747. *Polyene Acids. Part III. A Reinvestigation of Karrer's β-Methylmuconic Acid.*

By J. A. Elvidge, R. P. Linstead, and Peter Sims.

We have confirmed Karrer's preparation of β-methyl-*cis-cis*-muconic anhydride (I) but find that its reaction with water leads to β-methyl-*cis-trans*-muconic acid, and not the *cis-cis*-isomer as claimed. With methanol, the anhydride yields a mixture of (α)-methyl (δ)-hydrogen and (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconates, whilst with ammonia the amide of Pauly's lactonic acid (VI) is given together with the two half amides of β-methyl-*cis-trans*-muconic acid (as their ammonium salts). No evidence for the formation of *cis-cis*-products could be obtained. Karrer's criticism of the Pauling–Zechmeister theory of stereoisomerism in the carotenoids thus loses its basis.

A PREPARATION of β-methylmuconic anhydride (I) was recently described by Karrer, Schwyzer, and Neuwirth (*Helv. Chim. Acta*, 1948, **31**, 1210). They claimed that this anhydride—necessarily a *cis-cis*-compound—on brief treatment with boiling water afforded the *cis-cis*-isomer of β-methylmuconic acid. No further evidence for the configuration of the product was provided. On the basis of this apparent isolation of an isoprene derivative in the *cis-cis*-form, Karrer *et al.* criticised the concepts which underlie the Pauling–Zechmeister theory of stereoisomerism in the carotenoids.

Karrer's preparation was seemingly in conflict with our conclusions concerning the stereochemistry of β-methylmuconic acid, which are set forth in the preceding paper. The extreme rapidity with which the lower homologue, *cis-cis*-muconic acid, is inverted by boiling water to the *cis-trans*-isomer (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235) also cast considerable doubt on Karrer's assignment of the *cis-cis*-configuration to his β-methylmuconic acid. We have accordingly reinvestigated Karrer's work.

β-Methylmuconic Anhydride.—There seems no doubt that the product of oxidation of 4-methyl-1 : 2-benzoquinone with monoperphthalic acid (Karrer, Schwyzer, and Neuwirth, *loc. cit.*) has the cyclic structure (I). This low-melting volatile compound is neutral and polymerises readily. It reacts with water to yield a diene-dicarboxylic acid from which β-methyladipic acid is formed by hydrogenation. The anhydride itself, however, is resistant to catalytic reduction, and in this respect resembles dimethylmaleic and citraconic anhydrides (Hancock, Linstead, and J. F. Smith, unpublished observations) : maleic anhydride is likewise a powerful catalyst poison (Braude, Linstead, and Mitchell, unpublished work). Also consistent with the cyclic structure (I) are the light-absorption characteristics. The maxima shown by the anhydride (at 2650 and 2800 Å) are shifted by ~150 Å to longer wave-lengths as compared with those of muconic and β-methylmuconic acids (max. at 2510—2650 Å). In the pair maleic acid (or ester) and anhydride the shift is ~110 Å (Wassermann and Smakula, *Z. physikal. Chem.*, 1931, **155**, 366; Sörensen, *Annalen*, 1941, **546**, 57), whilst for 1-methylbutadiene and *cyclo*pentadiene the shift is ~200 Å (Braude, *Ann. Reports*, 1945, **42**, 105).

The β-Methylmuconic Acid derived from the Anhydride.—Karrer *et al.* (*loc. cit.*) reported that the melting point of the β-methylmuconic acid derived from the anhydride (I) and water varied with the rate of heating but was 170—171·5° under specified conditions. The acid was regarded by these authors as probably identical with the " lower-melting β-methylmuconic acid " described in the older literature. We find by direct comparison that this is correct; not so their stereochemical conclusions.* The β-methylmuconic acid (II) derived from the anhydride (I) and water is identical with the acid obtained by Pauly and Will's method (*Annalen*, 1918, **416**, 1) from the lactone (V), or from the peracetic acid oxidation of either homocatechol or of *p*-cresol (Böeseken, Metz, and Pluim, *Rec. Trav. chim.*, 1935, **54**, 345). The last is contrary to a statement by Karrer (*loc. cit.*), doubtless made because of the apparent discrepancy in melting point. We have shown (Elvidge, Linstead, and Sims, preceding paper) that this β-methylmuconic acid (m. p. ~170°) has the *cis-trans*-configuration.

