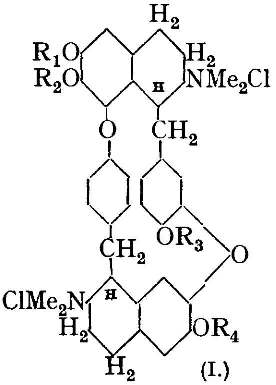
254. *Curare Alkaloids. Part IV. Bebeerine and Tubocurarine. Orientation of Phenolic Groups.*

By Harold King.

The object of this investigation was the determination of the relative position of methoxy- and hydroxy-groups in bebeerine. This has been achieved by ethylating the two free phenolic groups and degrading the *O*-ethylbebeerine so obtained by a two-stage Hofmann process to two isomeric tricarboxymethoxyethoxydiphenyl ethers. Both of these have been synthesised as well as a dimethoxy-acid corresponding to one of them. The constitution of bebeerine has therefore been completely determined and the methods used are applicable to the related substance tubocurarine.

Tubocurarine chloride, the active principle of tube-curare, and the methochloride of bebeerine, a prominent alkaloid of *Radix Pareiræ bravæ*, are diastereoisomeric bisbenzyl*iso*quinoline alkaloids to which the constitution (I) has been attributed (King, J., 1936, 1276), where two of the groups R are methyl and two are hydrogen. Both alkaloids thus contain two phenolic groups and two methoxy-groups, but the exact relative orientation of these is unknown except that a catechol arrangement of phenolic groups is excluded. A study of the Millon reaction, however, (King, J., 1937, 1481) had suggested that one phenolic group in both alkaloids was present in the position of OR_3 (I).



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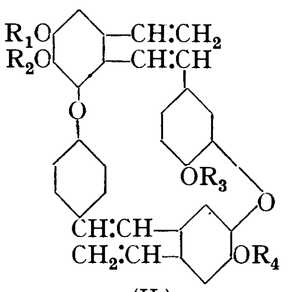

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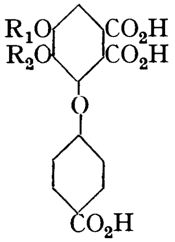

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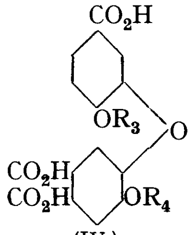
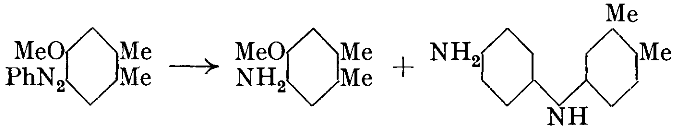


(IV.)

In this present work the device of ethylating the free phenolic groups used effectively by Späth for marking the position of phenolic groups in simpler *iso*quinolines has been utilised. The sodium salt of bebeerine was ethylated with ethyl iodide to give amorphous *O*-ethylbebeerine, which in turn was converted into the quaternary methiodide and methochloride, both of which were also amorphous. *O*-Ethylbebeerine methochloride was then subjected to a two-stage Hofmann degradation and gave finally crystalline *O-ethylbebeerilene* (II). When this neutral substance was oxidised first in acetone solution and then in aqueous medium with potassium permanganate, it furnished a mixture of two acids, each with a formula $C_{18}H_{16}O_9$ (III and IV), and each containing therefore one methoxy- and one ethoxy-group. Since decarboxylation of an acid such as (IV) would give a 2-methoxy-2′-ethoxydiphenyl ether which would not be diagnostic of the positions of the ethoxy- and methoxy-groups in the parent acid (IV), it was necessary to synthesise this acid. It was decided to rely on the validity of the deductions made from the Millon reaction mentioned above and synthesise the acid in which OR_3 was OEt and OR_4 was OMe. The intermediates for this synthesis were not very accessible substances, but eventually a practical method of approach was found.

When *o*-4-xylenol was coupled in alkaline solution with diazotised aniline, it gave a mixture of two isomeric azo-compounds, of which 2-hydroxy-4 : 5-dimethylazobenzene was the major constituent. Following a method used by Grewe (*Ber.*, 1938, **71**, 911), this was methylated, giving (V), which was reduced by sodium hyposulphite. Aniline and 2-methoxy-4 : 5-dimethylaniline (VI) were obtained, but the low yield of the latter precluded use of this route to the required substituted phthalic acid. The cause of the low yield was traced to the formation of a substance which is in all probability *4'-amino-3 : 4-dimethyldiphenylamine* (VII), a semidine transformation having occurred with loss of a methoxy-group. The other alternative, also used by Grewe, for obtaining 4-methoxyphthalic acid was eventually adopted, namely, methylation of *o*-4-xylenol and oxidation of the methyl ether to 4-methoxyphthalic acid. This was nitrated by the method of Cain and Simonsen (J., 1914, **105**, 163) as modified by Grewe and the two isomeric nitro-compounds were separated by esterification as recommended by these authors. A quantity of methyl 5-nitro-4-methoxyphthalate (VIII) was accumulated in this way and then reduced catalytically with palladised charcoal as catalyst to *methyl 5-amino-4-methoxyphthalate*, a by-product being the corresponding *azoxy*-compound. The amino-group was readily replaced by iodine, giving *methyl 5-iodo-4-methoxyphthalate* (IX) in good yield. When this was condensed with the potassium derivative of methyl *iso*vanillate (X) in presence of copper powder, a mixture of three acids was obtained. These were identified as veratric acid, 4-methoxyphthalic acid, and 4 : 5 : 5'-tricarboxy-2 : 2'-dimethoxydiphenyl ether (XI). The last-named acid was identical with an acid obtained by the degradation and oxidation of *O*-methylbebeerine (King, J., **1936**, 1276). The synthesis of this acid completed the proof of the constitution of *O*-methylbebeerine as distinct from *O*-ethylbebeerine, since the acid (III, $R_1 = R_2 = $ Me) had already been synthesised by Faltis and Frauendorfer (*Ber.*, 1930, **63**, 811). The formation of veratric acid is noteworthy and the reaction by which it arises has been studied (this vol., p. 1168).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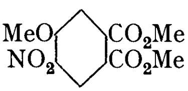
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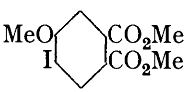
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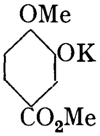
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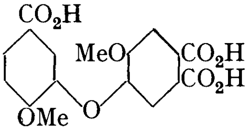
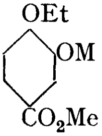

