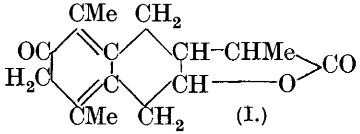
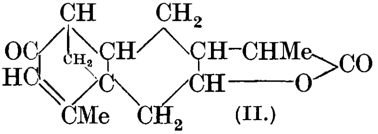
CCCX.—*The Constitution of Santonin. Part I. The Synthesis of* dl-*Santonous Acid.*

By GEORGE ROGER CLEMO, ROBERT DOWNS HAWORTH, and ERIC WALTON.

l-SANTONIN is a valuable anthelmintic which occurs to the extent of 2—3½% in the flower heads of *Artemisia maritima*, a plant widely distributed throughout Europe and Asia and cultivated for medicinal purposes more particularly in Turkestan.

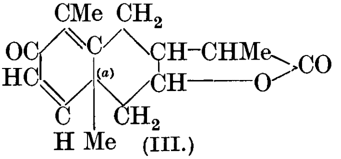
Our present knowledge of the chemistry of santonin is almost entirely derived from the investigations of Cannizzaro and other Italian chemists, carried out towards the close of the nineteenth century, and as a result of their labours various constitutional formulæ have been suggested for santonin, of which structure (I), first proposed by Grassi-Cristaldi and Gucci (*Gazzetta*, 1892, **22**, i, 1), is that generally accepted at the present day (see also Cannizzaro and Gucci, *ibid.*, 1893, **23**, i, 286; Andreocci, *Ber.*, 1893, **26**, 1375).


(I.)


(II.)

On the other hand, an alternative formula (II) has been proposed for santonin by Angeli and Marino (*Rend. Accad. Lincei*, 1907, **16**, i, 159; *Mem. Accad. Lincei*, 1908, **6**, 385) to account for the production of a heptanetetracarboxylic acid, $C_6H_{12}(CO_2H)_2{:}C(CO_2H)_2$, apparently containing a quaternary carbon atom, when santonin is oxidised with alkaline potassium permanganate. However, the catalytic reduction of santonin to a tetrahydro-derivative (Wienhaus and Oettingen, *Annalen*, 1913, **397**, 219; Asahina, *Ber.*, 1913, **46**, 1775) suggests the presence of at least two ethylenic linkages, and structure (II) fails in this respect. Still other constitutional formulæ have been suggested by Francesconi (*Gazzetta*, 1899, **29**, ii, 182), Francesconi and Cusmano (*ibid.*, 1908, **38**, ii, 109), and Bargellini (*Rend. Accad. Lincei*, 1907, **16**, ii, 264).

Criticisms of a general nature may, however, be made against all these structural formulæ and there is apparently no proof of the position of the α-propionic acid side chain in the reduced nucleus. In several phenolic derivatives of santonin, such as *desmotropo*santonin (IV), the relative para-positions of the two methyl groups in the phenolic ring have been determined, but it is now suggested that the migration of a methyl group occurs during the conversion of santonin into such phenolic derivatives, and that santonin itself has the structure (III). This formula (III) conforms better than any hitherto advocated, both with the chemical properties of santonin and with modern views regarding structural units. Although there is no direct evidence, as yet, that natural terpenes result from the polymerisation of isoprene, it is nevertheless an invariable principle that all terpenes of established constitution can be formulated on the principle of head to tail union of isoprene units. None of the hitherto proposed formulæ for santonin can be constructed on this principle, but structure (III) arises from the farnesene skeleton, by ring closure at either the 2 : 7- and 1 : 10- or the 3 : 8- and 1 : 10-positions, and places santonin in the selinene group of sesquiterpenes (compare *Ann. Reports*, 1923, **20**, 100; 1927, **24**, 122). Moreover, since all attempts to prepare a piperonylidene derivative of santonin were unsuccessful, the $-CH_2 \cdot CO-$ group indicated in structure (I) is apparently non-existent. In addition, the formula (III) possesses both a quaternary carbon atom, as necessitated by the work of Angeli and Marino (*loc. cit.*), and two ethylenic linkages, in accordance with that of Wienhaus and Oettingen (*loc. cit.*) and Asahina (*loc. cit.*). On general theoretical grounds, structure (I) should be an unstable form of the stable phenolic isomeride (IV); but santonin exhibits ketonic properties and it is only after prolonged treatment with concentrated hydrochloric acid that it yields the isomeric phenolic *desmotropo*santonin to which formula (IV) has been ascribed. The suggested structure (III) readily explains the stability of the ketone, santonin, and its conversion into *desmotropo*santonin (IV) involves the migration of the methyl group connected to the quaternary carbon atom (*a*), together with the wandering of a nuclear hydrogen atom. Several such migrations are known, *e.g.*, the conversion of 1 : 5-dimethylchinol (V) into 2 : 5-dimethylquinol (VI) by the action of hydrochloric acid (Bamberger and Brady, *Ber.*, 1901, **33**, 3642). The isomeric change suggested above involves the destruction of the asymmetry of the carbon atom (*a*), and it is perhaps significant that all the dextrorotatory derivatives of *l*-santonin are phenolic.



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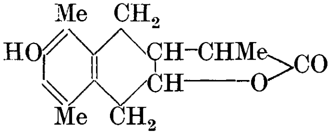

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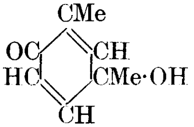

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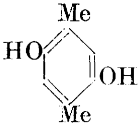

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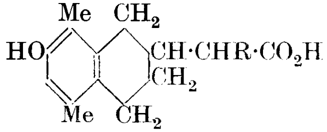


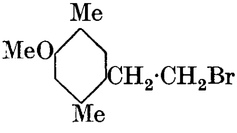
(VII.)

As hitherto all the evidence pertaining to the structure of santonin has accrued from degradation experiments, it was considered highly desirable to attempt the synthetical verification of the views here advanced of the structure of this compound and its simple derivatives. One such derivative, obtained with ease by the reduction of *l*-santonin, is *dl*-santonous acid (VII, R = Me) (Cannizzaro and Carnelutti, *Gazzetta*, 1882, **12**, 393), and this communication describes investigations culminating in the synthesis of this acid.

The preparation of β-4-methoxy-2 : 5-dimethylphenylpropionitrile and its ultimate conversion into β-4-*methoxy*-2 : 5-*dimethylphenylethyl bromide* (VIII) were first considered. Preliminary experiments showed that anisole, β-cyanoethyl toluene-*p*-sulphonate and aluminium chloride do not react normally (compare the preparation of β-phenylpropionitrile; Clemo and Walton, J., 1928, 723) and similar experiments with *p*-xylyl methyl ether were therefore abandoned. Moreover, *p*-xylene, β-cyanoethyl toluene-*p*-sulphonate and aluminium chloride were found to react to give β-2 : 4-*dimethylphenylpropionitrile*; this on hydrolysis afforded β-2 : 4-dimethylphenylpropionic acid, which was also produced by a similar process from *m*-xylene. The peculiar migration of a methyl group involved has already been noticed by Francesconi and Mundici (*Gazzetta*, 1902, **32**, ii, 467; 1904, **34**, ii, 114), who prepared 2 : 4-dimethylbenzaldehyde from both *m*- and *p*-xylene and showed that *p*-xylene is partly converted into *m*-xylene by aluminium chloride.

