Constituents of "Cortex Piscidiae Erythrinae." Part II. The Synthesis of O-Methylpiscidic Acid.*

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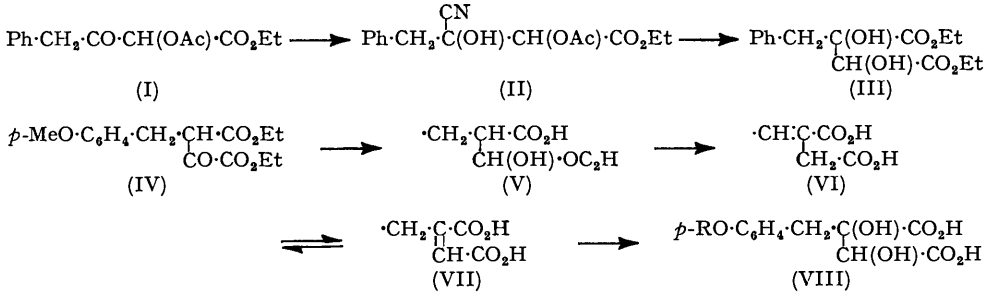
On being heated *p*-methoxybenzylidenesuccinic acid gave a poor yield of *p*-methoxybenzylmaleic acid which on hydroxylation with osmium tetroxide in the presence of pyridine furnished a racemate of *p*-methoxybenzyltartaric acid. Resolution of this compound gave (+)-*p*-methoxybenzyltartaric acid, identical with natural *O*-methylpiscidic acid.

In Part I (*J.*, 1948, 257) piscidic acid, from "Cortex Piscidiae Erythrinae," was shown to be a (+)-*p*-hydroxybenzyltartaric acid (VIII; R = H) and this has now been confirmed by the synthesis of (+)-*O*-methylpiscidic acid (VIII; R = Me). Of the several possible routes for the synthesis of tartaric acids of this type (VIII) two were simultaneously examined, *viz.*, (*a*) the preparation and hydroxylation of the requisite maleic acid and (*b*) the addition of hydrogen cyanide to ketonic esters of type (I) followed by hydrolysis of the resulting cyanohydrin, a method which would be expected to furnish the two racemates possible with tartaric acids of the piscidic acid type. In model experiments by route (*b*) the acetoxylation of ethyl γ-phenylacetoacetate with lead tetra-acetate furnished ethyl α-acetoxy-γ-phenylacetoacetate (I), the orientation of which was confirmed by its preparation, albeit in poor yield, from ethyl α-diazo-γ-phenylacetoacetate, formed by the interaction of phenylacetyl bromide and ethyl diazoacetate. On treatment with alcoholic hydrogen chloride the cyanohydrin (II) from (I) was converted into ethyl benzyltartrate (III) which was separated by fractional crystallisation into the two racemic forms, characterised by conversion into the corresponding diamides.



Because of the meagre yields obtained in the cyanohydrin route our efforts were concentrated on route (*a*). The oxidation of citraconic acid with osmium tetroxide and sodium chlorate furnished one of the racemates of methyltartaric acid obtained from ethyl α-acetoxyacetoacetate by the cyanohydrin method † (cf. Schmidt and Perkow, *Chem. Ber.*, 1950, **83**, 484) but attempts to convert phenylmaleic acid into phenyltartaric acid with the osmium tetroxide–sodium chlorate reagent were unsuccessful. By the osmium tetroxide–pyridine procedure of Craigie, Marchand, and Wannowius (*Annalen*, 1942, **550**, 99), however, phenylmaleic acid was hydroxylated to a racemate of phenyltartaric acid. The phenylmaleic acid for this was prepared by dehydrating the mixed racemates of phenylmalic acid which were obtained by the reduction of ethyl phenyloxaloacetate with aluminium amalgam, a method superior to Alexander's (*Annalen*, 1890, **258**, 76). Similarly the condensation of ethyl β-*p*-methoxyphenylpropionate with ethyl oxalate furnished the keto-ester (IV) and this on reduction gave ethyl α-hydroxy-β-*p*-methoxybenzylsuccinate which was hydrolysed

* Part I, *J.*, 1948, 257.