(XI.)

A similar method of condensation was now applied, *methyl 3-hydroxy-4-ethoxybenzoate* (XII, M = H) being used instead of methyl *iso*vanillate. *3-Hydroxy-4-ethoxybenzoic acid* was prepared by oxidising ethyl *iso*eugenol in aqueous acetone with potassium permanganate to *O*-ethylvanillic acid (XIII) and demethylating this by boiling hydrobromic acid (*d* 1·3); some protocatechuic acid also was formed. Incidentally a simple method is described for preparing protocatechuic acid in very good yield by demethylating vanillic acid.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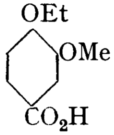
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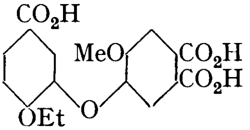
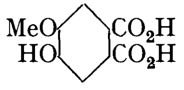

(XIV.)

When the potassium derivative of methyl 3-hydroxy-4-ethoxybenzoate (XII, M = K) was condensed with methyl 5-iodo-4-methoxyphthalate (IX) in presence of copper powder, a mixture of four acids was obtained. These were identified as 3-methoxy-4-ethoxybenzoic acid, 4-methoxyphthalic acid, *m*-hemipinic acid, and 4 : 5 : 5'-tricarboxy-2-methoxy-2'-ethoxydiphenyl ether (XIV). This acid proved to be identical with one of the acids obtained in the degradation and oxidation of *O*-ethylbebeerine. This synthesis fixes the position of one phenolic group at OR_3 in (I) and incidentally lends support to the reliability of the deductions made from the Millon reaction.

The constitution of the remaining isomeric acid (III) obtained in the degradation of

O-ethylbebeerine could have been settled in a simple manner by decarboxylation, since the isomeric methoxyethoxydiphenyl ethers were synthesised for this purpose (following paper). Unfortunately, with the amount of natural acid available, decarboxylation did not proceed smoothly and attention was therefore turned to synthesis. The preparation of the required acid was facilitated by making use of methyl 5-iodo-4-methoxyphthalate (IX) which had been used in the above described syntheses.

When this ester was boiled with 50% sodium hydroxide solution, the parent acid was recovered unchanged, but if a little copper powder was added, the iodine was quantitatively removed by brief boiling with 20% sodium hydroxide solution, giving *O*-methylnor-*m*-hemipinic acid (XV) in good yield. This was brominated by a modification of a method described by Faltis and Frauendorfer (*Ber.*, 1930, **63**, 811) to give 3-bromo-4-hydroxy-5-methoxyphthalic acid (XVI). The *dimethyl* ester of this acid was readily ethylated by diazoethane to yield *methyl* 3-*bromo*-5-*methoxy*-4-*ethoxyphthalate* (XVII). When this ester was condensed in the usual manner with the potassium derivative of methyl *p*-hydroxybenzoate, it gave a mixture of acids from which anisic acid, 4-methoxy-5-ethoxyphthalic acid, and 5 : 6 : 4′-tricarboxy-3-methoxy-2-ethoxydiphenyl ether (XVIII) were isolated. The last-named acid proved to be identical in all respects with one of the two acids obtained by degradation of *O*-ethylbebeerine.



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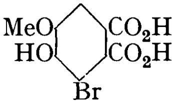

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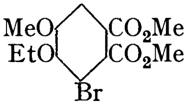

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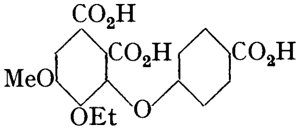
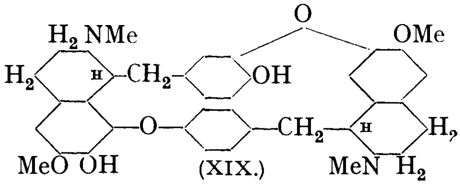


(XVIII.)