It was then proposed to obtain β-4-methoxy-2 : 5-dimethylphenylethyl chloride by condensing β-chloroethyl toluene-*p*-sulphonate with magnesium 4-methoxy-2 : 5-dimethylphenyl bromide (compare Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839; 1925, **47**, 518), but all attempts to prepare the latter from 4-*methoxy*-2 : 5-*dimethylphenyl bromide* were unsuccessful.

The synthesis of the bromide (VIII) was finally achieved in the following manner. Methylation of 4-hydroxy-2 : 5-dimethylbenzaldehyde (Gattermann, *Annalen*, 1907, **357**, 321) gave 4-*methoxy*-2 : 5-*dimethylbenzaldehyde*, which was condensed with malonic acid. The 4-*methoxy*-2 : 5-*dimethylcinnamic acid* (IX) obtained was reduced to β-4-*methoxy*-2 : 5-*dimethylphenylpropionic acid*, and the latter converted into β-4-*methoxy*-2 : 5-*dimethylphenylpropionyl chloride*.



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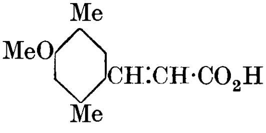

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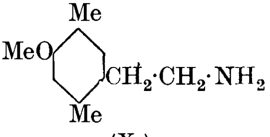
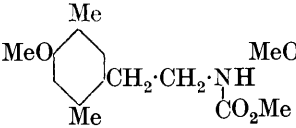


(X.)

This chloride, with aluminium chloride, afforded 6-*methoxy*-4 : 7-*dimethyl*-α-*hydrindone*, proving the propionic acid side chain to be in the *p*- and not the *o*-position with respect to the methoxy-group. β-4-Methoxy-2 : 5-dimethylphenylpropionyl chloride, with ammonia, yielded β-4-*methoxy*-2 : 5-*dimethylphenylpropionamide.* The conversion of this amide into β-4-methoxy-2 : 5-dimethylphenylethylamine (X) presented difficulties owing to the low yields at first obtained. The use of sodium hypobromite for this purpose resulted in a 90% yield of β-3-*bromo*-4-*methoxy*-2 : 5-*dimethylphenylpropionamide*, and treatment of the amide with sodium hypochlorite and methyl alcohol produced *methyl* β-4-*methoxy*-2 : 5-*dimethylphenylethylcarbamate* (XI), which after hydrolysis gave the amine (X). Eventually the best yields were obtained by carrying out the Hofmann reaction on a small scale with aqueous sodium hypochlorite. The amine (X), with nitrous acid, yielded β-4-methoxy-2 : 5-dimethylphenylethyl alcohol, which was converted into the bromide (VIII) by means of 45% hydrobromic acid. With phosphorus pentabromide, the phenylethyl alcohol derivative gave chiefly β-3-*bromo*-4-*methoxy*-2 : 5-*dimethylphenylethyl bromide*, the nuclear bromination being proved by conversion of the latter by way of the corresponding nitrile and acid into β-3-bromo-4-methoxy-2 : 5-dimethylphenylpropionamide, already obtained as above from the amide. This conversion also confirms the existence of the primary alcoholic group in β-4-methoxy-2 : 5-dimethylphenylethyl alcohol.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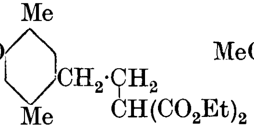
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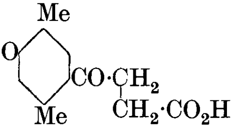

(XIII.)

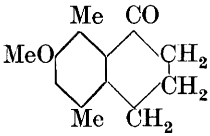
The condensation of β-4-methoxy-2 : 5-dimethylphenylethyl bromide (VIII) with ethyl sodiopropane-ααβ-tricarboxylate (Bischoff, *Annalen*, 1882, **214**, 53) afforded, not the expected ethyl ε-4-methoxy-2 : 5-dimethylphenylpentane-βγγ-tricarboxylate, but a comparatively low-boiling oil together with a smaller high-boiling fraction, which on hydrolysis yielded a non-purifiable tarry acid. Since a crystalline bromine addition compound was prepared from the low-boiling fraction, it is probable that the latter consists of 4-methoxy-2 : 5-dimethylstyrene, produced by the elimination of hydrogen bromide from the bromide (VIII) (compare Dox, *J. Amer. Chem. Soc.*, 1924, **46**, 2844). On the other hand, β-4-methoxy-2 : 5-dimethylphenylethyl bromide with ethyl sodiomalonate afforded ethyl β-4-methoxy-2 : 5-dimethylphenylethylmalonate

(XII) in 40% yield, but attempts to prepare ethyl ε-4-methoxy-2 : 5-dimethylphenylpentane-βγγ-tricarboxylate from the sodio-derivative of the substituted malonic ester (XII) and ethyl α-bromopropionate were again unsuccessful. On hydrolysis, the ester (XII) yielded β-4-*methoxy*-2 : 5-*dimethylphenylethylmalonic acid*, which, on heating, lost carbon dioxide to give γ-4-*methoxy*-2 : 5-*dimethylphenylbutyric acid.* For subsequent work, however, this phenylbutyric acid derivative was prepared by condensing *p*-xylyl methyl ether with succinic anhydride in the presence of aluminium chloride and reducing the β-4-*methoxy*-2 : 5-*dimethylbenzoylpropionic acid* (XIII) obtained with zinc and concentrated hydrochloric acid (compare Burcker, *Ann. Chim.*, 1882, **26**, 435; Krollpfeiffer and Schafer, *Ber.*, 1923, **56**, 620).

γ-4-Methoxy-2 : 5-dimethylphenylbutyric acid, with concentrated sulphuric acid, yielded 1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIV), and this reacted readily with two molecules of bromine, giving 2 : 6-*dibromo*-1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene.* Attempts to condense ethyl sodiomalonate with the latter afforded tarry products, together with some ethyl ethanetetracarboxylate, indicating the replacement of the alicyclic bromine by hydrogen. Attention was then turned to 2-iso*nitroso*-1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* prepared from the ketotetrahydronaphthalene derivative and amyl nitrite (compare Straus and Ekhard, *Annalen*, 1922, **444**, 146), but attempted reductions of the *iso*nitroso-derivative resulted in the formation of tarry products, from which neither 2-amino-1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene nor 2-amino-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene could be isolated.