† Schmidt and Perkow's paper (*Chem. Ber.*, 1950, **83**, 484) appeared after the experimental work on the cyanohydrin method had been completed in 1949; the results were presented in a Thesis for Degree of Master of Science by Dr. A. L. J. Buckle in 1949. A. R.

to the malic acid (V). This was separated into two racemic forms but attempts to convert it into the maleic acid (VII) or its anhydride were unsuccessful. With warm acetic anhydride alone or in ether, phosphoric oxide, or phosphoryl chloride, either racemate gave only *p*-methoxybenzylidenesuccinic anhydride, identical with a specimen prepared by the condensation of *p*-anisaldehyde and ethyl succinate with subsequent hydrolysis of the ester and dehydration of the resulting acid; in agreement with the structure (VI) the ultra-violet absorption spectrum of this acid closely resembled that of *p*-methoxycinnamic acid. Similarly, the dehydrogenation of *p*-methoxybenzylsuccinic acid with *N*-bromosuccinimide in the presence of a little benzoyl peroxide by the method of Miller, Staley, and Mann (*J. Amer. Chem. Soc.*, 1949, **71**, 374) gave only the benzylidenesuccinic acid (VI). The Kreb's heart muscle dehydrogenase, which converts succinic acid into maleic acid (*Biochem. J.*, 1937, **31**, 2095), did not attack *p*-methoxyphenylsuccinic acid, which in fact inhibited the succinic–maleic acid oxidation.

Brooke (*Annalen*, 1899, **305**, 21) observed that the solid obtained by the sudden cooling of molten benzylidenesuccinic acid contained a very small proportion of the isomeric maleic acid which at its melting point reverted almost completely to the itaconic acid. By the application of this thermal conversion process to *p*-methoxybenzylidenesuccinic acid (VI) there were obtained minute yields of the acid (VII), the ultra-violet absorption spectrum of which closely resembled that of citraconic acid and was readily distinguished from that of the parent acid. With the osmium tetroxide method the acid (VII) gave rise to one racemate of *p*-methoxybenzyltartaric acid (VIII; R = Me) which was resolved by means of its brucine salt, giving the (+)-isomeride identical with the *O*-methylpiscidic acid.

Experimental

Ethyl α-Acetoxy-γ-phenylacetoacetate.—Obtained (yield, *ca.* 60%) by the procedure employed by Attwood, Stevenson, and Thorpe (*J.*, 1923, **123**, 1755) for the preparation of the so-called ethyl " β-keto-γ-phenylbutyrate " (*i.e.*, ethyl γ-phenylacetoacetate), ethyl α-phenylacetoacetate was a pale yellow oil, b. p. 110°/0·8 mm., with a purple ferric reaction. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow needles, m. p. 94—95° (Found: N, 15·5. $C_{18}H_{18}O_6N_4$ requires N, 15·8%).

Lead tetra-acetate (22 g.) was added portion-wise to a stirred solution of this ester (10·2 g.) in acetic acid (25 ml.) at <40°. The mixture was diluted with water (50 ml.) and extracted with ether, giving *ethyl α-acetoxy-α-phenylacetoacetate* as a colourless oil (5 g.), b. p. 128—130°/0·2 mm. with a negative ferric reaction (Found: C, 63·8; H, 6·2. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). The absence of a ferric reaction with this derivative served to confirm that the parent ester is ethyl α-phenylacetoacetate as suggested by Scheibler, Emden, and Krabbe (*Ber.*, 1930, **63**, 1562).

(*a*) Lead tetra-acetate (44·3 g.) was added portion-wise to a stirred solution of ethyl γ-phenylacetoacetate (Sonn and Litten, *Ber.*, 1933, **66**, 1512) in acetic acid (40 ml.) at <40° and the yellow viscous reaction mixture treated with water (120 ml.). The resulting *ethyl α-acetoxy-γ-phenylacetoacetate* was isolated with ether and on distillation was obtained as a bright yellow oil (10 g.), b. p. 143—145°/0·5 mm., which on being kept for several months became colourless; distillation of the colourless specimen regenerated the yellow oil (Found: C, 63·7; H, 6·3%). This compound had a deep cherry-red ferric reaction in alcohol.