These syntheses therefore fix the positions of the phenolic groups in bebeerine and its structure must be represented by (XIX), both of the phenolic groups being in one of the component benzyl*iso*quinoline structures. Tubocurarine chloride, on the basis of the Millon reaction, has one phenolic group on the central benzene ring as in bebeerine, but the position of the other cannot be ascertained without access to more material. A position for the second phenolic group similar to that occupied by the second phenolic group in bebeerine is not excluded on the evidence at present available.



(XIX.)

EXPERIMENTAL.

O-Ethylbebeerine.—Bebeerine base (18 g.), purified by crystallisation of the hydrochloride to constant rotation, when dissolved in hot absolute ethyl alcohol (75 c.c.) readily crystallised. Sodium (1·5 g.) in absolute alcohol (100 c.c.) was added, and the mixture heated until the sodium salt almost completely dissolved. Ethyl iodide (7·5 c.c.) was then added, and the solution boiled for 3 hours. The alcohol was removed, and the residue treated with 2N-sodium hydroxide and chloroform. The combined chloroform extracts were washed with alkali to remove phenolic fractions and evaporated, the last trace of solvent being removed by addition of methyl alcohol and re-evaporation (yield, about 28·2 g.). Examination of the phenolic fraction showed that ethylation was almost complete.

O-Ethylbebeerine Methiodide.—The *O*-ethyl base in methyl alcohol (30 c.c.) was boiled with methyl iodide (15 c.c.) for 7 hours. On removal of the solvents the methiodide was left as a gum which could not be crystallised. It was sparingly soluble in hot water and separated in circular isotropic globules. The hot aqueous solution was treated with excess of silver chloride, and *O*-ethylbebeerine methochloride obtained as a syrup which showed no signs of crystallisation.

Hofmann Degradation.—The syrupy methochloride was boiled with 20% sodium hydroxide solution (220 c.c.) for 100 minutes. The methine or mixture of methines (21·1 g.) was completely soluble in chloroform and on removal of the solvent was remethylated by boiling in methyl alcohol (20 c.c.) with methyl iodide (10 c.c.) for 4 hours. The product crystallised readily in plates when cold, but was not further characterised. The solvents were removed and the residue, suspended in a large volume of hot water, in which it was sparingly soluble, was digested with freshly precipitated silver chloride (from 15 g. of silver nitrate). The methine methochloride so obtained was readily soluble in water and its aqueous solution (220 c.c.) was boiled with sodium hydroxide (40 g.) for 100 minutes. Trimethylamine was evolved and was collected in 3N-hydrochloric acid and characterised. The crude *O-ethylbebeerilene*, which had separated as a gum, was completely soluble in chloroform and on removal of this solvent crystallised readily on addition of a little glacial acetic acid (yield, about 20 g.). For analysis a portion (0·1 g.) was crystallised from glacial acetic acid, from which it separated in elongated plates, m. p. 168—169° (Found: C, 76·9; H, 6·2. $C_{38}H_{36}O_6$ requires C, 77·5; H, 6·2%). With sulphuric acid it gave an immediate cherry-red colour.

Permanganate Oxidation.—The crude *O*-ethylbebeerilene, dissolved in stabilised acetone (1 l.), was oxidised by additon of finely powdered potassium permanganate (37·5 g.) to the vigorously stirred solution. The hot water extracts of the filtered manganese oxides and of the small residue from the evaporated acetone were combined, concentrated to 450 c.c., and treated on the boiling water-bath with aqueous 5% permanganate until there was a marked retardation in the rate of decoloration of the permanganate. The amount of the latter consumed in aqueous solution was 84·5 g. The filtered aqueous solution and the hot water extracts of the oxides of manganese were concentrated to a small volume and acidified. The precipitate, partly crystalline, amounted to 5·6 g. (A) and ether-extraction of the mother-liquor gave a further 1·0 g. The solid (A), when extracted (Soxhlet) with ether for several days, left 1·3 g. of hydroxy-acids unextracted. The total ether-soluble material, which was partly crystalline, was titrated (phenolphthalein) and consumed 32 c.c. of N-sodium hydroxide. On this basis the neutral solution was transferred to a separator and fractionally acidified with eleven portions of N-hydrochloric acid, each 3 c.c., and extracted once with ether after each addition of acid. Each fraction after removal of the ether was warmed with water (5 c.c.) and kept. Fractions 1—3 showed no signs of crystallisation, whereas fractions 4—11 all deposited crystals, usually of two kinds, tablets and a microcrystalline powder. The tablets were the less acidic and preponderated in the earlier fractions; the microcrystalline powder represented a more acidic constituent and tended to accumulate in the later fractions. By careful fractional crystallisation there were eventually obtained 1·86 g. of well-formed plates, which were soluble in 55 c.c. of boiling water and had m. p. 197° (efferv.) (Found: loss at 100°, 4·5. $C_{18}H_{16}O_9,H_2O$ requires H_2O, 4·6%. Found for dried material: C, 57·8, 57·6; H, 4·4, 4·5. $C_{18}H_{16}O_9$ requires C, 57·4; H, 4·3%), and 0·83 g. of a microcrystalline powder. The latter was dissolved in 135 c.c. of boiling water and separated in clusters of microscopic needles, m. p. 255° (Found: loss at 100°, 1·7. $C_{18}H_{16}O_9,\frac{1}{2}H_2O$ requires H_2O, 2·3%. Found for dried material: C, 57·8, 57·8; H, 4·3, 4·4 $C_{18}H_{16}O_9$ requires C, 57·4; H, 4·3%). An attempt to decarboxylate the former acid by boiling with quinoline and copper was not successful.