Ultimately *ethyl* α-*chloro* (or *bromo*)-β-4-*methoxy*-2 : 5-*dimethylbenzoylpropionate* (XV) was found to be a suitable intermediate in the synthesis of *dl*-santonous acid (VII; R = Me). This ester (XV) was prepared by condensing *p*-xylyl methyl ether with maleic anhydride in the presence of aluminium chloride (compare von Pechmann, *Ber.*, 1882, **15**, 885) and treating the β-4-*methoxy*-2 : 5-*dimethylbenzoylacrylic acid* obtained with ethyl-alcoholic hydrogen chloride (or bromide) (see p. 2382) (compare Bougault, *Ann. Chim.*, 1908, **15**, 491). The structure of the benzoylacrylic acid derivative was confirmed by its oxidation with alkaline potassium permanganate to 4-*methoxy*-2 : 5-*dimethylbenzoic acid*, which was also obtained by the oxidation of 4-methoxy-2 : 5-dimethylbenzaldehyde. The ester (XV), with ethyl sodiomalonate, afforded a 90% yield of ethyl γ-4-methoxy-2 : 5-dimethylbenzoylpropane-ααβ-tricarboxylate

(XVI; R = H) as a syrup, and this, on hydrolysis and loss of carbon dioxide, gave a mixture of γ-4-*methoxy*-2 : 5-*dimethylbenzoylpropane*-αβ-*dicarboxylic acid* (XVII; R = H), its *anhydride*, and a small amount of 4-*methoxy*-2 : 5-*dimethylacetophenone*. The last is probably produced from a small amount of unchanged ester (XV) by hydrolysis and simultaneous elimination of hydrogen chloride, with the formation of β-4-methoxy-2 : 5-dimethylbenzoylacrylic acid, which is then split at the ethylenic linkage by the further action of alkali with production of glyoxylic acid and the substituted acetophenone (compare von Pechmann, *loc. cit.*). The structure of this compound was confirmed by synthesis from *p*-xylyl methyl ether, acetyl chloride, and aluminium chloride.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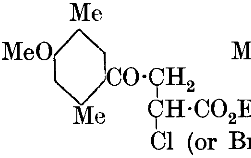
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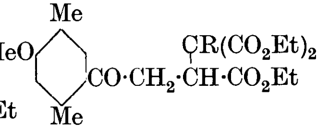
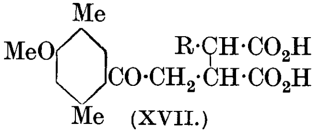

(XVI.)

Both the succinic acid derivative (XVII; R = H) and the crude tricarboxylic acid, from which it was obtained by loss of carbon dioxide, with amalgamated zinc and concentrated hydrochloric acid, yielded β-4-*methoxy*-2 : 5-*dimethylphenylethylsuccinic acid*, and this, with concentrated sulphuric acid, gave 1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*acetic acid* (XVIII; R = H). On reduction with amalgamated zinc and concentrated hydrochloric acid, (XVIII) yielded 7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*acetic acid*, and demethylation of the latter with hydriodic acid gave 7-*hydroxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*acetic acid* (VII; R = H), for which the name *norsantonous acid* is proposed.

In the analogous synthesis of *dl*-santonous acid (VII; R = Me) the sodio-derivative of pure ethyl methylmalonate—prepared from ethyl α-cyanopropionate and ethyl-alcoholic hydrogen chloride (compare Meyer and Jacobsen, "Lehrbuch der Organischen Chemie," B. 1, T. ii, s. 328)—and ethyl α-chloro-β-4-methoxy-2 : 5-dimethylbenzoylpropionate (XV) yielded *ethyl* δ-4-*methoxy*-2 : 5-*dimethylbenzoylbutane*-ββγ-*tricarboxylate* (XVI; R = Me), which, unlike the syrupy ester (XVI; R = H), is a highly crystalline compound. Hydrolysis of this butane ester (XVI; R = Me) afforded an acid, which lost carbon dioxide spontaneously to give δ-4-*methoxy*-2 : 5-*dimethylbenzoylbutane*-βγ-*dicarboxylic acid* (XVII; R = Me), probably as a mixture of the two racemic forms. The presence of two asymmetric carbon atoms in this compound probably accounts for the isolation at this and the succeeding stages of lower yields of pure substances than in the corresponding synthesis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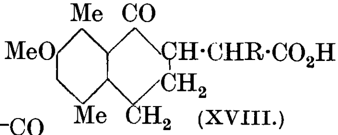
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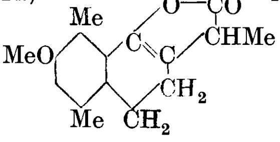
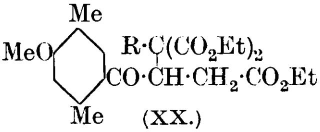

(XIX.)

of *dl*-norsantonous acid. 4-Methoxy-2 : 5-dimethylacetophenone again appeared during the preparation of the butane acid (XVII; R = Me) and was no doubt formed as previously suggested. Reduction of the mixture of the two forms of (XVII; R = Me) with amalgamated zinc and concentrated hydrochloric acid yielded the two inactive forms of α-[β-4-*methoxy*-2 : 5-*dimethylphenylethyl*]-α′-*methylsuccinic acid*, both of which, with concentrated sulphuric acid, gave the *lactone* (XIX) of α-1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic acid.* The free acid from the lactone, with amalgamated zinc and concentrated hydrochloric acid, afforded *dl*-santonous acid methyl ether, which, on demethylation with hydriodic acid, yielded *dl*-santonous acid (VII; R = Me), m. p. 150—152°, which was identical with a specimen prepared from santonin (Cannizzaro and Carnelutti, *Gazzetta*, 1882, **12**, 393). Further, the identity of their respective ethyl esters, m. p. 125°, establishes the synthesis of *dl*-santonous acid beyond all doubt.

This synthesis of *dl*-santonous acid conclusively proves the correctness of formula (VII), provided that hydrogen chloride adds to β-4-methoxy-2 : 5-dimethylbenzoylacrylic acid to give the α-chloro-ester (XV), and not the unlikely β-isomeride (compare Bougault, *loc. cit.*). The latter, with sodiomalonic or sodiomethylmalonic ester, would give esters having the constitution (XX; R = H or Me respectively). Attempts to settle this question by the formation and identification of a dimethylsuccinic acid by the alkaline fusion of ethyl 4-methoxy-2 : 5-dimethylbenzoylbutanetricarboxylate, and also by preparing a piperonylidene derivative of the latter, have as yet been unsuccessful. The production of one lactone from the two forms of the reduced dicarboxylic acid is, however, almost conclusive evidence against formula (XX), which would be very unlikely to give the lactone (XXI). Further, the latter structure contains two asymmetric carbon atoms, and hence, if any lactone were formed, it would be expected to exist in two inactive forms.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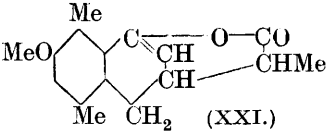
(XXI.)

The isolation of a pure lactone in good yield is only consistent with structure (XVI) for the ethyl 4-methoxy-2 : 5-dimethylbenzoylbutanetricarboxylate, and hence furnishes almost certain proof of the correctness of structure (VII) for *dl*-santonous acid and therefore of the position of the α-propionic acid side chain in santonin itself.

EXPERIMENTAL.

p-*Xylene.*—The preparation of *p*-xylene from *p*-xylidine has apparently hitherto not been described. *p*-Xylidine (100 g.) in concentrated hydrochloric acid (300 c.c.) and water (2000 c.c.) was treated at —5° with sodium nitrite (75 g.) and stirred for 45 minutes. The resulting clear solution was poured into ice-cold 10% sodium hydroxide solution (1500 c.c.), and the mixture added to a solution of stannous chloride (300 g.) and sodium hydroxide (120 g.) in water (3000 c.c.) also at 0°. Steam-distillation of the product yielded *p*-xylene (58 g.), b. p. 138°/760 mm., m. p. 13°.

