702. *The Constitution of Chlorophorin. Part II. Further Oxidation Experiments, and the Completion of the Structural Problem.*

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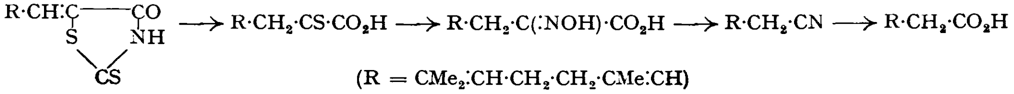
The position of the second double bond in the di-isoprenoid side-chain of chlorophorin (*J.*, 1949, 3348) has been demonstrated by alkaline hydrogen peroxide oxidation of the phenol to 4 : 8-dimethylnona-3 : 7-dienoic acid * (homogeranic acid) which has been synthesised from citral by the rhodanine method. Syntheses of 4-carboxy-2 : 6-dimethoxyphenylacetic acid, which was earlier obtained by permanganate oxidation of *O*-tetramethylchlorophorin, and of 2 : 6-dimethoxyphenylacetic acid, a potential decarboxylation product of the dicarboxylic acid, are also described.

In the structure (I) recently suggested for chlorophorin, a tetrahydric phenol isolated by ether extraction from the heartwood of the tree *Chlorophora excelsa* (King and Grundon, *J.*, 1949, 3348), only the nature of the terminal C_5H_9 group was left unsettled. The isolation of acetone as the 2 : 4-dinitrophenylhydrazone following permanganate oxidation of *O*-tetramethylchlorophorin suggested a Δ^2-*iso*pentenyl structure for the component C_5H_9, but among the various ozonolysis products of the tetramethyl ether no trace was observed of any simple ketone or aldehyde such as would be expected from the presence of the pentenyl group.

In order, therefore, to simplify the detection and isolation of ozonolysis products arising from the aliphatic side-chain of (I), a preliminary oxidation of the molecule was undertaken to destroy the aromatic constituent leaving the hydrocarbon substituent untouched. The desired elimination of the phenolic residues was accomplished by the oxidation of chlorophorin in alkaline solution with hydrogen peroxide, whereupon, after steam-distillation of the acidic product, a liquid unsaturated acid was obtained, which as the result of analyses of the *S*-benzylthiuronium salt and *p*-bromophenacyl ester was given the formula $C_{11}H_{18}O_2$. On ozonolysis the appearance of acetone, isolated as the 2 : 4-dinitrophenylhydrazone, and of lævulaldehyde, characterised by preparation of the 2 : 4-dinitrophenylhydrazone and semicarbazone of the derived acid, identified the new product $C_{11}H_{18}O_2$ as 4 : 8-dimethylnona-3 : 7-dienoic acid * (homogeranic acid), $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2CMe{:}CH{\cdot}CH_2{\cdot}CO_2H$, thus establishing the terminal C_5H_9 group of the chlorophorin side-chain as $CH_2{\cdot}CH{:}CMe_2$. The possibility that specimens of chlorophorin, which as already stated cannot be obtained crystalline, contain the tautomer (I; $R = CH_2{\cdot}CH_2{\cdot}CMe{:}CH_2$) is not entirely excluded by this evidence, but it renders unlikely the presence of significant quantities of other isomeric compounds.

The structure of the hydrogen peroxide oxidation product $C_{11}H_{18}O_2$ was further demonstrated by a synthesis from citral, using the rhodanine condensation and subsequent stages of the general method due to Julian and Sturgis (*J. Amer. Chem. Soc.*, 1935, **57**, 1126) as follows :



$$R{\cdot}CH{:}C{<}\begin{matrix}CO{\cdot}NH\\S{\cdot}CS\end{matrix}{>} \longrightarrow R{\cdot}CH_2{\cdot}CS{\cdot}CO_2H \longrightarrow R{\cdot}CH_2{\cdot}C({:}NOH){\cdot}CO_2H \longrightarrow R{\cdot}CH_2{\cdot}CN \longrightarrow R{\cdot}CH_2{\cdot}CO_2H$$

$(R = CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH)$

The identity of the natural and the synthetic acid was confirmed by mixed melting point determinations of specimens of the *S*-benzylthiuronium salts and the *p*-bromophenacyl esters.