Action of Diazotised Aniline on o-*4-Xylenol.*—*o*-4-Xylenol (12·2 g.) in water (1000 c.c.) containing sodium hydroxide (10 g.) was stirred vigorously and treated with a diazo-solution prepared from aniline (9·3 g.) in 3N-hydrochloric acid (83·3 c.c.) and sodium nitrite (7·6 g.) in water (38 c.c.) at 5—10°. The temperature of the main solution was kept down by addition of ice. The red azo-compound readily separated in almost quantitative yield (21·7 g.). On crystallisation from boiling alcohol 2-hydroxy-4 : 5-dimethylazobenzene (14·5 g.) separated. The mother-liquors on concentration gave mainly the isomeric 6-hydroxy-2 : 3-dimethylazobenzene, which crystallised in needles, m. p. 70°, unchanged by repeated crystallisation from alcohol: from acetic anhydride, however, it crystallised in well-formed tablets, m. p. 69—70° (Found: C, 74·4; H, 6·2; N, 12·8. Calc.: C, 74·3; H, 6·2; N, 12·4%). Diepolder (*Ber.*, 1909, **42**, 2919) describes this substance as the 3-phenylhydrazone of 1 : 2-dimethyl-3 : 4-benzoquinone, but records no m. p.

Reductive Fission of 2-Methoxy-4 : 5-dimethylazobenzene (VI).—The corresponding phenol was methylated as described by Grewe (*loc. cit.*). The methoxy-compound (10 g.) in boiling absolute alcohol (100 c.c.) was treated with a freshly prepared solution of the highest quality sodium hyposulphite (20 g.) in water (100 c.c.) during 15 minutes. The alcohol was distilled off, and the colourless solution extracted with ether. On removal of the solvent the residual oil was fractionally distilled, first at 15 mm., aniline (1·5 g.), b. p. below 100°, and 2-methoxy-4 : 5-dimethylaniline (1·5 g.), b. p. 130—150°, being readily separated, and then at 1 mm., a rapidly solidifying oil (1·5 g.) coming over at 170°. On two crystallisations from alcohol this base, *4'-amino-3 : 4-dimethyldiphenylamine* (VII), separated in needles, m. p. 114—115° (Found: C, 79·4; H, 7·6; N, 13·2. $C_{14}H_{16}N_2$ requires C, 79·2; H, 7·6; N, 13·2%). In agreement with the analytical figures it contained no methoxy-group. With excess of hydrochloric acid it formed a *monohydrochloride*, fine needles of a grey-blue colour, m. p. 205° (Found: C, 67·7;

H, 7·0; N, 11·6. $C_{14}H_{16}N_2$,HCl requires C, 67·6; H, 6·9; N, 11·3%). Like other members of its class, this *N*-substituted *p*-phenylenediamine is instantaneously oxidised in aqueous solution by sodium nitrite, ferric chloride, iodine or bromine water with production of an intense crimson colour.

O-*Ethyl*iso*eugenol.*—*iso*Eugenol (16·4 g.) in 2N-sodium hydroxide (50 c.c.) was heated to 90° and vigorously stirred, ethyl sulphate (15·4 g.) and 2N-sodium hydroxide (50 c.c.) run in simultaneously during 20 minutes, and stirring continued for 30 minutes. When cold, the *O*-ethyl*iso*eugenol was collected by ether extraction; yield, 16·8 g. (compare Puxeddu, *Gazzetta*, 1909, **39**, i, 134).

O-*Ethylvanillic Acid.*—*O*-Ethyl*iso*eugenol (9·6 g.) was suspended in a stirred mixture of acetone (100 c.c.) and water (100 c.c.) and 3% aqueous potassium permanganate run in fairly quickly, about ½ hour being required for the first 880 c.c., and then more slowly until a pink colour was obtained which remained for 10 minutes. The solution was filtered, and the manganese oxides extracted twice with 0·5N-potassium hydroxide (225 c.c. each time) on the water-bath. The combined filtrates were concentrated to 250 c.c. and acidified; yield 7·6 g., m. p. 194—195°.

3-*Hydroxy*-4-*ethoxybenzoic Acid.*—*O*-Ethylvanillic acid (40 g.) and hydrobromic acid (200 c.c.; *d* 1·3) were boiled under reflux for 27 hours. Water (100 c.c.) was added, the solid (27·8 g.) collected, and the mother-liquor extracted with ether, which gave crude protocatechuic acid (6·3 g.). The solid was extracted (Soxhlet) for 16 hours with benzene, which removed crude parent unhydrolysed acid (2·6 g.). The residue in the bag was then warmed with 10 volumes of water to 50° to remove protocatechuic acid (5·7 g.). The solid left undissolved was 3-*hydroxy*-4-*ethoxybenzoic acid* (7·2 g.), which crystallised from about 8 volumes of boiling alcohol in clusters of broad leaflets, m. p. 218—219° (Found : C, 59·6, 59·6; H, 5·4, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The **methyl** ester was prepared by saturating a suspension of the acid (15·8 g.) in dry methyl alcohol (79 c.c.) with hydrogen chloride at 0° and boiling the resulting solution for 3 hours. On removal of the solvent, dilution with water at 0°, and addition of solid potassium carbonate the ester (16·3 g.) separated as a granular solid, sparingly soluble in ether. For analysis it was recrystallised from 3 volumes of boiling ethyl alcohol and separated in large compact crystals, m. p. 127—128° (Found : C, 61·5; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

