and yielded an oil (16·7 g.), b. p. 66°/15 mm., n_D^{20} 1·4192, which contained *ca.* 35% of ketone.

Ethyl α-Cyano-β-methoxymethyl-γ-methoxycrotonate.—Fractional distillation of the above alcohol–ketone mixtures gave a fraction (20·5 g.) containing *ca.* 40% of ketone. This was added to ammonium acetate (1·35 g.), ethyl cyanoacetate (9·9 g.), acetic acid (3·9 c.c.), and benzene (20 c.c.), and the mixture was heated under reflux, in a flask fitted with a Dean and Stark water-separator, in an oil-bath at 140° for 7 hours; 1·8 c.c. of water were collected during that period. The solution was then washed with water and evaporated to an oil, fractionation of which furnished *ethyl α-cyano-β-methoxymethyl-γ-methoxycrotonate* (6 g.), b. p. 90—91°/0·003 mm., n_D^{19} 1·4590 (Found: C, 55·9; H, 7·0; N, 6·7. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1; N, 6·6%).

Hydrolysis of the Cyano-ester.—(*a*) The ester (1·5 g.) was heated on the steam-bath for 24 hours with 5N-hydrochloric acid (15 c.c.). Considerable charring occurred. The solution was filtered and extracted with ether; acidic products were taken up from the ether with aqueous sodium hydrogen carbonate, and the latter solution was then acidified and extracted with ether. Evaporation of these dried (Na_2SO_4) extracts gave a small yield of a semi-solid product which was drained on porous tile and crystallised from benzene–light petroleum in small prisms (0·06 g.), m. p. 110—111°. The *substance* was saturated towards permanganate and bromine water, and did not show any significant light absorption (Found: C, 45·7; H, 5·9. $C_5H_8O_4$ requires C, 45·5; H, 6·1%).

(*b*) The cyano-ester (1 g.) was warmed on the steam-bath with 5N-aqueous sodium hydroxide (4 c.c.). It dissolved rapidly, and after ½ minute the solution was cooled and acidified; addition of

aqueous 2 : 4-dinitrophenylhydrazine sulphate then gave a precipitate, indicating isomerisation to the $\beta\gamma$-unsaturated form.

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