(*b*) Phenylacetyl bromide (4 g.) was added dropwise to ethyl diazoacetate kept at −5° during ½ hr. and the resulting viscous product, which did not solidify, was heated with acetic acid (3 g.) on the steam-bath for 20 min. From the reaction mixture, which had been diluted with water (80 ml.), ethyl α-acetoxy-γ-phenylacetoacetate was isolated with ether and on distillation in a vacuum obtained as a yellow oil (0·8 g.) identical with the ester prepared by method (*a*).

Ethyl α-Benzyltartrate.—A mixture of ethyl α-acetoxy-γ-phenylacetoacetate (2·6 g.), hydrogen cyanide (0·6 ml.), and powdered sodium hydroxide (0·1 g.) was kept for 12 hr., diluted with alcohol (20 ml.), saturated with hydrogen chloride, heated under reflux for 4 hr., cooled, and filtered to remove ammonium chloride. Triturated with a little ether, the residue left on evaporation of the filtrate solidified and on crystallisation from methanol gave *ethyl benzyltartrate* as a mixture (0·4 g.) of needles and prisms which were separated manually and by repeated recrystallisation into approximately equal amounts of *racemate* (A) which formed needles, m. p. 174—175°, from

methanol (Found: C, 60·1; H, 6·8. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%) and *racemate* (B), irregular prisms, m. p. 194—195°, from acetic acid (Found: C, 60·2; H, 6·7%). With methanolic ammonia racemate (A) gave a *diamide* which separated from 90% alcohol in parallelopipeds, m. p. 204—206° (decomp.) (Found: N, 11·4. $C_{11}H_{14}O_4N_2$ requires N, 11·8%). Similarly racemate (B) gave a *diamide*, rectangular plates, m. p. 185—186° (decomp.), from alcohol (Found: N, 11·4%).

α-Hydroxy-β-phenylsuccinic Acid (*β-Phenylmalic Acid*).—Ethyl phenyloxaloacetate (Wislicenus, *Ber.*, 1894, **27**, 1091) (10 g.) was reduced by moist aluminium amalgam (from 8 g. of aluminium) in ether (200 ml.) with the addition of small amounts of water during 3—5 hr.; the completion of the reaction was indicated by the negative ferric reaction of a test portion. On distillation, the resulting *ethyl β-phenylmalate* was obtained as a colourless oil (8 g.), b. p. 131°/0·04 mm. (Found: C, 63·0; H, 7·0. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). This ester (20 g.) was hydrolysed with 10% aqueous potassium hydroxide (120 ml.) and on being kept in a vacuum over phosphoric oxide the resulting syrupy acid crystallised, having m. p. 150—160°, after purification from ethyl acetate; the yield was 14 g. Fractional crystallisation of this from ethyl acetate and then ethyl acetate–light petroleum (b. p. 60—80°) gave the less soluble racemic *isomeride* (A), forming irregular prisms, m. p. 172°, from ethyl acetate (Found: C, 57·3; H, 4·7. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8%), and the more soluble racemic *isomeride* (B) which separated from ethyl acetate–light petroleum in elongated hexagonal prisms, m. p. 162° (Found: C, 57·2; H, 4·6%).

A mixture (3 g.) of (A) and (B) was boiled with acetic anhydride (20 g.) for 3 hr., and about half of the anhydride distilled. On cooling, the residue deposited phenylmaleic anhydride in colourless rectangular plates (1·7 g.), m. p. 120°, which on treatment with alkali furnished phenylmaleic acid, m. p. 90—92° (decomp), quantitatively (cf. Alexander, *Annalen*, 1890, **258**, 67).

Phenyltartaric Acid.—On the addition of pyridine (2 ml.) a solution of phenylmaleic acid (1·54 g.) and osmium tetroxide (2 g.) in ether (200 ml.) became dark brown and slowly deposited a light brown precipitate. 2 Days later this osmium *adduct* (3·6 g.) was isolated with ether (Found: Os, 31·0. $C_{20}H_{18}O_4N_2Os$ requires Os, 31·5%), and treated with 7% aqueous potassium hydroxide (20 ml.). After the removal of the liberated pyridine with ether the red solution was acidified with hydrochloric acid, extracted twice with a little benzene, and evaporated over phosphoric oxide in a vacuum at room temperature. Extraction of the residue in a Soxhlet apparatus with ether gave *phenyltartaric acid*, which separated from ethyl acetate in hexagonal prisms (0·6 g.), m. p. 173—174°, soluble in water, alcohol, or acetone and insoluble in benzene or chloroform (Found: C, 53·0; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%).