Methyl iso*Vanillate.*—*iso*Vanillic acid (12·3 g.) (Perkin and Stoyle, J., 1923, **123**, 3175) was esterified by saturating a solution in dry methyl alcohol (62 c.c.) with hydrogen chloride at 0° and then boiling it for 5½ hours. The solvent was removed, the residue made alkaline with potassium carbonate, and the ester extracted with ether, yield 11·6 g., m. p. 64—65°. The alkaline mother-liquor on acidification gave unchanged *iso*vanillic acid (1·1 g.). Methyl *iso*vanillate crystallised from low-boiling petroleum (130 vols.) or other solvents in short rods, m. p. 67° (Found : C, 59·5, 59·4; H, 5·5, 5·6. Calc. : C, 59·3; H, 5·5%). Santos (Dissert., Munster i. W., 1929) gives m. p. 83—84°. A mixed m. p. of our methyl *iso*vanillate with methyl vanillate, m. p. 64°, was depressed to 40°. Späth and Pikl (*Ber.*, 1929, **62**, 2259) used the ester in synthetic work but give no record of its properties.

Protocatechuic Acid.—Vanillic acid (20 g.) was boiled under reflux for 16 hours with hydrobromic acid (100 c.c.; *d* 1·3). Protocatechuic acid separated in long needles (15·4 g.), m. p. 202°. The mother-liquor on dilution and extraction with ether gave a further 2·6 g., m. p. 195°. The acid so obtained is often coloured, but it may be obtained almost colourless by dissolving it in 10 parts of water at 50° (charcoal) and concentrating the filtered solution under reduced pressure.

o-4-*Xylyl Methyl Ether.*—*o*-4-Xylenol (11·2 g.) in 2N-sodium hydroxide (50 c.c.) was heated to 90° and into the vigorously stirred solution methyl sulphate (19 c.c.) and 2N-sodium hydroxide (50 c.c.) were run simultaneously. The cooled solution was extracted with ether, and the ethereal residue distilled; yield 11·4 g., b. p. 96—97°/17 mm. (compare Moschner, *Ber.*, 1900, **33**, 742).

4-*Methoxyphthalic Acid.*—This acid is readily obtained by a process based on that given by Grewe (*Ber.*, 1938, **71**, 910). *o*-4-Xylyl methyl ether (20 g.), suspended in sodium hydroxide solution (50 c.c.; 10%) in a 3-litre flask fitted with stirrer and condenser (the xylyl ether is readily volatile), was heated on the water-bath, and a solution of potassium permanganate (130 g.) in water (2000 c.c.) run in drop-wise during 5 hours. After a further 2 hours' heating, the solution was filtered, and the manganese oxides extracted once with 0·2N-sodium hydroxide (250 c.c.). The combined filtrates were acidified with concentrated hydrochloric acid (110 c.c.) and cooled and the 5-methoxy-*o*-toluic acid (2·4 g.) which separated was collected. The mother-liquor was evaporated under reduced pressure to 450 c.c. and kept at 0°; 4-methoxyphthalic acid (23·3 g.) then separated, sufficiently pure for the subsequent nitration process.

Nitration of 4-Methoxyphthalic Acid.—This was carried out by Grewe's modification (*loc. cit.*) of Cain and Simonsen's process (J., 1914, **105**, 162). The methoxyphthalic acid (10 g.) was heated on the water-bath for 2 hours with nitric acid (30 c.c.; *d* 1·4), and finally boiled for 10 minutes. The solution was diluted and extracted four times with ether, and the extracts washed with small volumes of water and evaporated. The crystalline residue still contained nitric acid, which was removed in a high vacuum over sodium hydroxide powder. The mixed nitro-acids (about 10 g.) were dissolved in dry methyl alcohol (10 vols.), and the solution saturated with hydrogen chloride at 0° and finally boiled for 2 hours. After removal of the solvent, dilution with water, and addition of solid sodium bicarbonate the neutral crystalline ester was taken up in ether (400 c.c.). (With larger batches it is preferable to collect this ester by filtration.) The ether on evaporation gave methyl 5-nitro-4-methoxyphthalate (VIII) (5·1 g.), m. p. 114°. The acid ester (4·3 g.), m. p. 175°, liberated by acid from the alkaline solution, on crystallisation from water (100 c.c.) gave pure 2-*methyl* 1-*hydrogen* 3-*nitro*-4-*methoxyphthalate* in small flattened prisms, m. p. 186—187° (Found: C, 47·1, 47·1; H, 3·8, 3·8. $C_{10}H_9O_7N$ requires C, 47·1; H, 3·6%). On hydrolysis with 2N-alkali, this ester gave 3-nitro-4-methoxyphthalic acid, m. p. 223—224° (efferv.) after crystallisation from 1·6 parts of water. Cain and Simonsen (*loc. cit.*) give m. p. 215—217°.