β-2 : 4-*Dimethylphenylpropionitrile.*—*m*-Xylene (80 c.c.), β-cyanoethyl toluene-*p*-sulphonate (11·2 g.), and powdered aluminium chloride (10 g.) were refluxed for 2 hours. The product was decomposed with dilute hydrochloric acid (500 c.c.), and the oily layer dried and fractionated, the *nitrile* (4·1 g.) being obtained as a colourless oil, b. p. 264—267°/760 mm., with an odour resembling that of nasturtiums (Found : C, 83·3 ; H, 8·5. $C_{11}H_{13}N$ requires C, 83·0 ; H, 8·2%).

β-2 : 4-*Dimethylphenylpropionic Acid.*—The nitrile (1 g.) was refluxed with 10% methyl-alcoholic potassium hydroxide (10 c.c.) for 2 hours. The alcohol was removed, water (25 c.c.) added, and impurities extracted with ether. The alkaline layer was acidified, and the β-2 : 4-dimethylphenylpropionic acid collected ; it crystallised from alcohol in colourless rhombic plates, m. p. 106° (Francesconi and Mundici, *loc. cit.*).

A similar experiment with *p*-xylene gave an oil, b. p. 264—267°/760 mm. (yield, 52%), which, on hydrolysis, also yielded β-2 : 4-dimethylphenylpropionic acid.

p-*Xylenol.*—Sodium nitrite (75 g.) was added during 40 minutes to a well-stirred mixture of *p*-xylidine (121 g.), crushed ice (2000—2500 g.), and concentrated hydrochloric acid (300 c.c.) at —8°.

After a further 20 minutes' stirring, the diazo-solution was poured into a boiling 50% sulphuric acid solution (100 c.c.) containing copper sulphate crystals (20 g.), care being taken to avoid excessive frothing. The mixture was steam-distilled, and the crude *p*-xylenol (85 g.) collected and purified by distillation; it then had b. p. 212°/760 mm. and m. p. 74° (Noelting, Witt, and Forel, *loc. cit.*). A further quantity (5 g.) was obtained from the mother-liquor of the steam distillation by extraction with benzene.

p-*Xylyl Methyl Ether.*—This compound was prepared from *p*-xylenol and methyl sulphate as a colourless oil, b. p. 186—188°/760 mm. (Jacobsen, *loc. cit.*).

4-*Methoxy*-2 : 5-*dimethylacetophenone.*—Powdered aluminium chloride (0·5 g.) was dusted into a mixture of *p*-xylyl methyl ether (0·7 g.) and acetyl chloride (0·4 g.) in light petroleum (b. p. 60—80°) (3 c.c.). When the reaction was complete, dilute hydrochloric acid (10 c.c.) was added and the crystalline solid was extracted with ether and dried. Removal of the solvent yielded 4-*methoxy*-2 : 5-*dimethylacetophenone* as an oil, which crystallised from light petroleum (b. p. 60—80°) in large plates, m. p. 78—79° (Found : C, 74·5; H, 8·1. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

4-*Hydroxy*-2 : 5-*dimethylbenzaldehyde and* 6-*Hydroxy*-2 : 5-*dimethylbenzaldehyde.*—*p*-Xylenol (100 g.), aluminium chloride (150 g.), and liquid hydrogen cyanide (120 c.c.) in dry benzene (400 c.c.) were allowed to react and the product was decomposed as described by Gattermann (*loc. cit.*) and distilled in steam. The volatile products were extracted with ether, dried, and fractionated and 6-hydroxy-2 : 5-dimethylbenzaldehyde (5 g.), m. p. 62° (Anselmino, *Ber.*, 1902, **35**, 4108), was isolated. The non-volatile residue from the steam-distillation was cooled, and the solid collected and extracted with hot benzene (A), from which 4-hydroxy-2 : 5-dimethylbenzaldehyde separated in colourless needles (85 g.), m. p. 132—133° (Gattermann, *loc. cit.*).

Di-(4-*hydroxy*-2 : 5-*dimethylphenyl*)*acetonitrile*,

$$(OH\cdot C_6H_2Me_2)_2CH\cdot CN$$

(compare Bell and Henry, J., 1928, 2215), remained insoluble in the hot benzene (A) in the previous experiment. It crystallised slowly from alcohol in yellowish tablets, m. p. 250° (Found : C, 76·9; H, 6·4; N, 5·2. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%). On methylation with methyl sulphate and sodium hydroxide, it yielded a non-phenolic compound, which crystallised from light petroleum (b. p. 80—100°) in slender white prisms, m. p. 190°.

4-*Hydroxy*-2 : 5-*dimethylcinnamic Acid.*—4-Hydroxy-2 : 5-dimethylbenzaldehyde (1·5 g.), malonic acid (2·5 g.), pyridine (5 c.c.), and piperidine (1 drop) were heated at 100° for 2 hours, the product was poured into excess of dilute hydrochloric acid, and the precipitated *acid* collected. It crystallised from dilute alcohol in yellowish prisms, m. p. 223—225°. Gattermann (*loc. cit.*) gives m. p. 171° (see, however, acetyl derivative below) (Found: C, 69·0; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The *acetyl* derivative formed prisms, m. p. 168—169°, from dilute acetic acid (Found: C, 66·6; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

4-*Methoxy*-2 : 5-*dimethylbenzaldehyde*.—Methyl sulphate (190 g.) and 25% methyl-alcoholic potassium hydroxide (300 g.) were gradually added to a hot solution of 4-hydroxy-2 : 5-dimethylbenzaldehyde (100 g.) in 10% methyl-alcoholic potassium hydroxide (350 c.c.) and, after a further 30 minutes' heating, the alcohol was removed and the residue diluted with water and extracted with ether. The extract was dried and fractionated; 4-*methoxy*-2 : 5-*dimethylbenzaldehyde* (90 g.), b. p. 147—149°/12 mm., was obtained and rapidly solidified to a practically colourless, crystalline mass, m. p. 34° (Found: C, 72·9; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%).

4-*Methoxy*-2 : 5-*dimethylbenzoic acid*, obtained by oxidising 4-methoxy-2 : 5-dimethylbenzaldehyde with potassium permanganate in boiling acetone solution, crystallised from 50% acetic acid in colourless plates, m. p. 163—165° (Found: C, 66·4; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%).

4-*Methoxy*-2 : 5-*dimethylcinnamic Acid* (IX).—Malonic acid (50 g.), 4-methoxy-2 : 5-dimethylbenzaldehyde (33 g.), pyridine (100 c.c.), and piperidine (1·5 c.c.) were heated on a water-bath for 4—5 hours, then boiled for ½ hour and poured into excess of dilute hydrochloric acid (1000 c.c.). The precipitated 4-*methoxy*-2 : 5-*dimethylcinnamic acid* was collected when cold, dried (38 g.), and was pure enough for subsequent reactions. The acid (IX) is insoluble in water and crystallises from benzene in colourless slender prisms, m. p. 200—202° (Found: C, 69·8; H, 6·9. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%).