Now it is clear from our work in the muconic series (*a*) that the *cis-cis*- and *cis-trans*-isomers may resemble each other closely and (*b*) that the inversion of the *cis-cis*-acid may be very easy. We therefore examined the ring-opening of the anhydride with considerable care. Ice-water and water vapour in the cold gave the same (*cis-trans*-) product as did boiling water. The *cis-trans*-acid (II) was also formed from the anhydride and cold aqueous sodium hydrogen carbonate, barium hydroxide, and dilute ammonia solution, so that the pH of the medium was evidently unimportant as regards the configuration of the product. It appears that the *cis-trans*-acid arises directly from the *cis-cis*-anhydride. In these and the subsequently described reactions, the precaution was taken of performing the operations as far as possible in the dark.

Esters and Amides derived from the Anhydride.—An attempt to open the ring of the anhydride (I) under neutral and anhydrous conditions, with dry methanol containing diazomethane, led only to a nitrogenous product. With cold dry methanol alone, a mixture of (α)-methyl (δ)-hydrogen and (δ)-methyl (α)-hydrogen β-methyl *cis-trans*-muconates, (III) and (IV), resulted, which was separated by fractional crystallisation. After a longer reaction time, the product was a mixture of the former half-ester (III) with Pauly and Will's lactonic ester (V). Thus the half-ester product (IV), with the free α-carboxyl group, rapidly underwent lactonisation (see preceding paper). The anhydride (I) was also treated with barium hydroxide in absolute methanol, and the precipitated barium salt decomposed with sulphuric acid in methanol. Following treatment with diazomethane, methyl β-methyl-*cis-trans*-muconate was isolated.

Karrer *et al.* (*loc. cit.*) reported that with dry ammonia in benzene, the anhydride gave a half-amide of β-methyl-*cis-cis*-muconic acid with m. p. 147—149° (decomp.). Since their method of isolation merely involved evaporation of the reaction mixture and crystallisation of the residue from ethanol–ether, it seemed unlikely that their product could have been an *acid*. Repetition of the experiment afforded a similar product (m. p.; solubility) which, however, was a mixture. The main constituent (extracted by ethanol) was the amide (VI), m. p. 148—149°, of Pauly and Will's lactone, presumably the product isolated by Karrer and his collaborators. The ethanol-insoluble fraction was evidently a mixture of ammonium salts, since after acidification the presence of both the acid amides of β-methyl-*cis-trans*-muconic acid, (VII) and (VIII), was demonstrated. Thus by treatment of the acidified mixture with diazomethane, and fractional crystallisation, β-methyl-*cis-trans*-muconic (α)-methyl ester (δ)-amide (IX) was obtained. On the other hand, by making use of the facts (preceding paper) that the (α)-acid (δ)-amide (VII) readily isomerises in boiling water to the lactonic amide (VI) whereas the positionally-isomeric (α)-amide (δ)-acid (VIII) is unaffected, isolation of the latter amide acid was achieved. Esterification gave the β-methyl-*cis-trans*-muconic (α)-amide (δ)-methyl ester (X), whilst from the aqueous filtrate the product of lactonisation of the acid amide (VII), *viz.* the lactonic amide (VI), was obtained.

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* Incidentally the melting point and the four references which Karrer *et al.* give for *β*-methyl-*trans-trans*-muconic acid actually relate to muconic acid.