C-*Methyltartaric Acid.*—A mixture of citraconic acid (10 g.), sodium chlorate (12 g.), 1% aqueous osmium tetroxide (10 ml.), and water (150 ml.) was kept at 50° for 3 hr., cooled, extracted with benzene, basified with ammonia, and treated with a concentrated solution of barium acetate (30 g.) in water. The resulting barium salt was decomposed with a slight excess of dilute sulphuric acid, the excess of sulphuric acid was removed, and the filtered liquor concentrated in a vacuum, and finally dried over phosphoric oxide at room temperature, giving a solid which on recrystallisation from ethyl acetate furnished methyltartaric acid in colourless prisms (8 g.), m. p. 144—145° (Found: C, 36·4; H, 4·8; equiv., 84·1. Calc. for $C_5H_8O_6$: C, 36·6; H, 4·9%; equiv., 82·0) (cf. Schmidt and Perkow, *Chem. Ber.*, 1950, **83**, 484, who give m. p. 146°). This compound is easily soluble in water or alcohol, and insoluble in ether, benzene, or chloroform. The methyl ester separated from light petroleum (b. p. 60—80°) in elongated rectangular prisms, m. p. 99—100° (Found: C, 43·9; H, 6·3. Calc. for $C_7H_{12}O_6$: C, 43·8; H, 6·2%), and the diamide in hexagonal prisms, m. p. 152—153° (decomp.), from 90% alcohol (Found: N, 16·9. Calc. for $C_5H_{10}O_4N_2$: N, 17·3%) (cf. Schmidt and Perkow, *loc. cit.*).

β-Hydroxy-α-p-methoxybenzylsuccinic Acid (*p-Methoxybenzylmalic Acid*).—When the initial reaction between sodium ethoxide (prepared *in situ* from 7·2 g. of sodium and 18·16 ml. of alcohol) in ether (140 ml.) and ethyl oxalate had subsided, ethyl β-*p*-methoxyphenylpropionate (32 g.) was introduced and the mixture heated under reflux for 16 hr., poured on ice, and acidified. The product was isolated with much ether, and the ethereal solution was concentrated to *ca.* 200 ml. and repeatedly extracted with small amounts of 25% aqueous potassium carbonate until the residue left on evaporation of the ethereal solution gave a negative ferric reaction. The combined aqueous potassium carbonate extracts were acidified with dilute sulphuric acid and extracted with ether, and the combined extracts, containing ethyl α-ethoxalyl-β-*p*-methoxyphenylpropionate, were treated with an excess of moist aluminium amalgam (from 8 g. of aluminium). On isolation the resulting *ethyl β-hydroxy-α-p-methoxybenzylsuccinate* was obtained as

a colourless oil (28 g.), b. p. 75—77°/0·1 mm. (Found: C, 62·2; H, 7·3. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%). Hydrolysis of this ester (6 g.) with boiling 10% aqueous potassium hydroxide (35 ml.) gave the mixture of acids as a syrup which crystallised in contact with ethyl acetate–light petroleum (b. p. 60—80°), having m. p. *ca.* 130° (4·5 g.). Fractional crystallisation of this solid from the same solvent ultimately gave *racemate* (A) in colourless leaflets, m. p. 136—137° (Found: C, 56·8; H, 5·4. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%), and *racemate* (B) in rhombic prisms, m. p. 125—126° (Found: C, 56·9; H, 5·7%).

p-*Methoxybenzylidenesuccinic Acid.*—(*a*) A solution of the foregoing mixture of racemic acids (A) and (B) (2·3 g.) in acetic anhydride (15 ml.) was boiled for 3 hr. and concentrated in a vacuum to 5 ml. On cooling, this gave a quantitative yield of p-*methoxybenzylidenesuccinic anhydride* which separated from ethyl acetate in irregular prisms, m. p. 160° (Found: C, 66·1; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). This compound is insoluble in aqueous sodium hydrogen carbonate and readily decolorised aqueous potassium permanganate. On being boiled with water it gave *p*-methoxybenzylidenesuccinic acid, m. p. and mixed m. p. 194—195° (decomp.).