Methyl 5-Amino-4-methoxyphthalate.—Methyl 5-nitro-4-methoxyphthalate (8·07 g.) in suspension in methyl alcohol (300 c.c.) was reduced with palladised charcoal (0·3 g.) as catalyst. The solution was then warmed, filtered, and concentrated and gave *methyl 5-amino-4-methoxyphthalate* (6·0 g.), which crystallised from 25 vols. of methyl alcohol in stout rods, m. p. 149° (Found: C, 55·6; H, 5·4. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·5%). In some experiments a sparingly soluble by-product was obtained and was freed from the amino-compound either by fractional crystallisation or by solution of the amino-compound in warm 3N-hydrochloric acid. The non-basic product, *methyl 5-azoxy-4-methoxyphthalate*, crystallised from methyl alcohol in small orange-coloured rods, m. p. 175—180° to a red liquid (Found: C, 53·8, 54·0; H, 4·5, 4·4. $C_{22}H_{22}O_{11}N_2$ requires C, 53·9; H, 4·6%).

Methyl 5-Iodo-4-methoxyphthalate (IX).—The foregoing amino-compound (2·4 g.) was treated with 3N-hydrochloric acid (10 c.c.) at 0°, and the suspension of crystals of the hydrochloride diazotised with 10% sodium nitrite solution (7·3 c.c.). To the clear solution, potassium iodide (8 g.) in water (10 c.c.) was slowly added; after evolution of nitrogen ceased, the resinous solid which had separated gradually crystallised, the process being accelerated by warming the suspension to 50°. The *methyl 5-iodo-4-methoxyphthalate* (3·5 g.) was crystallised from 10 vols. ot 80% alcohol, forming delicate elongated leaflets having a garnet-red colour in bulk, m. p. 111—112° (Found: C, 38·0, 38·0; H, 3·5, 3·2. $C_{11}H_{11}O_5I$ requires C, 37·7; H, 3·2%).

Condensation of Methyl 5-Iodo-4-methoxyphthalate and Methyl iso*Vanillate.*—Potassium (0·39 g.) was dissolved in dry methyl alcohol (25 c.c.), methyl *iso*vanillate (1·82 g.), the iodo-ester (3·5 g.), and copper powder (0·4 g.) added, and the methyl alcohol then removed under reduced pressure. The residue was heated in a paraffin bath from 145° to 195° in 3 hours. The product was dissolved in water–ether with addition of a little sodium bicarbonate to ensure alkalinity. The ether was separated, and the aqueous liquor again extracted with ether. The combined ethereal extracts were rapidly washed thrice with N-sodium hydroxide and then with water. After removal of the solvent, the syrupy residue (2·85 g.) was boiled with 10% methyl alcoholic potassium hydroxide (50 c.c.). After dilution with water the methyl alcohol was removed and the solution acidified, yielding veratric acid (1·13 g.), m. p. 178°, identified by analysis and by comparison with an authentic specimen. The mother-liquor was repeatedly extracted with ether and the oil (1·38 g.) obtained on removal of the solvent was titrated with N-sodium hydroxide and phenolphthalein; it required 11·7 c.c. Accordingly, the neutralised solution was fractionally acidified with ten successive portions, each 1·5 c.c., of N-hydrochloric acid and the successive crops of acid were taken up in ether (20 c.c. each time). On removal of the solvent ether, fractions 1—5 crystallised readily, giving crude veratric acid. Fractions 6—10 were syrups which gradually crystallised. They were individually much more soluble in water than fractions 1—5. Fractions 8—10, on keeping in water, each deposited a finely crystalline precipitate of needles. These (90 mg.) were collected and combined and crystallised from boiling water (5·5 c.c.); a microscopic crystalline powder separated. After a second crystallisation the acid separated in microscopic needles (55 mg.). It melted at 268°, and when mixed with one of the oxidation products obtained in the degradation of *O*-methylbebeerine to which the constitution 4 : 5 : 5′-tricarboxy-2 : 2′-dimethoxydiphenyl ether (XI) has been assinged (King, J., 1936, 1278) and which had m. p. 264°, it also melted at 264°. The solubilities of the two acids in water were identical, each requiring about 60 vols. of boiling water for solution (Found for the air-dried acid: C, 53·0; H, 4·5; loss at 100°, 4·4. Calc. for $C_{17}H_{14}O_9,H_2O$: C, 53·7;

H, 4·2; H_2O, 4·7%). The natural acid was previously described as occurring in two forms with 2 or 2½ molecules of water of crystallisation. Small samples of the natural and the synthetic acid were therefore crystallised under parallel conditions and kept for several days in contact with the mother-liquor and then collected and air-dried; both proved to be dihydrates (Found for the natural acid: C, 51·0; H, 4·6: for the synthetic acid: C, 51·2; H, 4·6. Calc. for $C_{17}H_{14}O_9,2H_2O$: C, 51·2; H, 4·6%). From the combined mother-liquors of fractions 8—10, 4-methoxyphthalic acid (0·16 g.) was isolated, m. p. 176° (efferv.), giving an anhydride, m. p. 93°. From the final mother-liquor a further 10 mg. of the tricarboxydimethoxydiphenyl ether separated as a fine powder.

When the experiment was repeated without the addition of copper powder, the only two products obtained were iodomethoxyphthalic acid and veratric acid.