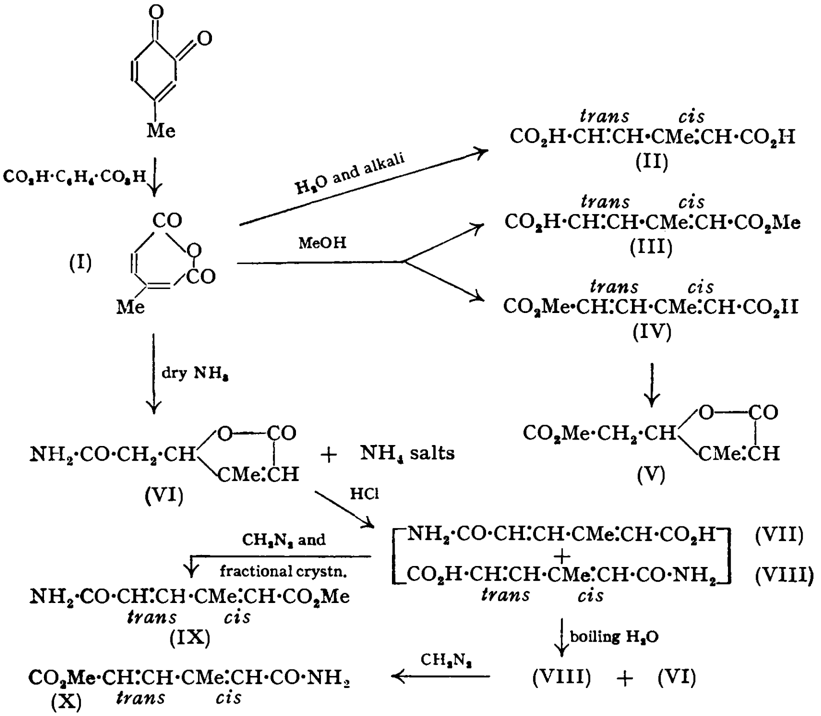
The immediate formation of the lactonic amide (VI) from the anhydride (I) and ammonia suggests that it arises directly and not through the intermediate formation of an amic acid.

The various experimental results are summarised in the scheme below.

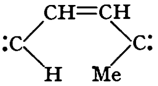
In summary, therefore, only *cis-trans* products have been obtained from the *cis-cis*-anhydride (I), and we consider the claims of Karrer, Schwyzer, and Neuwirth to have isolated the *cis-cis*-isomer of β-methylmuconic acid and one of its half-amides to be in error. Karrer, Schwyzer, and Neuwirth (*loc. cit.*) wrote : " The existence of β-methyl-*cis-cis*-muconic acid has a connection of interest with the theory proposed by Pauling (*Fortschr.*, 1939, **3**, 203) for carotenoid structure. This theory states that in carotenoid molecules only double bonds at carbons carrying methyl groups can have *cis*-configurations, except the central double bond; on the other hand a *cis*-configuration for the other double bonds is not possible on steric grounds." . . . " The existence and stability of β-methyl-*cis-cis*-muconic acid show that this theory can hardly be correct because here is encountered in an atomic environment identical with that in the carotenoids a –CH=CH– group which shows no resistance to taking up a *cis*-configuration." In the light of our new experimental work this criticism loses its validity.

In a reply to Karrer, Pauling (*Helv. Chim. Acta*, 1949, **32**, 2241) has reiterated his original concepts (that resonance can occur within conjugated systems, leading to enhanced stability, provided a planar configuration is possible), and he has re-stated his central conclusion that in a carotenoid molecule only certain of the double bonds will (therefore, for steric reasons) be capable of assuming a *cis*-configuration. He emphasises that the conclusion is more rigorously applicable to long conjugated systems than to short, and suggests that exceptions, especially in the latter case, could be expected. The immediate reason for expanding the original views is now seen to exist no longer.

The essential point is whether any of the geometrical forms of a diene or polyene can exist in an unhindered planar state and thus be *fully* conjugated. If there is a difference in this respect between the *cis*- and the *trans*-form about one double bond then the hindered form will have a much enhanced instability (or energy content) over its geometrical isomer and be either difficult or impossible to prepare. If, on the other hand, *both* geometrical forms are prevented by hindrance from becoming planar the *difference* in energy content between them will be much less and we can conceive that both isomerides will be obtainable and that the *cis*-form may be relatively stable.



Scale models indicate that in β-methylmuconic acid, the *cis-trans*-isomer is unhindered, whereas the *cis-cis*-isomer would have a non-planar structure. Pauling has calculated a value of 7·1 kcal./mol. for the instability of the non-planar β-methyl *cis-cis*-muconic acid over the *trans-trans*-form, and a corresponding reduction in resonance stabilisation of more than twice this value for longer conjugated systems (*e.g.* carotenoid molecules) which are not fully coplanar because they possess the *cis*-configuration about one double bond of the type shown inset. It seems unlikely that such forms would ordinarily be obtainable.



