379. *The Addition of Halogens to Unsaturated Acids and Esters. Part V. The Bromination of* m-*Methoxycinnamic Acid and its Ethyl Ester.*

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In an endeavour to prepare *m*-methoxyphenylpropiolic acid, the action of bromine on *m*-methoxycinnamic acid and its ethyl ester has been re-examined. Previous work on the subject (Bauer and Vogel, *J. pr. Chem.*, 1913, **88**, 341; Davies and Davies, J., 1928, 602; Reimer and Kamerling, *J. Amer. Chem. Soc.*, 1933, **55**, 4643) has indicated that in a variety of solvents and under various conditions of temperature the action of one molecular proportion of bromine on the acid results in nuclear substitution with no addition to the ethylenic linkage in the side chain, 6-bromo-3-methoxycinnamic acid being formed in quantitative

yield. Larger proportions of bromine yield mixtures which are difficult to separate, 6-bromo-3-methoxy-, 4 (or 2) : 6-dibromo-3-methoxy-cinnamic acids, and other products with bromine also in the side chain being obtained.

We have observed that when a molecular proportion of bromine is gradually added to *m*-methoxycinnamic acid or its ethyl ester in carbon tetrachloride kept in bright sunlight, no evolution of hydrogen bromide occurs. Under these conditions, and especially when the solution is boiling, the addition reaction takes place rapidly and exclusively, giving quantitative yields of *αβ-dibromo-β-3-methoxyphenylpropionic acid* and its *ethyl* ester respectively.

Similar results are obtained when carbon disulphide is used as solvent, but in chloroform and glacial acetic acid, under identical conditions, the reaction is almost entirely substitutive. In diffused daylight or in the dark, the substitution reaction invariably sets in, irrespective of the nature of the solvent. Apparently, therefore, two competing reactions are involved, but the type of reaction occurring in this series can be controlled by modifying the conditions. In non-polar solvents, in incident sunlight, addition of bromine to the unsaturated side chain takes place solely, but preferential nuclear substitution occurs in polar solvents when light is excluded. Rigorous purification of the solvents used in these experiments had no marked effect on the course of the reactions.

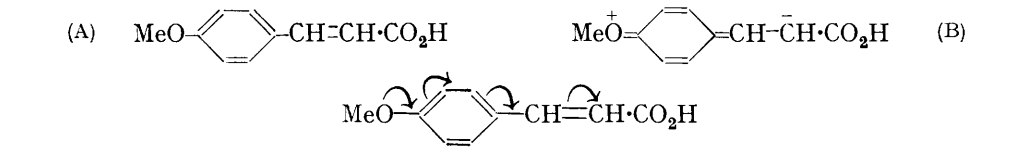
Considerable activation of the double bond towards halogens is possible through the agency of light and certain specific chemical reagents, *e.g.*, the polar substance hydrogen bromide (Williams and James, J., 1928, 343; Williams, J., 1932, 2911; Anantakrishnan and Ingold, this vol., p. 984). Bromination of *m*-methoxycinnamic acid in carbon tetrachloride solution saturated with hydrogen bromide, however, gave as product the substituted acid, 6-bromo-3-methoxycinnamic acid. On the other hand, photoactivation of the acid and its ethyl ester by means of ultra-violet radiation from a quartz mercury vapour lamp was effective in promoting the addition reaction in non-polar solvents. Similarly, in boiling carbon tetrachloride in sodium light, addition solely was observed, but the rate was decidedly slower. The photochemical addition of halogens to cinnamic acid has been extensively studied (Berthoud and Porret, *Helv. Chim. Acta*, 1934, **17**, 237; Purkayastha and Ghosh, *J. Indian Chem. Soc.*, 1926, **2**, 261; 1927, **4**, 409, 553; Purkayastha, *ibid.*, 1928, **5**, 721; Berthoud and Beranek, *J. Chim. Phys.*, 1927, **24**, 213; *Helv. Chim. Acta*, 1927, **10**, 289; 1930, **13**, 385). For the photobromination of cinnamic acid, Berthoud, Purkayastha, and Ghosh proposed a chain mechanism involving photochemically atomised bromine. Bauer and Daniels (*J. Amer. Chem. Soc.*, 1934, **56**, 378), however, found that their experimental observations were more in agreement with an energy chain involving activated bromine molecules. The issue has been complicated by the recent discovery made by the last-named authors (*J. Amer. Chem. Soc.*, 1934, **56**, 2014) that the bromination (or photobromination) of cinnamic acid is an oxygen-inhibited reaction.