β-4-*Methoxy*-2 : 5-*dimethylphenylpropionic Acid*.—4% Sodium amalgam (1000 g.) was gradually added to a warm stirred solution of 4-methoxy-2 : 5-dimethylcinnamic acid (60 g.) in 5% aqueous sodium hydroxide (300 c.c.), and the temperature allowed to rise slowly from 60° to 90° while excessive alkalinity was prevented by frequent additions of hydrochloric acid. After 3 hours, the solution was cooled, filtered, and acidified with concentrated hydrochloric acid and the precipitated *acid* was collected and washed with cold water; it crystallised from boiling water in plates (52 g.), m. p. 120—121° (Found: C, 69·5; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

β-4-*Methoxy*-2 : 5-*dimethylphenylpropionyl Chloride.*—A mixture of the preceding acid (5 g.), thionyl chloride (4 g.), and chloroform (15 c.c.) was kept for 12 hours, and the product fractionated, the acid chloride being obtained as a colourless oil, b. p. 171°/12 mm., which quickly solidified to give silky crystals, m. p. 34°. These decomposed on exposure to the atmosphere.

6-*Methoxy*-4 : 7-*dimethyl-α-hydrindone.*—A mixture of β-4-methoxy-2 : 5-dimethylphenylpropionyl chloride (1 g.), light petroleum (b. p. 80—100°) (5 c.c.), and aluminium chloride (1 g.) was heated on the water-bath for 1 hour, and dilute hydrochloric acid added. The *hydrindone*, after being washed with hot sodium hydroxide solution, crystallised from light petroleum (b. p. 100—120°) in jagged prisms, m. p. 162—164° (Found : C, 75·7 ; H, 7·2. $C_{12}H_{14}O_2$ requires C, 75·8 ; H, 7·4%).

β-4-*Methoxy*-2 : 5-*dimethylphenylpropionanilide*, obtained by warming a mixture of aniline (0·5 g.) and the acid chloride (1 g.) on the water-bath for 2 minutes, crystallised from dilute alcohol in colourless prisms, m. p. 134—135° (Found : C, 76·7 ; H, 7·4. $C_{18}H_{21}O_2N$ requires C, 76·3 ; H, 7·4%).

β-4-*Methoxy*-2 : 5-*dimethylphenylpropionamide.*—Thionyl chloride (40 g.) was added with cooling to a solution of β-4-methoxy-2 : 5-dimethylphenylpropionic acid (50 g.) in chloroform (150 c.c.). After 12 hours, the resulting brown solution was poured into concentrated aqueous ammonia (600 c.c.), the chloroform removed by distillation, and the residual *amide* collected after cooling. A further quantity was obtained by extracting the filtrate with benzene. The amide was recrystallised from benzene, colourless prisms (36 g.), m. p. 127—128°, being obtained (Found : C, 69·4 ; H, 7·9. $C_{12}H_{17}O_2N$ requires C, 69·5 ; H, 8·2%).

β-3-*Bromo*-4-*methoxy*-2 : 5-*dimethylphenylpropionamide* was obtained by warming a mixture of the preceding amide (3 g.) and sodium hypobromite (2·7 g. of bromine in 55 c.c. of 10% sodium hydroxide solution). It separated as an oil, which solidified on cooling and then crystallised from benzene in colourless jagged prisms, m. p. 152° (Found : C, 50·1 ; H, 5·8. $C_{12}H_{16}O_2NBr$ requires C, 50·3 ; H, 5·6%) (compare p. 2380).

β-4-*Methoxy*-2 : 5-*dimethylphenylethylamine* (X).—(*a*) A solution of sodium hypochlorite, prepared by passing chlorine (4·2 g.) into 10% aqueous sodium hydroxide (120 c.c.) at 0°, was added with vigorous shaking to finely powdered β-4-methoxy-2 : 5-dimethylphenylpropionamide (10 g.), the temperature being slowly raised to 60°. At this point, the temperature rose spontaneously and a clear solution was obtained, from which β-4-methoxy-2 : 5-dimethylphenylethylamine separated as an oil. The mixture was warmed at 80—85° for 1½ hours, solid sodium hydroxide (30 g.) added, and the heating at 80—85° continued for a further ½ hour. The amine was extracted with ether, dried over powdered potassium hydroxide, and fractionated under reduced pressure (yield, 5·5 g.).

(*b*) β-4-Methoxy-2 : 5-dimethylphenylpropionamide (2·5 g.), sodium hypochlorite solution [prepared by passing chlorine (1·5 g.) into 10% aqueous sodium hydroxide (30 c.c.)], and methyl alcohol (35 c.c.) were refluxed for 3 hours. After the alcohol had been removed, the mixture was poured into water (200 c.c.) and extracted with ether. The solvent was removed and, after the oily residue (A) had been refluxed with 10% methyl-alcoholic potassium hydroxide (8 c.c.), the product was poured into water, extracted with benzene, and dried, and the amine precipitated as hydrochloride (1·3 g.) by saturating the solution with dry hydrogen chloride.

β-4-Methoxy-2 : 5-dimethylphenylethylamine, b. p. 120—122°/0·25 mm., is a colourless oil with strongly basic properties. On exposure to air it quickly absorbs carbon dioxide to form a solid white carbonate, and with hydrochloric acid it yields a hydrochloride which crystallises from very dilute hydrochloric acid in leaflets, m. p. 212—215° (decomp.). The *acetyl* derivative crystallises from hot water in prisms, m. p. 147—148° (Found : C, 70·8; H, 8·4. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%).

Methyl β-4-*Methoxy*-2 : 5-*dimethylphenylethylcarbamate* (XI).—Fractionation of the above dried residue (A) gave some of the amine (X) at 150—160°/12 mm., and then the *carbamate* (XI), b. p. 175—185°/12 mm., which crystallised from ligroin in large hexagonal prisms, m. p. 57·5° (Found : C, 65·6; H, 8·1. $C_{13}H_{19}O_3N$ requires C, 65·8; H, 8·0%).

β-4-*Methoxy*-2 : 5-*dimethylphenylethyl Alcohol*.—Sodium nitrite (7·2 g.) was slowly added at room temperature to a solution of β-4-methoxy-2 : 5-dimethylphenylethylamine (18 g.) in excess of 30% acetic acid. Heat was developed and the solution turned yellow and turbid. The reaction was completed by warming on the water-bath for 3 hours. β-4-Methoxy-2 : 5-dimethylphenylethyl alcohol separated as an oil, which was extracted with ether, washed first with sodium hydroxide solution and then with hydrochloric acid, dried, and fractionated; the alcohol (16·5 g.) was then obtained as a yellow oil, b. p. 125—126°/0·25 mm., with a faint sweetish odour. It was slightly soluble in hot water, volatile in steam, and gave a brown solution in concentrated sulphuric acid. β-4-*Methoxy*-2 : 5-*dimethylphenylethyl phenylcarbamate* was prepared in ethereal solution and crystallised from light petroleum (b. p. 80—100°) in feathery needles, m. p. 110° (Found : C, 72·5; H, 7·0. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0%).