In our view the ideas of Pauling and Zechmeister (Zeichmeister, *Chem. Reviews*, 1944, **34**, 267) concerning stereoisomerism in the carotenoids are strengthened by the known facts concerning the isomeric β-methylmuconic acids.

EXPERIMENTAL.

(M. p.s marked * were taken from a bath at 165° with the temperature rising at 8°/minute. Other m. p.s were determined normally.)

Authentic materials employed for the various mixed-m. p. comparisons have been described in the preceding paper).

β-Methylmuconic Anhydride.—To freshly prepared 4-methyl-1 : 2-benzoquinone (3·2 g.) [prepared in 32% yield by Willstätter and Müller's method (*Ber.*, 1911; **44**, 2171)] suspended in ice-cooled anhydrous ether (250 c.c.), crystalline monoperphthalic acid (13 g.; 51% of $CO_3H\cdot C_6H_4\cdot CO_2H$) was added slowly. The mixture was kept at room temperature overnight and then filtered, the filtrate evaporated under reduced pressure, and the residue treated with dry benzene (20 c.c.). Evaporation of the filtered benzene extract afforded a mixture of needles with a gum, which was extracted with boiling light petroleum (b. p. 60—80°) (6 × 100 c.c.). β-Methylmuconic anhydride (2·2 g., 61%) crystallised from the extract as needles, m. p. 72—73° raised to 73—74° on repeated crystallisation (4 times) from dry ether (Found : C, 61·15; H, 4·8. Calc. for $C_7H_6O_3$: C, 60·9; H, 4·4%). Karrer *et al.* (*loc. cit.*) give m. p. 75—76°, taken from a bath at 70°. Light absorption in dry dioxan : Max. at 2650 and 2800 Å; ε = 4970 and 4970.

Reactions of the Anhydride.—(a) *With water.* (i) The anhydride (0·2 g.) was treated with boiling water (2 c.c.) for 1 minute. The solution was cooled, and the product recrystallised from hot water yielding needles (0·13 g., 57%), m. p. 173—174° *, and m. p. 177—178° * when mixed with β-methyl-*cis-trans*-muconic acid. Treatment of the product with ethereal diazomethane afforded methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38·5°. (ii) The anhydride (0·2 g.) was kept with ice-cold water (2 c.c.) for 1 hour and the product recrystallised from ethanol giving micro-needles (0·15 g., 66%), m. p. 178—179° * not depressed by β-methyl-*cis-trans*-muconic acid. Treatment of the product with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38—38·5°.

(b) *With water vapour.* The finely powdered anhydride (0·1 g.) was spread on a watch glass and kept for 24 hours in a closed vessel containing a dish of water. Treatment of the product with ethereal diazomethane afforded only needles, m. p. 35—36°, and m. p. 36—37° when mixed with methyl β-methyl-*cis-trans*-muconate.

(c) *With aqueous alkali.* (i) The anhydride (0·2 g.) was stirred with saturated aqueous sodium hydrogen carbonate (2 c.c.), the solution cooled in ice and acidified (10% hydrochloric acid; Congo-red). The precipitate (0·13 g., 57%), collected at once and washed with cold water, had m. p. 178—179° * alone and when mixed with β-methyl-*cis-trans*-muconic acid. With diazomethane in ether the product gave methyl β-methyl-*cis-trans*-muconate (needles), m. p. 35—36° and mixed m. p. 35—38°. (ii) The anhydride (0·2 g.) was added to cold N-barium hydroxide (2 c.c.), and the solution then made acid (hydrochloric acid; Congo-red). Crystallisation of the precipitate from ethanol afforded β-methyl-*cis-trans*-muconic acid (0·15 g., 66%) as micro-needles, m. p. and mixed m. p. 177—178° *. With ethereal diazomethane, methyl β-methyl-*cis-trans*-muconate was obtained, m. p. and mixed m. p. 38°. (iii) The anhydride (0·1 g.) was dissolved in 2N-aqueous ammonia (2 c.c.), and the solution cooled in ice and acidified. β-Methyl-*cis-trans*-muconic acid was obtained as micro-needles (from ethanol), m. p. and mixed m. p. 177—178° *. Treatment of the crude product with ethereal diazomethane gave methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 37—38°.