Condensation of Methyl 5-*Iodo*-4-*methoxyphthalate and Methyl* 3-*Hydroxy*-4-*ethoxybenzoate.*—Potassium (0·39 g.) was allowed to react with pure methyl alcohol (25 c.c.), and the solution evaporated to dryness. The iodo-ester (3·5 g.), the ethoxy-ester (1·96 g.), and copper powder (0·4 g.) were then added and the temperature of the mixture was raised from 120° to 196° during 3·5 hours. The neutral ester fraction (2·59 g.), isolated as described in the previous condensation, was hydrolysed; the acid (1·01 g.) obtained on acidification in aqueous medium proved to be 3-methoxy-4-ethoxybenzoic acid. The acid (1·48 g.) extracted from the aqueous mother-liquors by ether was titrated with N-sodium hydroxide (11·2 c.c.) and then fractionated into eight portions of differing acidity as described above. Fractions 1—5 were each crystallised from alcohol and gave in every case 3-methoxy-4-ethoxybenzoic acid. Fractions 6—9 were each dissolved in a small volume of water and each on keeping deposited a micro-crystalline powder (total, 73 mg.). This required 170 parts of boiling water for solution and it then separated in microscopic filmy needles. It melted at 258—259° and a mixed m. p. with the natural acid from the oxidation of *O*-ethylbebeerine to which the constitution 4 : 5 : 5′-tricarboxy-2-methoxy-2′-ethoxydiphenyl ether (XIV) must be assigned, showed no depression. The solubility of both acids in boiling water was also the same (Found: C, 57·1, 57·2; H, 4·2, 4·3. Calc. for $C_{18}H_{16}O_9$: C, 57·4; H, 4·3%). The mother-liquors of fractions 7 and 8 both gave 4-methoxyphthalic acid (90 mg.), and the final mother-liquor of fraction 8 also gave *m*-hemipinic acid (28 mg.), m. p. 206° (efferv.), forming an anhydride, m. p. 175° (Found: C, 52·8; H, 4·4. Calc.: C, 53·1; H, 4·5%).

O-*Methylnor*-m-*hemipinic Acid* (XV).—Methyl 5-iodo-4-methoxyphthalate (10 g.) was boiled for 4 hours with water (100 c.c.) containing sodium hydroxide (20 g.) and with addition of copper bronze (1·0 g.). The filtered solution was acidified with concentrated hydrochloric acid and kept at 0°. *O*-Methylnor-*m*-hemipinic acid, m. p. 203° (efferv.), anhydride, m. p. 217°, separated in well-formed prisms; yield, 82% (Found: C, 50·7; H, 3·9. Calc.: C, 50·9; H, 3·8%). This acid does not give a Millon reaction.

3-*Bromo*-4-*hydroxy*-5-*methoxyphthalic Acid* (XVI).—This acid was prepared by an improved modification of the method of Faltis and Frauendorfer (*Ber.*, 1930, **63**, 806). Finely powdered *O*-methylnor-*m*-hemipinic acid (4·24 g.) and anhydrous sodium acetate (1·64 g.) were suspended in pure glacial acetic acid (47 c.c.) and heated to about 80°, the acid becoming converted into the sodium salt. The temperature was then allowed to fall to 37°, and bromine (1·07 c.c.; 1 mol.) in acetic acid (7 c.c.) run in slowly with vigorous stirring. The sodium salt gradually disappeared and the required crystalline bromo-acid and a little sodium bromide separated. The solution was kept at 0° to complete the separation. The acid was collected and washed with a little water; yield 4·4 g., m. p. 229° (efferv.). When recrystallised from 12 parts of boiling water, it separated in bold hydrated crystals which effloresced in the air, m. p. 233° (efferv.). The resolidified melt, probably the anhydride, melted at about 229°. Faltis and Frauendorfer give m. p. 230°. Further small quantities can be obtained from the acetic acid mother-liquor by evaporating it to dryness and crystallising the residue from water. This acid gives a strong typical Millon reaction.

Methyl 3-*Bromo*-4-*hydroxy*-5-*methoxyphthalate.*—A solution of the pure acid (11·9 g.) in dry methyl alcohol (60 c.c.) was saturated at 0° with hydrogen chloride and then boiled for 4 hours, a gentle stream of hydrogen chloride being passed through. After removal of most of the solvent the partly solid residue was shaken with ether and excess of sodium bicarbonate solution, and the sparingly soluble ester collected by filtration; yield, 5·6 g. The ethereal solution contained a further 3·3 g. The sodium bicarbonate solution gave on acidification partially esterified acid (3·4 g.); this was re-esterified and gave 2·9 g. of fully esterified acid and 0·4 g. of partially esterified acid. *Methyl* 3-*bromo*-4-*hydroxy*-5-*methoxyphthalate* crystallised from methyl alcohol, in which it was very soluble, in hexagonal plates, m. p. 153—154° (Found: C, 41·8; H, 3·6. $C_{11}H_{11}O_6Br$ requires C, 41·4; H, 3·5%).