β-4-*Methoxy*-2 : 5-*dimethylphenylethyl Bromide*.—The preceding alcohol (14 g.) was refluxed with 45% aqueous hydrobromic acid (30 c.c.) for 3 hours, the mixture changing from green to dark purple. The product was extracted with ether, dried, and fractionated, the *bromide* (11·5 g.) being collected at 128—130°/1 mm. (Found : Br, 31·6. $C_{11}H_{15}OBr$ requires Br, 32·9%). The low bromine value is probably due to the presence of a small amount of unchanged alcohol. The use of concentrated sulphuric acid as catalyst in this reaction is liable to give rise to high-boiling by-products. Phosphorus pentabromide acted on the alcohol, giving a product, b. p. 180—200°/12 mm., which when refluxed with ethyl-alcoholic potassium cyanide, and then hydrolysed with methyl-alcoholic potassium hydroxide, gave β-3-bromo-4-methoxy-2 : 5-dimethylphenylpropionic acid, as proved by conversion into the amide (compare p. 2378). The brominated acid, on reduction with sodium amalgam, yielded β-4-methoxy-2 : 5-dimethylphenylpropionic acid.

Attempts to condense β-4-methoxy-2 : 5-dimethylphenylethyl bromide with ethyl sodiopropane-ααβ-tricarboxylate (Bischoff, *loc. cit.*) in benzene yielded a product which on distillation gave a main fraction, b. p. 135—150°/12 mm., and a smaller fraction, b. p. 235—250°/12 mm., consisting of a brown viscous syrup. Treatment of the low-boiling fraction with methyl-alcoholic potassium hydroxide gave a residual oil, b. p. 120°/12 mm., which formed a crystalline addition compound with bromine in carbon tetrachloride, and was probably 4-methoxy-2 : 5-dimethylstyrene. The high-boiling fraction on hydrolysis yielded an oily acid which lost carbon dioxide at 140—160°, but attempts to prepare a crystalline amide have been unsuccessful.

Ethyl β-4-*Methoxy*-2 : 5-*dimethylphenylethylmalonate* (XII).—β-4-Methoxy-2 : 5-dimethylphenylethyl bromide (24·3 g.) was added to a solution of ethyl sodiomalonate, prepared from sodium (2·3 g.), ethyl malonate (16 g.), and absolute alcohol (50 c.c.). The mixture was warmed at 45° for 1 hour, and then slowly to 70° during the course of 3 hours, sodium bromide separating. Most of the alcohol was removed under reduced pressure and the product was poured into water, extracted with ether, dried, and fractionated. The first fraction (6·5 g.), b. p. up to 155°/12 mm., consisted mainly of ethyl malonate, the second of ethyl β-4-methoxy-2 : 5-dimethylphenylethylmalonate (17·5 g.), b. p. 175—195°/0·25 mm., obtained as a pale yellow syrup, b. p. 185°/0·25 mm., by redistillation, and there was a residual tar (5 g.).

β-4-*Methoxy*-2 : 5-*dimethylphenylethylmalonic acid*, prepared by hydrolysing the ester, described above, with 20% methyl-alcoholic potassium hydroxide, crystallised from hot water in colourless prisms, m. p. 145° (decomp.) (Found : C, 63·0; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

β-4-*Methoxy*-2 : 5-*dimethylbenzoylpropionic Acid* (XIII).—Powdered aluminium chloride (27 g.) was slowly added to a cold mixture of *p*-xylyl methyl ether (27 g.), succinic anhydride (20 g.), and benzene (50 c.c.). Hydrogen chloride was evolved and water-cooling was necessary. The reaction was completed by warming the resulting dark brown tarry mass at 65° for 3 hours, and the product decomposed with ice and dilute hydrochloric acid. The white solid was collected and washed with dilute hydrochloric acid, the residue extracted with sodium carbonate solution, and the *acid* reprecipitated and crystallised from hot water, giving slender prisms (35 g.), m. p. 131° (Found : C, 66·2; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

γ-4-*Methoxy*-2 : 5-*dimethylphenylbutyric Acid*.—(*a*) β-4-Methoxy-2 : 5-dimethylphenylethylmalonic acid (10 g.) was heated in an oil-bath at 160—170° for 1 hour until the evolution of carbon dioxide ceased; the residue crystallised from dilute alcohol in small plates (7 g.).

(*b*) A mixture of β-4-methoxy-2 : 5-dimethylbenzoylpropionic acid (30 g.), amalgamated zinc (150 g.), and concentrated hydrochloric acid (150 c.c.) was kept at room temperature for 3 hours, then refluxed for 12 hours and diluted, and extracted thoroughly with chloroform. The solvent was removed, and the residue, after purification through its sodium salt, gave the desired *acid* (26 g.), which crystallised from dilute alcohol in small plates, m. p. 101—102° (Found : C, 70·4; H, 8·0. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). Attempts to α-brominate this acid were unsuccessful.

1-*Keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIV).—γ-4-Methoxy-2 : 5-dimethylphenylbutyric acid (10 g.) was heated with concentrated sulphuric acid (50 c.c.) at 70° for 10 minutes, cooled, and poured on ice (150 c.c.). The oil which separated was extracted with chloroform and washed with sodium carbonate solution, and the solvent removed; the residual 1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* crystallised from light petroleum (b. p. 40—60°) in large plates (7 g.), m. p. 63—64° (Found : C, 76·2; H, 7·6. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). This ketone was recovered after being heated with ethyl α-bromopropionate and copper powder.

2 : 6-*Dibromo*-1-*keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Bromine (16 g.) was added to the preceding ketone (10 g.) in chloroform (50 c.c.). Copious evolution of hydrogen bromide occurred and on one occasion the formation of a crystalline intermediate compound prior to such emission was noticed. After

48 hours at room temperature, the chloroform was removed under reduced pressure and the residue crystallised from light petroleum (b. p. 40—60°), the dibrominated *ketone* (11 g.) being obtained in colourless stout prisms, m. p. 93° [Found : Br (hydrolysable), 20·7; Br (total), 45·2. $C_{13}H_{14}O_2Br_2$ requires Br (hydrolysable), 22·1; Br (total), 44·2%]. Attempts to condense this compound with ethyl sodiomalonate in benzene solution yielded a little ethyl ethanetetracarboxylate, m. p. 76°, and an intractable tar.

2-iso*Nitroso-1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene.*—A mixture of 1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (4 g.) and freshly prepared amyl nitrite (2·4 g.) in well-cooled ether (50 c.c.) was added to a solution of potassium (0·8 g.) and absolute alcohol (6 c.c.) in dry ether (50 c.c.), slowly and with shaking. The chocolate-coloured potassium salt obtained was collected and decomposed with a slight excess of hydrochloric acid, and the iso*nitroso-compound* crystallised from benzene, stout yellowish-brown prisms (1·5 g.), m. p. 170—180° (decomp.), being obtained (Found : N, 5·9. $C_{13}H_{15}O_3N$ requires N, 6·0%). Attempts to reduce the *iso*nitroso-derivative have been unsuccessful.