(d) *With methanol.* (i) The anhydride (0·5 g.) was dissolved in anhydrous methanol (5 c.c.), the solution evaporated under reduced pressure, and the residue fractionally crystallised from dry benzene, yielding two crystal crops. The least-soluble fraction (0·25 g., 40%) had m. p. 168—169°, undepressed by (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate † (m. p. 170°), and afforded with ethereal diazomethane methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38°. The more-soluble fraction (0·2 g., 32%) had m. p. 125—126°, alone and in admixture with (δ)-methyl (α)-hydrogen β-methyl-*cis-trans*-muconate,† and reacted with ethereal diazomethane to yield methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38°. (ii) The anhydride (2·5 g.) was kept with anhydrous methanol (20 c.c.) for 48 hours in the dark, and the solution then allowed to evaporate spontaneously. A mixture of an oil and needles was obtained. This solid (1·4 g., 45%) had m. p. 168—169°, undepressed by (α)-methyl (δ)-hydrogen β-methyl-*cis-trans*-muconate. The oil was taken up in ether (50 c.c.), the solution washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated under reduced pressure, and the residue distilled to give γ-carbomethoxymethyl-β-methyl-Δ^{α}-butenolide (0·42 g., 14%), b. p. 179°/11 mm., which soon crystallised as needles, m. p. 34—35° undepressed by authentic material.

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† For nomenclature see Elvidge, Linstead, and Sims, preceding paper.

(e) ***With methanolic barium hydroxide.*** The anhydride (0·5 g.) was treated with anhydrous methanolic barium hydroxide (5 c.c; 1N). The precipitate was suspended in fresh anhydrous methanol (100 c.c.) and a 1% solution of sulphuric acid in anhydrous methanol (35 c.c.) added. The filtrate was evaporated under reduced pressure and the residue treated with diazomethane in ether to yield methyl β-methyl-*cis-trans*-muconate, m. p. and mixed m. p. 38·5°.

(f) *With dry ammonia.* (i) A stream of dry ammonia was passed for 3 minutes into a solution of the anhydride (0·15 g.) in anhydrous benzene (5 c.c.). The benzene was evaporated under reduced pressure and the deliquescent residue extracted with boiling absolute ethanol (5 c.c.). The extract was filtered from insoluble material, concentrated under reduced pressure to a small bulk, cooled in ice, and treated dropwise with dry ether. The amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide crystallised (40 mg., 25%) as needles, m. p. and mixed m. p. 148—149°. (ii) Dry ammonia was passed for 3 minutes into an ice-cooled solution of the anhydride (1 g.) in dry benzene (10 c.c.). The benzene was then evaporated under reduced pressure, the residue dissolved in water (3 c.c.), and the solution acidified (hydrochloric acid; Congo-red). A mixture (*A*), mainly of the acid amide (VII) and amide acid (VIII), was precipitated (650 mg., 58%), m. p 140—175°. The filtrate was evaporated, the residue extracted with ethanol (5 c.c.), and the solution concentrated. The amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (300 mg., 26%) crystallised; it had m. p. and mixed m. p. 149—150°. A portion of the mixture (*A*) (200 mg.) was treated with an excess of diazomethane in ether, and the product fractionally crystallised from methanol. β-Methyl-*cis-trans*-muconic (α)-methyl ester (δ)-amide (IX) (80 mg.) was obtained, m. p. and mixed m. p. 160—161°. A second portion of the mixture (*A*) (50 mg.) was heated with water (5 c.c.) under reflux for 3 hours and the solution cooled. β-Methyl-*cis-trans*-muconic (α)-amide (δ)-acid (VIII) (30 mg., 60%) crystallised [filtrate (*B*)], m. p. and mixed m. p. 210—211°, and reacted with diazomethane to yield β-methyl-*cis-trans*-muconic (α)-amide (δ)-methyl ester (X), m. p. and mixed m. p. 141°. The filtrate (*B*) from the amide acid (VIII) was evaporated to yield the amide of γ-carboxymethyl-β-methyl-Δ^{α}-butenolide (10 mg.), which after crystallisation from ethanol had m. p. and mixed m. p. 146—148°.

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

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