(*b*) A mixture of anisaldehyde (8·25 g.), ethyl succinate (10·5 g.), and alcoholic sodium ethoxide (from 7 g. of sodium and 70 ml. of alcohol) was boiled for 3 hr., the greater part of the alcohol was evaporated in a vacuum and replaced by an equal volume of water, and the solution concentrated to *ca.* 35 ml. Acidification with hydrochloric acid then gave p-*methoxybenzylidenesuccinic acid* which was purified by means of aqueous sodium carbonate and crystallised from acetic acid, forming colourless needles (8 g.), m. p. 194—195° (decomp.), readily soluble in alcohol or ethyl acetate and moderately soluble in chloroform, hot water, or benzene (Found: C, 61·3; H, 5·3%; equiv., 117·7. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%; equiv., 118). With boiling acetic anhydride this acid (10 g.) gave the anhydride (8·2 g.), m. p. 160°, which by the boiling methanol–sulphuric acid method (6 hr.) furnished *methyl* p-*methoxybenzylidenesuccinate* as a viscous oil, b. p. 165°/0·5 mm. (70%) (Found: C, 63·5; H, 7·8. $C_{14}H_{16}O_5$ requires C, 63·6; H, 7·6%).

p-*Methoxybenzylsuccinic Acid.*—(*a*) Hydrogenation of the foregoing benzylidenesuccinic acid (4·7 g.) in methanol (150 ml.) with hydrogen and a palladium catalyst (from 0·2 g. of palladium chloride and 1 g. of charcoal) gave p-*methoxybenzylsuccinic acid* as a viscous oil which crystallised from benzene in rosettes of needles (4 g.), m. p. 98—101° (Found: 60·3; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). By the same procedure methyl *p*-methoxybenzylidenesuccinate gave *methyl* p-*methoxybenzylsuccinate* as a colourless oil, b. p. 156°/1 mm., which slowly solidified, m. p. 35—37° (Found: C, 63·2; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). On hydrolysis this ester regenerated the acid, m. p. and mixed m. p. 98—101°. Distillation of *p*-methoxybenzylsuccinic acid (3·5 g.) at 180°/0·5 mm. gave the *anhydride* which separated from ethyl acetate–light petroleum (b. p. 60—80°) in needles (2·3 g.), m. p. 91—92°, readily soluble in acetone or benzene (Found: C, 65·3; H, 5·3. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

(*b*) *p*-Methoxybenzyl alcohol (1·9 g.) (Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905) was converted into *p*-methoxybenzyl chloride with phosphorus trichloride (2·5 g.) in ether (30 ml.); this was obtained as an unstable oil (5·2 g.), b. p. 125—127°/25 mm. Interaction of this chloride (20 g.) with ethyl sodiomalonate (from 20 g. of ester and 2·9 g. of sodium) in alcohol (60 ml.) at room temperature and then on the steam-bath for 4 hr. gave *ethyl* p-*methoxybenzylmalonate* (18 g.), b. p. 145°/0·5 mm. (Found: C, 64·5; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1%). A mixture of this ester (28 g.), sodium (2·3 g.), and alcohol (60 ml.) was heated under reflux for 2 hr., cooled, treated dropwise with ethyl bromoacetate (16·7 g.) during ½ hr., and then boiled for 2 hr. On isolation the resulting *ethyl* α-*ethoxycarbonyl*-α-p-*methoxybenzylsuccinate* was obtained as a colourless viscous liquid (23 g.), b. p. 166—169°/0·2 mm. (Found: 62·5; H, 7·3. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·1%). This succinate (12·3 g.) was heated with a solution of potassium hydroxide (14 g.) in 50% alcohol (75 ml.) on the steam-bath until a homogeneous solution was formed; this was then kept for 24 hr. and acidified. Isolated with ether, α-*carboxy*-α-p-*methoxybenzylsuccinic acid* was digested with hot benzene (80 ml.) and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), forming elongated rectangular prisms (7·5 g.), m. p. 157—159° (decomp.) (Found: C, 55·4; H, 5·0. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). When this was heated at 160°/25 mm. for 15 min. and the residue crystallised from hot water, this acid (2 g.) gave *p*-methoxybenzylsuccinic acid, m. p. and mixed m. p. 98—100°.