β-4-*Methoxy-2 : 5-dimethylbenzoylacrylic Acid.*—Powdered aluminium chloride (70 g.) was slowly added with stirring to a cold mixture of *p*-xylyl methyl ether (69 g.), maleic anhydride (50 g.), and light petroleum (b. p. 80—100°; 300 c.c.). Some hydrogen chloride was evolved, and the mixture, which rapidly changed to a reddish-black brittle mass with evolution of heat, was maintained at 70° for 1½ hours and then decomposed with cold dilute hydrochloric acid, the resulting yellow solid collected, washed with water and dried, and *p*-xylyl methyl ether (19 g.) recovered from the light petroleum. After crystallisation from benzene β-4-*methoxy-2 : 5-dimethylbenzoylacrylic acid* was obtained in slender, yellow prisms (45 g.), m. p. 156—157° (Found: C, 66·9; H, 5·8. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). Cold hydrobromic acid (45%) was without action on the acid, but on being heated at 100° the mixture changed to a tarry mass, which was not further investigated.

α-*Bromo*-β-4-*methoxy-2 : 5-dimethylbenzoylpropionic Acid.*—The preceding acid (2 g.) and acetic acid (25 c.c.), saturated with dry hydrogen bromide, were kept in the cold for ½ hour; the yellow colour of the solution then disappeared and α-*bromo*-β-4-*methoxy-2 : 5-dimethylbenzoylpropionic acid* separated almost quantitatively as a white crystalline solid. This was collected, and rapidly recrystallised from dilute acetic acid, small plates, m. p. 144—147°, being obtained (Found : Br, 25·0. $C_{13}H_{15}O_4Br$ requires Br, 25·4%).

The *ethyl* ester (XV) was deposited (6·5 g.) from a mixture of β-4-methoxy-2 : 5-dimethylbenzoylacrylic acid (7 g.) and a saturated solution of hydrogen bromide in absolute alcohol (30 c.c.) after standing for 3 days in the cold, and recrystallised from light petroleum (b. p. 60—80°), giving large stout prisms, m. p. 90—91° (Found : Br, 22·9. $C_{15}H_{19}O_4Br$ requires Br, 23·3%). This ester condenses with ethyl sodiomalonate in a similar manner to the corresponding chlorinated ester (see below).

Ethyl α-Chloro-β-4-methoxy-2 : 5-dimethylbenzoylpropionate.—When β-4-methoxy-2 : 5-dimethylbenzoylacrylic acid (20 g.) in absolute alcohol (100 c.c.) was saturated with dry hydrogen chloride, it gradually dissolved and after 12 hours a crystalline mass of the chlorinated *ester* (22 g.) separated. After being washed with a little absolute alcohol, dried at 70°, and recrystallised from light petroleum (b. p. 80—100°), the ester formed large colourless prisms, m. p. 89—90° (Found : C, 60·4; H, 6·5; Cl, 11·8. $C_{15}H_{19}O_4Cl$ requires C, 60·3; H, 6·4; Cl, 11·8%). Reduction of this ester with amalgamated zinc and concentrated hydrochloric acid yielded γ-4-methoxy-2 : 5-dimethylphenylbutyric acid.

Ethyl γ-4-Methoxy-2 : 5-dimethylbenzoylpropane-ααβ-tricarboxylate.—Powdered sodium (1·15 g.), ethyl malonate (8 g.), and benzene (50 c.c.) were warmed at 50° until the formation of ethyl sodiomalonate was complete. Ethyl α-chloro-β-4-methoxy-2 : 5-dimethylbenzoylpropionate (15 g.) was then added with stirring. Heat was evolved and sodium chloride separated as a gelatinous solid. The reaction was completed by heating at 80° for 2 hours, water was then added, the benzene layer separated, and the aqueous portion extracted with ether. The combined extracts were dried, and the solvents removed under reduced pressure; ethyl γ-4-methoxy-2 : 5-dimethylbenzoylpropane-ααβ-tricarboxylate (18 g.) remained as an oil. This crude ester (15 g.) and 20% methyl-alcoholic potassium hydroxide (36 c.c.) were refluxed for 3 hours, the bulk of the alcohol was removed, and the mixture poured into cold water (100 c.c.). The 4-methoxy-2 : 5-dimethylacetophenone (1 g.), which separated as a solid, was collected; the filtrate was acidified with hydrochloric acid and evaporated to dryness under reduced pressure. An acetone extract of the residue yielded a light brown solid, probably consisting mainly of γ-4-methoxy-2 : 5-dimethylbenzoylpropane-ααβ-tricarboxylic acid (11·4 g.), which was deliquescent, very soluble in water, but insoluble in chloroform. It was used without further purification for the following operations.

γ-4-Methoxy-2 : 5-dimethylbenzoylpropane-αβ-dicarboxylic Acid (XVII, R = H) *and its Anhydride.*—The above acid (8 g.) was heated at 160° for 1 hour; carbon dioxide and water were evolved and the mixture assumed a dark brown colour. Trituration with ether yielded *γ-4-methoxy-2 : 5-dimethylbenzoylpropane-αβ-dicarboxylic anhydride* (2 g.) as a white solid, which was collected and washed with ether; it crystallised from alcohol in stout prisms, m. p. 152—153° (Found: C, 65·2; H, 5·6. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). The anhydride is moderately easily soluble in hot glacial acetic acid and benzene, but insoluble in cold sodium hydroxide solution. Addition of benzene to the residue from the ethereal mother-liquor gave the corresponding *acid* (2 g.), which separated from hot water as a crystalline powder, m. p. 148—150° (Found: C, 60·8; H, 6·5. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2%).

β-4-Methoxy-2 : 5-dimethylphenylethylsuccinic Acid.—Crude γ-4-methoxy-2:5-dimethylbenzoylpropane-ααβ-tricarboxylic acid (11 g.), amalgamated zinc (50 g.), and concentrated hydrochloric acid (70 c.c.) were kept in the cold for 3 hours and then refluxed for 12 hours. The product was extracted with chloroform, the extract washed with water and dried, and the solvent removed. The residual *β-4-methoxy-2 : 5-dimethylphenylethylsuccinic acid* (7·7 g.), which rapidly solidified, was crystallised first from benzene and then from hot water; small prisms, m. p. 140—142°, were obtained (Found: C, 63·9; H, 7·3. $C_{15}H_{20}O_5$ requires C, 64·2; H, 7·2%).