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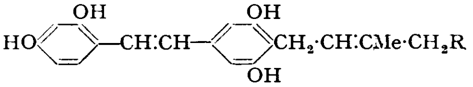
* Aliphatic carboxylic acids are here named and numbered according to Geneva nomenclature, *i.e.*, $CO_2H = 1$. In Part I (*J.*, 1949, 3348) these acids were numbered with $CO_2H = 0$. Thus, the acid now called 4 : 8-dimethylnona-3 : 7-dienoic acid was named 3 : 7-dimethylnona-2 : 6-dienoic acid in Part I.—Ed.

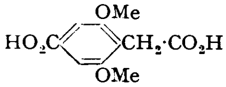
After this part of our work had been completed there appeared an account by Barnard and Bateman (*J.*, 1950, 926) of the synthesis of homogeranic acid from the above oximino-acid, prepared from ethyl geranylmalonate by the action of amyl nitrite.

The constitution of the phenolic portion of the molecule (I) rests, as already shown (Part I, *loc. cit.*), on the formation of 2 : 4-dimethoxybenzoic acid and of 4-carboxy-2 : 6-dimethoxyphenylacetic acid (II) on permanganate oxidation of *O*-tetramethylchlorophorin, the structure of the dicarboxylic acid being inferred from the isolation of 3 : 5-dimethoxy-4-methylbenzoic acid as one of its partial decarboxylation products The survival, after oxidation, of the methylene group adjacent to the aromatic ring is noteworthy and may be ascribed to the protection afforded by the adjacent methoxyls. The resistance to oxidation of the $CH_2\cdot CO_2H$ group linked to a di-*ortho*-substituted benzene ring was utilised in the synthesis of (II), which was finally achieved by treating 2 : 6-dimethoxy-4-methylphenylacetic acid with alkaline permanganate, the dimethoxymethylphenylacetic acid being prepared by application of the rhodanine synthesis to 2 : 6-dimethoxy-4-methylbenzaldehyde. The acid (II) had earlier proved inaccessible from 2 : 6-dimethoxy-4-methylbenzoic acid by an Arndt–Eistert synthesis since the dimethoxymethylbenzoyl chloride failed to react with diazomethane, a further illustration of the anomalous properties induced by the *o*-methoxy-groups. In another attempt to prepare (II), necessitating side-chain bromination of 3 : 5-dimethoxy-4-methylbenzoic acid, for which *N*-bromosuccinimide was used, nuclear substitution occurred giving 2-bromo-3 : 5-dimethoxy-4-methylbenzoic acid, whilst 3 : 5-diacetoxy-4-methylbenzoic acid failed to react with the bromo-imide. *p*-Toluic acid, on the other hand, gave with *N*-bromosuccinimide a very satisfactory yield of *p*-carboxybenzyl bromide from which the cyanide and hence homoterephthalic acid were readily prepared. Homoterephthalic acid resists sulphonation with fuming acid at 180°; had the formation of a disulphonic acid been possible, alkali fusion, etc., of the product might have afforded an alternative synthesis of (II).

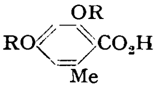
As already reported (King and Grundon, *loc. cit.*), pyrolysis of (II) yielded in addition to 3 : 5-dimethoxy-4-methylbenzoic acid a second derivative, m. p. 119—120°. Being available in only small amount this more-soluble substance could not with certainty be regarded as the pure isomeric monodecarboxylation product; a comparison with the authentic 2 : 6-dimethoxyphenylacetic acid was not at that time feasible since of the six possible dimethoxyphenylacetic acids this alone had not then been described. By using the rhodanine method the remaining member of this series has now been synthesised from 2 : 6-dimethoxybenzaldehyde. Its melting point (155—156°) is considerably higher than that of the second pyrolysis product which must therefore be assumed to be impure. 2 : 6-Dimethoxyphenylacetic acid, like the dicarboxylic acid (II), resists oxidation by cold aqueous potassium permanganate.



(I.) *Chlorophorin* ($R = CH_2\cdot CH{:}CMe_2$).



(II.)



(III.)