A stirred mixture of *N*-bromosuccinimide (3·6 g.), *p*-methoxybenzylsuccinic anhydride (2·2 g.), carbon tetrachloride (40 ml.), and benzoyl peroxide (0·02 g.) was heated under reflux for 12 hr.; the solution became red and after 1—2 hr. hydrogen bromide was evolved. The filtered mixture was evaporated and the reddish-brown residue extracted with ethyl acetate,

giving *p*-methoxybenzylidenesuccinic anhydride, m. p. and mixed m. p. 159—160°. The same product was formed with carbon disulphide as the solvent.

p-*Methoxybenzylmaleic Acid.*—*p*-Methoxybenzylidenesuccinic anhydride (45 g.) was heated in a Pyrex tube (oil-bath at 180°) until completely molten and then rapidly poured on to a cold sheet of glass. The solid was immediately pulverised and heated with carbon disulphide (100 ml.) under reflux for 20 min., collected, and washed with more solvent (100 ml.). After having been freed from traces of carbon disulphide the unchanged acid was remelted and the process repeated. Evaporation of the combined carbon disulphide extracts from 22 experiments (equivalent to 891 g. of the benzylidenesuccinic anhydride) left an orange semi-solid which was extracted with a little ether, leaving a trace of the benzylidenesuccinic anhydride. The residue left on evaporation of the ether was extracted with light petroleum (b. p. 40—60°) and, on cooling, the solution deposited p-*methoxybenzylmaleic anhydride*, m. p. 64—65°, which, on recrystallisation from chloroform–light petroleum (b. p. 60—80°), formed almost colourless prisms, m. p. 65—66° (yield 1·85 g. from 22 experiments) (Found: C, 66·2; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). This compound is readily soluble in alcohol, benzene, or chloroform. On being melted, it reverts almost completely to *p*-methoxybenzylidenesuccinic anhydride, m. p. 160°.

p-Methoxybenzylmaleic anhydride (0·5 g.) was heated with water (30 ml.) (shake) at 55—60° for 2 hr. and the solution filtered to remove a trace of solid and evaporated in a vacuum. The residue was washed with a little chloroform to recover unchanged anhydride and recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving p-*methoxybenzylmaleic acid* in colourless rhombic plates (0·4 g.), m. p. 120° with sintering at 117°, readily soluble in alcohol, benzene, or acetone (Found: C, 61·2; H, 5·2. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%).

p-*Methoxybenzyltartaric Acid.*—Pyridine (0·5 ml.) and osmium tetroxide (0·5 g.) were added to a solution of *p*-methoxybenzylmaleic acid (0·47 g.) in ether (10 ml.), and the mixture kept in a closed vessel for 3 days. The light brown precipitate (1·2 g.) was collected, washed with ether, and treated with 7% aqueous potassium hydroxide (10 ml.), forming a deep purple solution. This was extracted with ether to remove pyridine, acidified, and evaporated in a vacuum at room temperature. The residue was extracted with ether in a Soxhlet apparatus for 9 hr. and the extract evaporated, leaving p-*methoxybenzyltartaric acid*, which separated from ethyl acetate in colourless prisms (0·2 g.), m. p. 205—207° (decomp.) (Found: C, 53·1; H, 5·1. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·2%).

Brucine (197 mg.) was added to a hot solution of *p*-methoxybenzyltartaric acid (67·5 mg.) in water (5 ml.), and the mixture decanted from a trace of solid and concentrated in a vacuum over phosphoric oxide at room temperature to *ca.* 3 ml. The brucine salt, which had separated in rectangular prisms (48 mg.), was collected, washed with a little water, and dried; it had $[\alpha]_D^{23\cdot5}$ −14·39° ± 0·6° (*c*, 2·96 in 50% alcohol). This salt (40 mg.) was decomposed with 10% aqueous sodium carbonate, the solution was filtered to remove the precipitate of brucine (wash with water), the filtrate and washing were evaporated in a vacuum at room temperature, and the residue was continuously extracted with chloroform to remove traces of brucine. The solid was then decomposed with hydrochloric acid, the mixture evaporated in a vacuum at room temperature, and the residue extracted with ether, giving *p-O*-methylpiscidic acid, $[\alpha]_D^{23}$ +44·01° ± 5·0° (*c*, 1·262 in H_2O), m. p. 169—170°, undepressed on admixture with a natural specimen. Mixed with the racemic acid, m. p. 205—207°, it melted at 173—176°.