1-Keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-acetic Acid (XVIII; R = H).—The preceding acid (2·5 g.) and concentrated sulphuric acid (10 c.c.)* were warmed on the water-bath for 1 minute with stirring. The red solution was diluted with ice (30 g.) and extracted with chloroform, the extract dried, and the solvent removed. The residual *1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-acetic acid* (1·9 g.) crystallised from benzene in plates, m. p. 143—145° (Found: C, 68·9; H, 6·7. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

7-Methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-acetic acid was obtained when the keto-acid (3·5 g.) was reduced with amalgamated zinc (16 g.) and concentrated hydrochloric acid (22 c.c.), as described in the preparation of β-4-methoxy-2 : 5-dimethylphenylethylsuccinic acid. It crystallised from light petroleum (b. p. 80—100°) in prisms (2·5 g.), m. p. 130—131° (Found: C, 72·3; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

7-Hydroxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-acetic Acid (Norsantonous Acid).—The methoxy-acid (1 g.) and hydriodic acid (b. p. 127°; 5 c.c.) were refluxed for 5 minutes. Water (20 c.c.) was added, the solid extracted in ether, decolorised with sodium bisulphite solution, washed with water, and dried, and the ether removed. *Norsantonous acid*, thus obtained in theoretical yield,

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* The use of larger quantities decreases the yield of 1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-acetic acid.

crystallised from toluene in colourless, six-sided plates, m. p. 163—164° (Found: C, 72·0; H, 7·5. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Norsantonous acid is sparingly soluble in hot water, and its solution in concentrated sulphuric acid gives a purple coloration on the addition of ferric chloride.

Ethyl δ-4-*Methoxy*-2 : 5-*dimethylbenzoylbutane*-ββγ-*tricarboxylate* (XVI; R = Me).—Ethyl α-chloro-β-4-methoxy-2 : 5-dimethylbenzoylpropionate (47 g.) was added to ethyl sodiomethylmalonate [prepared from pulverised sodium (3·9 g.) and ethyl methylmalonate (29 g.) in dry benzene (100 c.c.)]. The mixture was treated as in the case of ethyl γ-4-methoxy-2 : 5-dimethylbenzoylpropane-ααβ-tricarboxylate and yielded the *ester* (XVI; R = Me) (67 g.), which rapidly solidified in the presence of ligroin (b. p. 40—60°). The ester crystallised from light petroleum (b. p. 80—100°) in large jagged prisms, m. p. 99° (Found: C, 63·0; H, 7·2. $C_{23}H_{32}O_8$ requires C, 63·3; H, 7·4%), and distilled with slight decomposition at 220°/0·1 mm.

δ-4-*Methoxy*-2 : 5-*dimethylbenzoylbutane*-βγ-*dicarboxylic Acid* (XVII; R = Me).—The preceding ester (22 g.) was refluxed with methyl-alcoholic potassium hydroxide (12 g. in 50 c.c. of alcohol) for 2 hours, the bulk of the alcohol removed, water added, and the precipitated 4-methoxy-2 : 5-dimethylacetophenone (0·7 g.) collected. The filtrate was acidified with hydrochloric acid and the resulting oil, which partly solidified after several hours, was collected and stirred with ether, giving apparently a mixture of the two racemic forms of δ-4-*methoxy*-2 : 5-*dimethylbenzoylbutane*-βγ-*dicarboxylic acid*, m. p. 155—162°. Crystallisation from dilute alcohol yielded slender prisms, m. p. 163—168°, consisting mainly of one form of the acid (XVII; R = Me) (Found: C, 62·5; H, 6·7; equiv., 153, 157, 153. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%; equiv., 154).

α-(β-4-*Methoxy*-2 : 5-*dimethylphenylethyl*)-α′-*methylsuccinic Acid*.—The above acid mixture, m. p. 155—162° (5 g.), amalgamated zinc (25 g.), and concentrated hydrochloric acid (35 c.c.) were kept for 2 hours in the cold and then refluxed for 15 hours. After dilution with water the product was shaken with ether, decanted from the zinc residues, and filtered from an *acid* (0·7 g.), which crystallised from dilute alcohol in long prisms, m. p. 181—182° (Found: C, 62·4; H, 6·5%; equiv., 148). The constitution of this compound has not yet been determined. The ethereal extract of the filtrate was washed with water and dried, the solvent removed, and the residual solid stirred with benzene and collected (1·8 g.). This crystallised from aqueous alcohol, giving leaflets, m. p. 169—171°, consisting of one form of α-(β-4-*methoxy*-2 : 5-*dimethylphenylethyl*)-

α′-methylsuccinic acid (Found : C, 65·6; H, 7·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). After addition of light petroleum (b. p. 80—100°) to the benzene mother-liquor, a second *form* of the acid (1·1 g.) was obtained after some hours, which crystallised from benzene–light petroleum (b. p. 80—100°) in flaky prisms, m. p. 130—132° (Found : equiv., 142. $C_{16}H_{22}O_5$ requires equiv., 147).

α-1-*Keto*-7-*methoxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic Acid* (XVIII; R = Me) *and its Lactone* (XIX).—Either of the preceding acids (0·5 g.) was warmed at 80° for 3 minutes with sulphuric acid (5 c.c.), water and ice (20 g.) were added, and the solid was collected, boiled for a short time with dilute sodium bicarbonate solution, and washed with water, giving the *lactone* (XIX) (0·4 g.), which crystallised from benzene–light petroleum (b. p. 80—100°) in stout prisms, m. p. 160—162° (Found : C, 74·3; H, 6·6. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). The lactone (0·5 g.) was refluxed with methyl-alcoholic potassium hydroxide, the alcohol removed, and the residue diluted with water, acidified, and extracted with ether. The residue from the dried extract, on treatment with benzene–light petroleum (b. p. 80—100°), gave a mixture of the two racemic forms of α-1-keto-7-methoxy-5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthyl-2-propionic acid (XVIII; R = Me) (0·45 g.), m. p. 105—115°. This was collected and used in the subsequent reduction without further treatment.

dl-*Santonous Acid Methyl Ether*.—The preceding acid (0·5 g.), amalgamated zinc (5 g.), and concentrated hydrochloric acid (8 c.c.) were refluxed for 15 hours, the mixture was diluted with water, extracted with ether, and dried, and the solvent removed. The residue was stirred with ligroin (b. p. 40—60°), giving a crystalline solid (0·4 g.), m. p. 97—110°, apparently consisting of a mixture of the two possible racemic forms of *dl*-santonous acid methyl ether (compare Andreocci, *Gazzetta*, 1895, **25**, i, 526).

dl-*Santonous Acid*.—The above mixture of *dl*-santonous acid methyl ethers (0·5 g.) was refluxed with hydriodic acid (5 c.c.) for 10 minutes, water (20 c.c.) added, the product extracted with ether, and the extract decolorised with aqueous sodium bisulphite and dried. Removal of the solvent yielded an oily residue, which partly solidified on standing; after being drained on porous plate, it was carefully crystallised twice from ether–ligroin (b. p. 40—60°), giving shining leaflets (0·2 g. approx.), m. p. 150—152°, unchanged by admixture with *dl*-santonous acid prepared from santonin (compare Cannizzaro and Carnelutti, *loc. cit.*) (Found for synthetic santonous acid : C, 72·4; H, 8·5. Calc. for $C_{15}H_{20}O_3$: C, 72·6; H, 8·1%). The acid in sulphuric acid gave with ferric chloride a purple coloration similar to that given by the acid from santonin. The ethyl ester from synthetic *dl*-santonous acid (0·2 g.) separated from ether in colourless plates, m. p. 125°, and was proved to be identical by mixed m. p. with a specimen made from the acid obtained from santonin (Found for the synthetic ester : C, 73·6 ; H, 9·0. Calc. for $C_{17}H_{24}O_3$: C, 73·9 ; H, 8·8%).

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