In the course of these experiments the hitherto unknown 2 : 4-dimethoxy-5-methylbenzoic acid (III; R = Me) was prepared by heating 2 : 4-dihydroxytoluene with aqueous sodium hydrogen carbonate, the resulting hydroxy-acid (m. p. 204—206°) being methylated by methyl iodide–potassium carbonate in boiling acetone. The orientation of the dimethoxytoluic acid was demonstrated by oxidation to the known 4 : 6-dimethoxy*iso*phthalic acid. It has been reported that 2 : 4-dihydroxy-5-methylbenzoic acid (III; R = H) can be obtained by formylation of methyl 2 : 4-dihydroxybenzoate with hexamethylenetetramine followed by Clemmensen reduction of the intermediate aldehyde, the latter operation being accompanied by hydrolysis of the ester group, but the product is given m. p. 163—164° (Desai and Radha, *Proc. Indian Acad. Sci.*, 1940, **11** *A*, 422; Desai, Radha, and Shah, *ibid.*, 1946, **23**, *A*, 338). No explanation of this anomaly can be offered, and attempts to repeat the synthesis by the method described by the Indian authors failed to produce an aldehyde from the dihydroxybenzoic ester.

Reference has already been made (King and Grundon, *loc. cit.*) to the relationship between chlorophorin and pinosylvin (3 : 5-dihydroxystilbene), a constituent of the heartwood of *Pinus sylvestris* (Erdtman, *Annalen*, 1939, **539**, 116). Further examples of natural hydroxystilbenes based on the structure of pinosylvin are rhapontigenin (3 : 5 : 3′-trihydroxy-4′-methoxystilbene) which occurs as a glucoside in Turkish rhubarb root (Kawamura, *J. Pharm. Soc. Japan*, 1938, **58**, 83), pterostilbene (4′-hydroxy-3 : 5-dimethoxystilbene) found in red sandelwood (Späth and Schläger, *Ber.*, 1940, **73**, 881), and resveratrol (3 : 5 : 4′-trihydroxystilbene) and hydroxyresveratrol (3 : 5 : 2′ : 4′-tetrahydroxystilbene) from the roots of the white hellebore (Takaoka, *Chem. Abstr.*, 1940, **34**, 7887), the hydroxyl pattern of the last being identical with that of chlorophorin.

EXPERIMENTAL.

Hydrogen Peroxide Oxidation of Chlorophorin.—A solution of chlorophorin (40 g.) in aqueous potassium hydroxide (800 c.c.; 10%) was treated with hydrogen peroxide (2000 c.c.; 6%), and left at room temperature for 24 hours. Excess of hydrogen peroxide was destroyed by the addition of manganese dioxide, and the solution extracted with ether (10 × 200 c.c.). Evaporation of the ether gave a viscous sweet-smelling oil (0·57 g.), which was not further investigated. The aqueous solution was acidified with concentrated hydrochloric acid, and, on extraction by ether (10 × 200 c.c.), a dark-brown viscous oil (30·6 g.) was obtained which was subsequently steam-distilled. Saturation of the distillate (2000 c.c.) with sodium chloride and extraction with ether (4 × 200 c.c.) gave a pale-yellow oil (3·15 g.), from which 4 : 8-dimethylnona-3 : 7-dienoic acid (2·65 g.) distilled at 119—125°/1·5 mm. The acid formed an S-*benzylthiuronium* salt, separating from aqueous ethanol in colourless elongated plates, m. p. 123° (Found : C, 65·5; H, 8·4; N, 7·9. $C_{19}H_{28}O_2N_2S$ requires C, 65·5; H, 8·0; N, 8·0%), and a p-*bromophenacyl* ester, crystallising from aqueous ethanol in colourless plates, m. p. 52—53° (Found : C, 59·7; H, 6·1. $C_{19}H_{23}O_3Br$ requires C, 60·2; H, 6·1%).