Methyl 3-*Bromo*-5-*methoxy*-4-*ethoxyphthalate* (XVII).—Diazoethane, obtained by warming a mixture of nitrosoethylurethane (10 g.) in ether (350 c.c.), and methyl-alcoholic potassium hydroxide (20 c.c. of 25% solution), was distilled with ether into a suspension of the hydroxy-ester (3·19 g.) in methyl alcohol (20 c.c.). Nitrogen was evolved and the ester readily passed into solution. After 48 hours the solvent was removed, leaving the required *ethoxy*-compound (3·5 g.) in fine needles. These were an unstable form, for on recrystallisation from a little methyl alcohol the needles separated first and then became transformed into tablets, m. p. 83—84° (Found: C, 45·0; H, 4·4. $C_{13}H_{15}O_6Br$ requires C, 45·0; H, 4·4%). 3-*Bromo*-5-*methoxy*-4-*ethoxyphthalic acid*, obtained by saponification, crystallised from 60 parts of boiling water in rectangular plates, m. p. 206° (efferv.), forming an anhydride, m. p. 147° (Found: C, 41·4; H, 3·4. $C_{11}H_{11}O_6Br$ requires C, 41·4; H, 3·5%). This acid was also obtained by direct ethylation of 3-bromo-4-hydroxy-5-methoxyphthalic acid with ethyl sulphate and alkali at 90°. A by-product in the reaction was a monoethyl ester, probably 1-*ethyl* 2-*hydrogen* 3-*bromo*-5-*methoxy*-4-*ethoxyphthalate*, which was sparingly soluble in boiling water and crystallised in delicate needles, m. p. 131° (Found: C, 45·0; H, 4·4. $C_{12}H_{15}O_6Br$ requires C, 45·1; H, 4·6%).

Condensation of Methyl 3-*Bromo*-5-*methoxy*-4-*ethoxyphthalate with Methyl* 4-*Hydroxybenzoate*.—Potassium (0·39 g.) was dissolved in methyl alcohol (15 c.c.) and a finely powdered mixture of the substituted methyl phthalate (3·47 g.) and methyl hydroxybenzoate (1·52 g.) added, followed by copper powder (0·4 g.). The methyl alcohol was removed under diminished pressure with slight warming and the residue was heated (oil-bath) during 2 hours to, and maintained for 1½ hours at 190°. The product, which had an odour of anise, was taken up in a little water and a large volume of ether (250 c.c. in all). The latter was washed with N-sodium hydroxide and then with water and distilled, the yield of neutral esters being 3·5 g. This was completely hydrolysed with methyl-alcoholic potassium hydroxide, and the acids collected through ether after acidification. On titration (phenolphthalein), they consumed 21·5 c.c. of N-alkali. The solution was then fractionated by addition of eight portions, each of 3 c.c., of N-hydrochloric acid, followed each time by extraction with 20 c.c. of ether. Each extract was separately evaporated; the residue in almost every case crystallised, but showed different crystalline properties from fraction to fraction. The first fraction (0·37 g.), on repeated crystallisation from water and sublimation, gave anisic acid. A contaminant of this fraction formed the main constituent of the second and third fractions. It was a very sparingly soluble acid crystallising as a micro-crystalline powder and has not been examined in detail. Fraction 6 (0·8 g.) on one crystallisation from water (35 c.c.) gave 5 : 6 : 4′-tricarboxy-3-methoxy-2-ethoxydiphenyl ether (XVIII) as a monohydrate, m. p. 195° (efferv.). It showed no depression of m. p. with the acid obtained from the degradation of *O*-ethylbebeerine. The water of hydration is the same and the solubility in boiling water the same. When samples of each were crystallised from water under parallel conditions, both separated in a very characteristic crystalline form, stout plates or discs with pointed ends. An aqueous solution of each gave an immediate, yellow, amorphous precipitate with ferric chloride (Found: C, 54·6; H, 4·8. Calc. for $C_{18}H_{16}O_9,H_2O$: C, 54·8; H, 4·6%). Unlike most of the phthalic acids recorded in this paper, the melt obtained after a m. p. determination shows no signs of crystallisation as the anhydride. This property is common to the synthetic and the natural acid.

A further quantity of the same acid was isolated from fraction 7, which, however, contained another acid also present in the ethereal residue from fraction 8. During the extraction of fraction 8 to which excess of mineral acid had been added, a crystalline acid separated, which, being very sparingly soluble in ether, was collected by filtration; yield, 0·3 g. It was soluble in 10 c.c. of boiling water and crystallised in pointed leaflets, m. p. 192° (efferv.), forming an anhydride, m. p. 198°. This substance proved on analysis to be a *monohydrate* of 5-methoxy-4-ethoxyphthalic acid (Found: C, 50·7; H, 5·6; H_2O, 8·2. $C_{11}H_{12}O_6,H_2O$ requires C, 51·1; H, 5·5; H_2O, 7·0%). A portion of the acid was converted into the *N*-ethylimide. It had m. p. 205° in agreement with that recorded in the literature (Found: C, 62·6; H, 6·1. Calc.: C, 62·6; H, 6·1%). Späth and Duschinsky (*Ber.*, 1925, **58**, 1945) describe this acid as having m. p. 184°, anhydride 197°, but give no analysis. Bruchhausen and Saway (*Arch. Pharm.*, 1925, **263**, 605) record m. p. 184—185° when taken slowly and give an analysis corresponding to an anhydrous acid; for the *N*-ethylimide they also record m. p. 205°.

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