Concerning the rôle of the solvent in determining the course of the bromination, two possibilities exist. The influence of the solvent on the two competing reactions may be (a) qualitatively, but not quantitatively, similar, *e.g.*, both reactions may be facilitated by polar solvents, but the one more markedly than the other and this would therefore preponderate in polar solvents : (b) qualitatively different, *e.g.*, polar solvents may facilitate the one and inhibit the other. The latter alternative seems to be the more plausible, the substitution reaction being favoured and the addition reaction inhibited by a polar environment.

The pronounced tendency towards nuclear bromine substitution observed with *m*-methoxycinnamic acid is in strange contrast to the facile addition observed with the *o*- and the *p*-methoxy-derivative (Reimer and Howard, *J. Amer. Chem. Soc.*, 1928, **50**, 196; Sudborough and Hariharan, *J. Indian Inst. Sci.*, 1925, 8*A*, *XI*, 189). Several attempts have been made to determine the effect of nuclear substituents on the additive reactivity of the ethenoid centre in cinnamic acid (Hanson, Williams, and James, J., 1928, 343; 1930, 1059; Sudborough and Hariharan, *loc. cit.*; van Duin, *Rec. trav. chim.*, 1922, **41**, 402; Müller, *Annalen*, 1882, **212**, 122; Reich and Kochler, *Ber.*, 1913, **46**, 3727). Hanson, Williams, and James found that the rate of bromine addition to the methoxycinnamic acids is several hundred times greater than to unsubstituted cinnamic acid. (In view of the results recorded here it is probable that the velocities for the *m*-methoxy-derivative

measured by these authors were mainly velocities of bromine substitution and not addition.) They attributed the enhanced rate of reaction to the promotion of nuclear substitution by the strongly activating methoxy-group, giving hydrogen bromide, the catalyst for the reaction. This, however, is not the only cause of enhanced reactivity. The methoxy-group when introduced into the *o*- and *p*-positions promotes addition in virtue of its polar effects. These comprise a somewhat weak inductive effect and a very powerful tendency towards tautomeric electron release, symbolised $-I + T$ (Ingold, J., 1933, 1122; Dippy, Watson, and Williams, this vol., p. 346). These polar effects increase the possibilities of resonance in the substituted cinnamic acid molecule. The resonance between the alternative benzenoid and quinonoid configurations (A) and (B) illustrated below in the case of *p*-methoxycinnamic acid constitutes a strong facilitating influence in the addition of bromine.

Similar considerations apply to the *o*-methoxy-acid, but in the case of *m*-methoxycinn-



amic acid this phenomenon is impossible owing to the absence of an available mechanism for the transmission of the electromeric effect of the substituent from the nucleus to the side chain. Consequently, the polar effects of the group are confined almost exclusively to the ring. In aromatic substitution by electrophilic reagents the methoxy-group is classed as a nuclear-activating, *op*-directing group, but the *o*/*p* ratio is found to vary with change of reagent (Griffiths, Walkey, and Watson, J., 1934, 631; Jones and Robinson, J., 1917, 903). Halogens are, however, directed almost exclusively to the *p*-position (Michaelis and Weitz, *Ber.*, 1887, **20**, 49; Bodroux, *Compt. rend.*, 1903, **136**, 378). Therefore, when the methoxy-group is in the 3 (or *m*)-position in cinnamic acid, considerable reactivity towards halogens is conferred on the 6-position. This explains why, when *m*-methoxycinnamic acid is brominated, preferential nuclear substitution in the 6-position occurs rather than addition at the double bond.

The action of bromine upon the substitution product, 6-bromo-3-methoxycinnamic acid, under the conditions conducive to addition, gave the tribromo-acid, *αβ-dibromo-β-6-bromo-3-methoxyphenylpropionic acid*. An identical product was obtained by brominating the addition product, αβ-dibromo-β-3-methoxyphenylpropionic acid, in cold chloroform solution, hydrogen bromide being evolved.