A solution of the acid (2·5 g.) in dry chloroform (20 c.c.) was treated with ozonised oxygen until excess of ozone was detected (12 hours). The gases leaving the reaction vessel were passed through a trap containing water (20 c.c.) which was subsequently treated with excess of aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. After 4 hours, the yellow solid was collected (0·14 g.) and crystallised from aqueous ethanol; it gave orange-yellow hair-like needles, m. p. and mixed m. p. with acetone 2 : 4-dinitrophenylhydrazone 124—125°. The chloroform solution was evaporated at room temperature and the residue, dissolved in acetic acid (5 c.c.), was slowly added to a mixture of dilute sulphuric acid (10 c.c.; 2·5%) and hydrogen peroxide (6 c.c.; 30%). The mixture was cautiously warmed, and finally heated on a steam-bath for 1 hour. After 24 hours it was steam-distilled, and the first portion of the condensate (5 c.c.) treated with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated yellow solid (0·13 g.) crystallised from aqueous ethanol in orange-yellow hair-like needles, or from light petroleum (b. p. 60—80°) in stout orange-red needles, m. p. 124·5—125·5° not depressed on admixture with acetone 2 : 4-dinitrophenylhydrazone (Found : C, 45·6; H, 4·2; N, 23·2. Calc. for $C_9H_{10}O_4N_4$: C, 45·8; H, 4·2; N, 23·5%). A further 30 c.c. of distillate was collected, and a portion (15 c.c.) of the residue (60 c.c.) treated with excess of aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. After 24 hours the precipitate (0·15 g.) was collected and crystallised from chloroform, and the yellow solid, m. p. 201—203°, shown to be identical with lævulic acid 2 : 4-dinitrophenylhydrazone by m. p. and mixed m. p. The remaining portion of the steam-distillation residue was saturated with sodium chloride and extracted with ether (5 × 20 c.c.). The oil obtained by evaporation of the ether was treated with a solution of semicarbazide hydrochloride (1·5 g.) and sodium acetate (2 g.) in water (10 c.c.), and after 36 hours the colourless solid (0·48 g.), m. p. 161—165° (decomp.), was collected. Recrystallisation from water gave lævulic acid semicarbazone in clusters of colourless prisms, m. p. 180—182°, with softening at 179° (Found : C, 41·9; H, 6·5; N, 24·4. Calc. for $C_6H_{11}O_3N_3$: C, 41·6; H, 6·4; N, 24·3%).

3 : 7-*Dimethylocta*-2 : 6-*dienylidenerhodanine.*—Citral (10 g.), rhodanine (10 g.), acetic acid (40 c.c.), and fused sodium acetate (15 g.) were heated on a steam-bath, and after one hour the deep orange-red solution was poured into water (300 c.c.). The oil which separated hardened, on being kept, to an orange solid (10·4 g., 59%), m. p. 134—139°, and on recrystallisation from benzene–light petroleum the *citrylidenerhodanine* was obtained in brownish-red needles, m. p. 140—141° (Found : C, 57·9; H, 6·3. $C_{13}H_{17}ONS_2$ requires C, 58·4; H, 6·4%).

5 : 9-*Dimethyl*-2-*oximino*-4 : 8-*decadienoic Acid* (cf. Barnard and Bateman, *loc. cit.*).—The foregoing product (15 g.) was hydrolysed by heating it on a steam-bath for 40 minutes with aqueous potassium hydroxide (105 c.c.; 15%). The thio-acid was obtained in semi-solid form by acidification of the cooled solution with dilute hydrochloric acid (130 c.c.; 10%). Owing to its excessive solubility in organic solvents this intermediate could not be obtained in a crystalline condition; its p-*bromophenacyl* ester separated from aqueous ethanol in faintly yellow rectangular plates, m. p. 137·5—138·5° (Found : C, 56·4; H, 5·3. $C_{20}H_{23}O_3SBr$ requires C, 56·7; H, 5·4%).

The crude acid was treated with a solution of hydroxylamine, prepared from the hydrochloride (12 g.) and alcoholic sodium ethoxide, and heated on a steam-bath for 20 minutes. After the alcohol had been removed and water (200 c.c.) added, the solution was extracted with ether (3 × 70 c.c.). By evaporation a brown gum (9·1 g.) was obtained which crystallised from benzene–light petroleum (b. p. 60—80°) in plates (1·7 g.), m. p. 128—130° becoming 99—100° on further crystallisations from benzene–light petroleum (Found : N, 5·7. Calc. for $C_{12}H_{19}O_3N$: N, 6·2%).

3 : 7-*Dimethylocta*-2 : 6-*dienyl Cyanide.*—The oximino-acid (1·2 g.) was added in small portions to acetic anhydride (5 c.c.), whereupon the solid dissolved with evolution of heat and vigorous effervescence. The solution was diluted with water (60 c.c.) and shaken with ether (2 × 20 c.c.), and the ether solution washed first with 5% aqueous potassium hydroxide and then water. Evaporation gave a pale-yellow oil (0·9 g.) from which the *nitrile* was obtained as a colourless oil (0·68 g.) by distillation at 125—128° (bath temp.)/17 mm. (Found : N, 8·7. $C_{11}H_{17}N$ requires N, 8·6%).

By evaporation of the benzene–light petroleum solution from which the oximino-acid had crystallised, and treatment of the residue with acetic anhydride, a further quantity of the nitrile (1·6 g.) was obtained; total yield of distilled product, calculated on citrylidenerhodanine, 31%.