Derivatives of Piscidic Acid.—The monomethyl ester had $[\alpha]_D^{23}$ +41·52° (*c*, 1·325 in H_2O), the monoethyl ester $[\alpha]_D^{17\cdot5}$ +59·70° (*c*, 1·551 in EtOH), the dimethyl ester $[\alpha]_D^{19}$ +23·71° (*c*, 6·367 in EtOH), methyl *p-O*-methylpiscidate $[\alpha]_D^{18°}$ +78·16° (*c*, 1·54 in EtOH), and methyl *p-O*-benzylpiscidate $[\alpha]_D^{19}$ +48·73° (*c*, 1·786 in EtOH) (Part I, *loc. cit.*).

Hydrolysis of methyl *p-O*-methylpiscidate (1 g.) with 10% aqueous potassium hydroxide (10 ml.) on the steam-bath for 5 hr. gave p-O-*methylpiscidic acid* which separated from ethyl acetate–light petroleum (b. p. 60—80°) in elongated rectangular prisms, m. p. 169—170, $[\alpha]_D^{22\cdot5}$ +41·97° (*c*, 1·129 in H_2O) (Found: C, 53·4; H, 5·2%; equiv., 136·7. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·2%; equiv., 135). Cinchonine (294 mg.) was added to a hot solution of this acid (135 mg.) in alcohol (3 ml.), and the solution decanted from a little solid and diluted with water (7 ml.). The *cinchonine* salt was collected several days later and recrystallised from dilute alcohol, forming rectangular prisms, $[\alpha]_D^{17}$ +139·6° (*c*, 6·1 in EtOH) (Found: N, 6·8. $C_{50}H_{58}O_9N_4$ requires N, 6·5%). Similarly prepared, the *brucine* salt separated from hot water in rectangular prisms, $[\alpha]_D^{24}$ −13·03° (*c*, 2·131 in 50% alcohol) (Found: N, 5·4. $C_{58}H_{66}O_{15}N_4$ requires N, 5·3%).

Cinchonine piscidate separated from dilute alcohol in clusters of needles, $[\alpha]_D^{21}$ +146·2° (*c*,

0·424 in EtOH) [Found: N, 6·9. $C_{11}H_{12}O_7,(C_{19}H_{22}N_2O)_2$ requires N, 6·6%], and the (+)-N-*methylphenyliso*propylamine salt in elongated hexagonal prisms, m. p. 179°, $[\alpha]_D^{24}$ +12·73° (*c*, 2·09 in H_2O) (Found: N, 3·7. $C_{11}H_{12}O_7,C_{10}H_{15}N$ requires N, 3·8%).

p-*Methoxyphenyl-lactic Acid*.—Reduction of *p*-methoxyphenylpyruvic acid (5 g.) in 5% aqueous sodium hydroxide (50 ml.) with 2% sodium amalgam (150 g.) gave p-*methoxyphenyl-lactic acid*, forming elongated rectangular prisms (3·5 g.), m. p. 88°, from ethyl acetate–light petroleum (b. p. 60—80°), soluble in alcohol or acetone and insoluble in chloroform or benzene (Found: C, 61·0; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·22; H, 6·1%). Prepared by hot methanolic sulphuric acid, the *methyl* ester was a colourless oil, b. p. 135°/0·1 mm. (Found: C, 62·7; H, 6·8. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

Methylation of this methyl ester (3·9 g.) in an excess of boiling methyl iodide for 7 hr. gave the *methyl ether* of methyl *p*-methoxyphenyl-lactate as a colourless oil (3·7 g.), b. p. 120°/0·5 mm. [Found: OMe, 40·7. $C_9H_7O(OMe)_3$ requires OMe, 41·5%]. This compound did not appear to condense readily and attempts to synthesise an *O*-dimethyl ether of piscidic acid by way of the oxalo-derivative were abandoned.

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