Boiling with water or methyl alcohol had no effect on αβ-dibromo-β-3-methoxyphenylpropionic acid. In this respect, the *m*-substituted compound differs from the isomeric *o*- and *p*-derivatives (Reimer and Howard; Sudborough and Hariharan; *locc. cit.*). When the dibromo-acid or -ester was treated with two molecular proportions of alcoholic potash, one mol. of hydrogen bromide was eliminated and the stereoisomeric α-bromo-acids melting at 122° and 91° were obtained. These were readily separated by the barium salt method (cf. Sudborough and Thompson, J., 1903, **83**, 666), and their stereochemical configurations established. The stable α-bromo-*m*-methoxycinnamic acid (m. p. 122°) has been obtained by Reimer and Kamerling (*loc. cit.*) by an indirect method from *m*-methoxybenzylidenepyruvic acid.

Removal of hydrogen bromide from this stable α-bromo-acid by boiling with two molecular proportions of alcoholic potash gave a good yield of the desired m-*methoxyphenylpropiolic acid*. Some of the addition reactions of this acetylenic acid have been investigated. Catalytic hydrogenation by a method parallel to that described by Paal and Hartmann (*Ber.*, 1909, **42**, 3930) for the preparation of *allo*cinnamic acid gave m-*methoxy*allocinnamic acid. Addition of iodine resulted in the formation of *αβ-di-iodo*-m-*methoxycinnamic acid*.

Experimental.

m-*Methoxycinnamic Acid*.—*m*-Hydroxybenzaldehyde was methylated (Chakravarti, Haworth, and Perkin, J., 1927, 2269) and the *m*-methoxybenzaldehyde obtained was condensed with malonic acid, with pyridine or α-picoline as solvent and piperidine as catalyst. The acid

had m. p. 117°. Its ethyl ester was obtained as a clear colourless viscid oil, b. p. 185—186°/15 mm., by the Fischer–Speier method.

Bromination of m-*Methoxycinnamic Acid.*—(i) 6-*Bromo*-3-*methoxycinnamic acid.* Bromination in glacial acetic acid in the dark (Davies and Davies, *loc. cit.*) gave 6-bromo-3-methoxycinnamic acid, m. p. 189°, in quantitative yield.

A suspension of *m*-methoxycinnamic acid (10 g.) in carbon tetrachloride or chloroform (100 c.c.) was treated at 0° in the dark with 1 mol. of bromine (3 c.c. + 3% excess), and the mixture kept for 48 hours. The product, recrystallised from benzene, gave colourless needles (14 g.) of 6-bromo-3-methoxycinnamic acid, m. p. 189°.

(ii) αβ-*Dibromo*-β-3-*methoxyphenylpropionic acid.* To a boiling solution of *m*-methoxycinnamic acid (20 g.) in dry carbon tetrachloride (100 c.c.) contained in a Pyrex flask attached to a reflux apparatus, a solution of bromine (6 c.c. + 3% excess) in the same solvent was slowly added, the reaction being conducted in bright sunlight. The bromine coloration rapidly disappeared, no hydrogen bromide was evolved, and the bromination was complete in 15 minutes. The product separated on cooling, and after being washed free from any excess of bromine the fine white crystals (37·5 g.) were recrystallised from hot benzene; m. p. 167° (Found: Br, 47·5; equiv., 337·9. $C_{10}H_{10}O_3Br_2$ requires Br, 47·3%; equiv., 338). αβ-*Dibromo*-β-3-*methoxyphenylpropionic acid* is insoluble in water or light petroleum, sparingly soluble in hot carbon tetrachloride, carbon disulphide, and chloroform, but readily soluble in cold alcohol and hot benzene. The acid was recovered unchanged after 2 hours' refluxing with ethyl alcohol. On oxidation with potassium permanganate it gave a quantitative yield of *m*-methoxybenzoic acid, m. p. and mixed m. p. 105°.

Bromination of an ice-cold suspension of *m*-methoxycinnamic acid in carbon tetrachloride in incident sunlight also gave the practically pure dibromo-acid, but the rate of addition was very slow compared with the rate in the above case. In boiling carbon disulphide solution in sunlight, addition of bromine was also observed, though the reaction took about 2 hours to complete.