4 : 8-*Dimethylnona*-3 : 7-*dienoic Acid.*—3 : 7-Dimethylocta-2 : 6-dienyl cyanide (0·8 g.) was hydrolysed by heating it with alcoholic potassium hydroxide (15 c.c.; 10%) for four hours. The solution was acidified

and after removal of alcohol the diene-carboxylic acid (0·83 g., 93%) was isolated by means of ether, the product distilling (bath temp. 90—100°) at 0·4 mm. as a colourless oil.

The p-*bromophenacyl* ester crystallised from light petroleum (b. p. 40—60°) or aqueous ethanol in plates, m. p. 52—53° (Found : C, 60·2; H, 5·9%), and the S-*benzylthiuronium* salt separated from aqueous ethanol in rectangular plates, m. p. 123° (Found : C, 64·9; H, 8·2%). Mixed m. p. determinations indicated the identity of these two derivatives with the corresponding compounds prepared from the acid $C_{11}H_{18}O_2$ derived from chlorophorin (see above).

2 : 6-*Dimethoxy*-4-*methylbenzaldehyde*.—This compound was prepared by Robertson and Robinson's method (*J.*, 1927, 2196) but with modification of the final stage. The aldimine salt (3·2 g.), obtained from 2 : 6-dimethoxy-4-methylbenzonitrile (2·5 g.) as described, was dissolved in water (70 c.c.), and sodium acetate (15 g.) added. The solution was heated on a steam-bath for 15 minutes, cooled, and extracted with ether (5 × 30 c.c.). The solid residue obtained by evaporation of the ether was heated for 10 minutes with boiling light petroleum (60 c.c.; b. p. 60—80°). On cooling, the filtered solution deposited the required aldehyde in long needles (0·92 g.), m. p. 90—91°. A further quantity (0·22 g.), m. p. 86—87° (total, 1·14 g., 43%), was obtained by concentration of the light petroleum solution.

2 : 6-*Dimethoxy*-4-*methylbenzylidenerhodanine*.—A mixture of the foregoing aldehyde (0·9 g.), rhodanine (0·77 g.), fused sodium acetate (1·3 g.), and acetic acid (5 c.c.) was heated on a steam-bath. Orange needles separated during the reaction, and after two hours, the mixture was cooled and diluted with water (20 c.c.). The orange *rhodanine* (1·15 g., 78%), m. p. 232—235°, which separated, crystallised from ethanol in yellow needles, m. p. 237—238° with sintering at 236° (Found : C, 53·2; H, 4·3; N, 5·0. $C_{13}H_{13}O_3NS_2$ requires C, 52·9; H, 4·4; N, 4·7%).

β-(2 : 6-*Dimethoxy*-4-*methylphenyl*)-α-*thiopropionic Acid*.—The benzylidenerhodanine (0·95 g.) was heated on a steam-bath with aqueous potassium hydroxide (5 c.c.; 15%) for 20 minutes. The *thio-acid* (0·8 g., 95%) obtained by acidification of the ice-cold solution with hydrochloric acid (6 c.c.; 10%) was crystallised from aqueous methanol and formed large pale-yellow needles, m. p. 184—186° (Found : C, 56·8; H, 5·5. $C_{12}H_{14}O_4S$ requires C, 56·7; H, 5·5%).

2 : 6-*Dimethoxy*-4-*methylbenzyl Cyanide*.—A solution of hydroxylamine was prepared from warm aqueous hydroxylamine hydrochloride (3 g. in 3 c.c. of water) and a solution of sodium (1 g.) in ethanol (30 c.c.). After removal of the sodium chloride, a portion (11 c.c.) was mixed with the above thioacid (0·8 g.), and the solution heated on a steam-bath for 20 minutes. When the alcohol had been evaporated under reduced pressure, the residue was treated with aqueous sodium hydroxide (5 c.c.; 5%). Unidentified insoluble material (0·1 g.), which crystallised from aqueous ethanol in colourless rods, m. p. 136—137° (Found : C, 67·0; H, 6·1; N, 12·5%), was removed, and the oximino-acid (0·7 g., 88%), m. p. 137—138°, obtained by acidification of the solution with 10% hydrochloric acid. The crude material (0·7 g.) was treated with acetic anhydride (2·2 c.c.), and the mixture warmed on a steam-bath until effervescence ceased (5 minutes). The brownish product left on evaporating the acetic anhydride, when recrystallised from aqueous ethanol gave 2 : 6-*dimethoxy*-4-*methylbenzyl cyanide* in colourless needles (0·37 g., 60%), m. p. 124—125° (Found : C, 69·0; H, 6·8; N, 7·4. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). It was later found that the nitrile may also be obtained merely by heating the oximino-acid with water.