When *m*-methoxycinnamic acid (5 g.) in boiling glacial acetic acid (50 c.c.) solution was treated in sunlight with 1 mol. of bromine (1·5 c.c.) in the same solvent (50 c.c.), the reaction was rapid but the product was almost pure 6-bromo-3-methoxycinnamic acid, m. p. 188—189°. In boiling chloroform solution, under the same conditions, the product of bromination was a mixture, m. p. 180—189°, in which the 6-bromo-3-methoxy-acid predominated.

(iii) *Methyl* 6-*bromo*-3-*methoxycinnamate.* To a boiling solution of *m*-methoxycinnamic acid (5 g.) in methyl alcohol (50 c.c.), 1 mol. of bromine (1·5 c.c.) in methyl alcohol (50 c.c.) was added in sunlight. The reaction was complete in 15 minutes. Most of the alcohol was boiled off, and the solution allowed to cool. Crystals separated, m. p. 81° after recrystallisation from light petroleum, which proved to be the methyl ester of 6-bromo-3-methoxycinnamic acid, identical with a sample obtained by esterification of this acid. The same ester was obtained by brominating a methyl-alcoholic solution of the acid, in the cold and dark, and keeping it for 48 hours.

Bromination of Ethyl m-*Methoxycinnamate.*—(i) *Ethyl* 6-*bromo*-3-*methoxycinnamate.* Ethyl *m*-methoxycinnamate (2·05 g.) in acetic acid or chloroform (25 c.c.) solution was treated in the cold and dark with 1 mol. of bromine (0·54 c.c.) in the same solvent (25 c.c.), and the mixture kept over-night. Hydrogen bromide was evolved. The bulk of the solvent was evaporated, and the residue poured into cold water. The oil obtained gave on hydrolysis a practically quantitative yield of the 6-bromo-acid, m. p. 189°.

(ii) *Ethyl* αβ-*dibromo*-β-3-*methoxyphenylpropionate.*—Ethyl *m*-methoxycinnamate (8 g.) in dry carbon tetrachloride (50 c.c.) was slowly treated with a solution of bromine (2·07 c.c.) in the same solvent (50 c.c.), in strong sunlight. Addition was rapid and no hydrogen bromide was evolved. The solution was then boiled to a small volume, and light petroleum (b. p. 80—110°) added. Colourless crystals of the *dibromo*-ester slowly separated, m. p. 58° after recrystallisation from light petroleum–chloroform. Yield, 14 g. (Found: Br, 43·6. $C_{12}H_{14}O_3Br_2$ requires Br, 43·7%).

αβ-*Dibromo*-β-6-*bromo*-3-*methoxyphenylpropionic Acid.*—6-Bromo-3-methoxycinnamic acid (3·43 g.) in boiling carbon tetrachloride solution (35 c.c.) was treated with 1 mol. of bromine (0·71 c.c.) in the same solvent (35 c.c.), in strong sunlight. The bromine disappeared rapidly with no visible evolution of hydrogen bromide. On cooling, pale yellow crystals separated; these, recrystallised from carbon tetrachloride–light petroleum (b. p. 80—110°), formed slightly cream-coloured clumps of needles, m. p. 163° (Found: Br, 57·3; equiv., 416·7. $C_{10}H_9O_3Br_3$ requires Br, 57·5%; equiv., 417).

The α-*Bromo*-m-*methoxycinnamic Acids.*—To a solution of αβ-dibromo-β-3-methoxyphenyl-