2 : 6-*Dimethoxy*-4-*methylphenylacetic Acid*.—Hydrolysis of the foregoing cyanide (0·37 g.) was achieved by heating it under reflux with 25% alcoholic potassium hydroxide (20 c.c.) for seven hours. After removal of the alcohol, water (25 c.c.) was added, and the cooled filtered solution acidified with hydrochloric acid. The *acid* (0·32 g., 80%), m. p. 163—164°, thus obtained crystallised from aqueous ethanol in prisms, m. p. 165° with slight sintering at 163° (Found : C, 62·7; H, 7·0. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

4-*Carboxy*-2 : 6-*dimethoxyphenylacetic Acid* (II).—Aqueous potassium permanganate (4%) was added during 36 hours to a solution of 2 : 6-dimethoxy-4-methylphenylacetic acid (0·32 g.) in 10% aqueous potassium hydroxide (5 c.c.), until a permanent pink colour was observed (required 12 c.c.). The mixture was saturated with sulphur dioxide, thus giving a colourless solid (0·25 g.), m. p. 271—280° with sintering from 250°, from which 4-*carboxy*-2 : 6-*dimethoxyphenylacetic acid* (0·22 g., 60%), m. p. 276—284°, was obtained by trituration with chloroform. The acid crystallised from aqueous ethanol in long needles, melting and darkening at 282—284°, alone or mixed with the acid $C_{11}H_{12}O_6$ obtained by permanganate oxidation of *O*-tetramethylchlorophorin (King and Grundon, *loc. cit.*) (Found : C, 54·7; H, 5·2. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%).

This acid (0·15 g.) was suspended in ether and treated with excess of ethereal diazomethane. After 30 minutes all the solid had disappeared, and on evaporation of the ether the *dimethyl* ester was obtained. It crystallised from aqueous ethanol in needles (0·11 g.), m. p. and mixed m. p. with the dimethyl ester of 2 : 6-dimethoxy-4-carboxyphenylacetic acid derived from chlorophorin, 108—109° (Found : C, 58·1; H, 6·0. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

3 : 5-*Dimethoxy*-4-*methylbenzoic Acid*.—Unpurified 3 : 5-dihydroxy-4-methylbenzoic acid (1 g.) (Charlesworth and Robinson, *J.*, 1934, 1531) was methylated by heating it in acetone solution for 60 hours with methyl iodide and anhydrous potassium carbonate. Methyl 3 : 5-dimethoxy-4-methylbenzoate (0·85 g.) obtained by evaporation of the filtered solution crystallised from aqueous ethanol in needles, m. p. 102—103° (Found : C, 62·9; H, 6·8. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%). 3 : 5-Dimethoxy-4-methylbenzoic acid, prepared by hydrolysis of the ester with 10% potassium hydroxide, crystallised from aqueous ethanol in faintly yellow needles, m. p. 213—215°.

2-*Bromo*-3 : 5-*dimethoxy*-4-*methylbenzoic Acid*.—A mixture of 3 : 5-dimethoxy-4-methylbenzoic acid (1·7 g.), *N*-bromosuccinimide (1 g.), and carbon tetrachloride (10 c.c.) was heated under reflux for five hours. The liquid was then removed by filtration and the residue treated with aqueous sodium hydrogen carbonate. Acidification of the filtered alkaline solution precipitated 2-*bromo*-3 : 5-*dimethoxy*-4-*methyl*-

benzoic acid (0·35 g.), m. p. 161—165°, which crystallised from light petroleum (b. p. 100—120°) in prisms, m. p. 176—178° (Found : C, 44·3 ; H, 4·1. $C_{10}H_{11}O_4Br$ requires C, 43·6 ; H, 4·0%). A further quantity (0·2 g.) was obtained by evaporation of the carbon tetrachloride solution and extraction of the residue with boiling light petroleum (b. p. 60—80°).

3 : 5-*Diacetoxy-4-methylbenzoic Acid*.—Concentrated sulphuric acid (0·5 c.c.) was added to a mixture of crude 3 : 5-dihydroxy-4-methylbenzoic acid (6 g.) (Charlesworth and Robinson, *loc. cit.*) and acetic anhydride (30 c.c.), and after two hours the solution was added to water (400 c.c.). The crystalline solid (6·1 g.) which appeared on keeping was collected and extracted with boiling light petroleum (b. p. 100—120°) (2 × 120 c.c.). The residue of 3 : 5-*diacetoxy-4-methylbenzoic acid* separated from aqueous ethanol (charcoal) in blades (2·1 g.), m. p. 198—199° raised by recrystallisation to 202—203° (Found : C, 57·1 ; H, 5·0. $C_{12}H_{12}O_6$ requires C, 57·1 ; H, 4·8%).

2-*Bromo*-3 : 5-*dimethoxyterephthalic Acid*.—The above bromo-acid (0·4 g.), dissolved in aqueous potassium hydroxide (10 c.c. ; 10%), was treated with a solution of potassium permanganate (0·5 g.) in water (30 c.c.), and kept at room temperature for two hours. The solution was clarified with sulphur dioxide, and kept at 0° for 24 hours. The pale-yellow crystalline deposit (0·27 g.) of 2-*bromo*-3 : 5-*dimethoxyterephthalic acid* separated from water in pale-yellow prisms (0·22 g.), m. p. 243—244° (Found : C, 39·4 ; H, 3·2. $C_{10}H_9O_6Br$ requires C, 39·3 ; H, 3·0%).

Homoterephthalic Acid.—A mixture of *p*-toluic acid (9·5 g., 1 mol.), *N*-bromosuccinimide (19 g., 1·5 mol.), and carbon tetrachloride (100 c.c.) was heated under reflux for four hours. The undissolved material crystallised from acetone in plates (6·1 g.), m. p. 219—224°, and with a further quantity (3·4 g.), m. p. 211—216°, obtained from the mother-liquors the total yield was 63%. The α-bromo-*p*-toluic acid crystallised from acetone in small plates, m. p. 227—227·5° (Found : C, 44·8 ; H, 3·4. Calc. for $C_8H_7O_2Br$: C, 44·7 ; H, 3·3%).

α-Cyano-*p*-toluic acid (2·4 g.) was prepared from the bromide (5 g.) with sodium cyanide (2·7 g.) in aqueous alcoholic solution, and hydrolysis of the cyanide with 15% aqueous potassium hydroxide afforded homoterephthalic acid (yield from *p*-toluic acid, 40%). The analytical specimen separated from water in fine needles, m. p. 239—240° (Found : C, 59·8 ; H, 4·6. Calc. for $C_9H_8O_4$: C, 60·0 ; H, 4·4%).

2 : 6-*Dimethoxybenzylidenerhodanine*.—2 : 6-Dimethoxybenzaldehyde (2 g.) (Wittig, *Angew. Chem.*, 1940, **53**, 241), rhodanine (1·8 g.), fused sodium acetate (4 g.), and acetic acid (10 c.c.) were heated on a steam-bath. After 45 minutes the mixture was treated with water (50 c.c.), and the remaining solid (2·5 g., 77%) collected and washed with water, a little ethanol, and finally with ether. The purified *dimethoxybenzylidenerhodanine* separated from acetone in rosettes of yellow prismatic needles, m. p. 267° with darkening (Found : C, 50·9 ; H, 3·9 ; N, 5·1. $C_{12}H_{11}O_3NS_2$ requires C, 51·2 ; H, 3·9 ; N, 5·0%).

β-2 : 6-*Dimethoxyphenyl-α-thiopropionic Acid*.—The crude 2 : 6-dimethoxybenzylidenerhodanine (2·5 g.) was heated on a steam-bath for 30 minutes with aqueous sodium hydroxide (20 c.c. ; 15%). Hydrochloric acid (30 c.c. ; 10%) was added to the solution cooled in a freezing mixture, and the buff-coloured precipitate of the *thio-acid* (2·2 g., 95%), m. p. 166—172°, was collected and washed with water. The analytical specimen, crystallised first from methanol and then from aqueous methanol, formed pale-yellow irregular prisms, m. p. 175—178° (Found : C, 54·6 ; H, 5·1. $C_{11}H_{12}O_4S$ requires C, 55·0 ; H, 5·0%).