propionic acid (20 g.) in ethyl alcohol (200 c.c.), 2 mols. of alcoholic potash (64 c.c. of 1·84*N*) were slowly added. The mixture was kept with occasional shaking for 2 days in a thermostat at 25°, the alcohol was then removed on a boiling water-bath, and the mixed potassium salts of the α-bromo-acids were taken up in water. No appreciable decomposition into ω-bromo-*m*-methoxystyrene was observed during the evaporation, though it was found that the potassium salts readily decomposed in warm aqueous solution. To the filtered solution of the potassium salts, excess of barium chloride solution (10%) was added. α-Bromo-*m*-methoxycinnamic acid (2·4 g.) was obtained by acidifying the insoluble barium salt; crystallised from light petroleum (b. p. 80—110°), it had m. p. 122°; it separated from boiling water in faintly cream-coloured, stiff needles (Found: Br, 31·1; equiv., 256·8. Calc. for $C_{10}H_9O_3Br$: Br, 31·1%; equiv., 257). α-*Bromo*-m-*methoxy*allo*cinnamic acid* (9·8 g.), obtained by acidifying the filtrate from the insoluble barium salt, came down as an oil which gradually solidified into a pale yellow, crystalline mass. Recrystallised from light petroleum (b. p. 40—60°)–chloroform, it separated as pale yellow crystals, m. p. 91° (Found: Br, 30·8%; equiv., 256·5). That this is the α-bromo-acid isomeric with the acid of m. p. 122° was proved by keeping it for a long time in the solid state or in chloroform solution, in strong sunlight, whereby the stable acid, m. p. 122°, was obtained. By analogy with the α-bromocinnamic acids and α-bromo-*p*-methoxycinnamic acids, the stable acid, m. p. 122°, is assigned the *trans*-configuration and the isomeric acid, m. p. 91°, must be the *allo*-acid with the *cis*-configuration. The conversion of the *allo*-acid into the stable modification was best effected by heating the solid in an oil-bath at 150° for several hours. The extent of the transformation was followed by the barium salt method.

Removal of hydrogen bromide from the dibromo-ester under the same conditions gave the same α-bromo-acids, the stable α-bromo-acid being produced in higher proportion.

m-*Methoxyphenylpropiolic Acid.*—α-Bromo-*m*-methoxycinnamic acid (20 g.) was boiled with alcoholic potash (2 mols. plus 5% excess) for 4 hours. The alcohol was then removed and the residue, dissolved in water, was acidified with dilute hydrochloric acid. The *acid* separated as an oil, but soon solidified. Small, slightly cream-coloured crystals, m. p. 109°, were obtained by crystallisation from light petroleum–chloroform. Yield, 13 g. (96% of the theoretical) (Found: equiv., 176·6. $C_{10}H_8O_3$ requires equiv., 176).

Addition Reactions of m-*Methoxyphenylpropiolic Acid.*—(i) *Addition of iodine.* The acid (2 g.) was dissolved in water (30 c.c.) containing potassium carbonate (0·78 g.), mixed with a solution of iodine (4·8 g.) and potassium iodide (7·2 g.) in water (100 c.c.), and kept for 2 days, a precipitate separating. After acidification with dilute hydrochloric acid, filtration, and washing with potassium iodide solution and then with water, a crystalline substance remained. Recrystallisation from light petroleum–chloroform gave αβ-*di-iodo*-m-*methoxycinnamic acid* in rosettes of shiny yellow needles, m. p. 142° (Found: I, 59·0; equiv., 431·4. $C_{10}H_8O_3I_2$ requires I, 59·1%; equiv., 430).

(ii) *Addition of hydrogen.* Potassium *m*-methoxyphenylpropiolate was catalytically hydrogenated by means of colloidal palladium " protected " by sodium protalbate (Paal and Hartmann's method, *loc. cit.*). m-*Methoxy*allo*cinnamic acid* was obtained as a solid, m. p. 109—110° after recrystallisation from cold chloroform by the addition of light petroleum (Found: equiv., 179. $C_{10}H_{10}O_3$ requires equiv., 178). Long exposure to sunlight transformed this acid into the stable isomeride, *m*-methoxycinnamic acid, m. p. 117°.

Bromination of m-*Methoxy*allo*cinnamic Acid.*—The *allo*-acid (5 g.) in chloroform (50 c.c.) was treated with 1 mol. of bromine (1·5 c.c.) in the same solvent (25 c.c.) in the cold, all light being excluded. Hydrogen bromide was evolved and the bromine coloration slowly disappeared. The solvent was removed under reduced pressure at room temperature. The residual 6-*bromo*-3-*methoxy*allo*cinnamic acid* after recrystallisation from chloroform–light petroleum melted at 133° (Found: Br, 30·9. $C_{10}H_9O_3Br$ requires Br, 31·1%). It gave 6-bromo-3-methoxybenzoic acid, m. p. 162°, on oxidation with potassium permanganate and must therefore be the geometrical isomeride of the 6-bromo-acid, m. p. 189°.

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