α-2 : 6-*Dimethoxybenzyl-α-oximinoacetic Acid*.—An aqueous solution of hydroxylamine prepared from aqueous hydroxylamine hydrochloride (2 g. in 2 c.c. of water) and alcoholic sodium ethoxide, and β-2 : 6-dimethoxyphenyl-α-thiopropionic acid (2·5 g.) was heated under reflux for 20 minutes. When the ethanol was evaporated and the residue treated with aqueous sodium hydroxide (10 c.c. ; 5%), an insoluble by-product (0·13 g.) remained which crystallised from aqueous ethanol in colourless plates, m. p. 93—94° undepressed by admixture with 2 : 6-dimethoxybenzyl cyanide (see below). The alkaline solution, cooled in a freezing mixture and mixed with hydrochloric acid (10 c.c. ; 10%), gave the oily *oximino-acid* (2·1 g., 84%), which solidified on being kept. The analytical specimen crystallised from ethyl acetate–benzene in hexagonal rods, m. p. 174—175° (efferv.) (Found : C, 54·8 ; H, 5·5 ; N, 5·9. $C_{11}H_{13}O_5N$ requires C, 55·2 ; H, 5·5 ; N, 5·9%).

2 : 6-*Dimethoxybenzyl Cyanide*.—The unpurified oximino-acid (2·1 g.) was heated on a steam-bath with acetic anhydride (6·5 c.c.) until effervescence ceased (5 minutes). The solution was then added to water and the precipitate crystallised from aqueous ethanol (charcoal). 2 : 6-*Dimethoxybenzyl cyanide* was thus obtained in hexagonal plates (1·25 g., 81%), m. p. 93—94° raised by further crystallisation to 95—96° (Found : C, 67·6 ; H, 6·1 ; N, 8·1. $C_{10}H_{11}O_2N$ requires C, 68·1 ; H, 6·3 ; N, 7·9%). It was later obtained from the oximino-acid by heating it with water or aqueous ethanol.

2 : 6-*Dimethoxyphenylacetic Acid*.—2 : 6-Dimethoxybenzyl cyanide (1·25 g.) was heated under reflux with aqueous potassium hydroxide (25 c.c. ; 15%) until a clear solution was obtained (4½ hours). This was acidified at 0° with hydrochloric acid, and the 2 : 6-*dimethoxyphenylacetic acid* (1·2 g., 87% yield), m. p. 149—154°, was collected and crystallised from aqueous ethanol ; it gave rectangular prisms, m. p. 155—156° (Found : C, 61·2 ; H, 6·4. $C_{10}H_{12}O_4$ requires C, 61·2 ; H, 6·1%).

Methyl 2 : 6-dimethoxyphenylacetate, prepared by the use of diazomethane, failed to crystallise. After being shaken with aqueous ammonia (5 c.c. ; *d* 0·88) for 12 hours, the ester (0·15 g.) was converted into 2 : 6-*dimethoxyphenylacetamide* (0·11 g.), m. p. 138—147°, which separated from water in long prismatic needles, m. p. 158—159° with slight softening from 149° (Found : C, 61·6 ; H, 6·7 ; N, 7·3. $C_{10}H_{13}O_3N$ requires C, 61·5 ; H, 6·7 ; N, 7·2%).

2 : 4-*Dimethoxy-5-methylbenzoic Acid* (III ; R = Me).—2 : 4-Dihydroxytoluene (2 g.) (Bell, Bridge, and Robertson, *J.*, 1937, 1542), sodium hydrogen carbonate (8 g.), and water (40 c.c.) were heated on a steam-bath for three hours. Heating the solution under reflux for 30 minutes while a stream of carbon

dioxide was passed into it gave 2 : 4-dihydroxy-5-methylbenzoic acid (0·95 g., 39%) as a brown solid, m. p. 201—203° raised by recrystallisation from water (charcoal) to 204—206°.

Methylation of the hydroxy-acid (1 g.) was achieved by heating it in acetone with methyl iodide and potassium carbonate for 48 hours. Evaporation of the acetone gave methyl 2 : 4-dimethoxy-5-methylbenzoate, separating from light petroleum (b. p. 40—60°) in clusters of orange triangular prisms (0·52 g.), m. p. 89—90°. 2 : 4-*Dimethoxy-5-methylbenzoic acid* was obtained by hydrolysis of the ester with 10% aqueous sodium hydroxide, and it crystallised from 50% aqueous acetic acid in needles, m. p. 166° (Found: C, 60·9; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). Oxidation with 5% aqueous potassium permanganate yielded a product, m. p. 262° (decomp.), probably identical with 4 : 6-dimethoxy*iso*phthalic acid, m. p. 264° (decomp.) (Spāth and Klager, *Ber.*, 1934, **67**, 859).

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