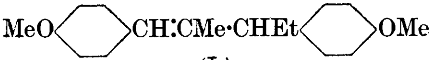
CCCXXVII.—*The Structure of* iso*Anethole.*

By George David Goodall and Robert Downs Haworth.

The work of Staudinger during the last ten years on polymeric substances of high molecular weight indicates that they can be represented by structural formulæ in which the monomeric forms are held together by ordinary valency bonds. However, in many cases, the structural formulæ are still unproved and therefore a systematic investigation of the polymerides of propenylbenzene derivatives was contemplated with a view to the determination of the structure of the simpler dimeric forms.

The polymerisation of anethole has been investigated and the constitution of *iso*anethole was established before Bergmann and Weiss (*Annalen*, 1930, **480**, 49) published the results of a similar investigation of asymmetrical diphenylethylene. As they state that investigations of other dimeric substances, including dianethole, are being undertaken, we submit our results on *iso*anethole.

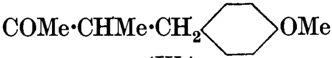
Two dimerides of anethole are known: one is an oil with unsaturated properties, known as *iso*anethole (Kraut and Schlun, *Jahresber.*, 1863, 552; Orndorff, Terrasse, and Morton, *Amer. Chem. J.*, 1897, **19**, 859), and the other, metanethole, is a crystalline substance (Gerhardt, *Annalen*, 1843, **48**, 234; Perrenoud, *ibid.*, 1877, **187**, 68; Orndorff, Terrasse, and Morton, *loc. cit.*; Staudinger, *Helv. Chim. Acta*, 1928, **12**, 972). Formulæ (I), (II), and (III) represent possible structures for *iso*anethole, and of these (I) or (III) appears the most probable. Stobbe and Posnjak (*Annalen*, 1909, **371**, 287) have shown that unsymmetrical addition is involved in the formation of liquid distyrene from cinnamic acid, and this suggests structure (I) for *iso*anethole. Stoermer and Kootz (*Ber.*, 1928, **61**, 2330), however, have shown that liquid distyrene isomerises in the presence of concentrated sulphuric acid, and therefore by analogy *iso*anethole may have structure (III).



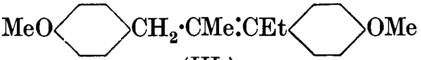
(I.)

(V.)

(II.)



(IV.)



(III.)

(VI.)

*iso*Anethole was readily obtained by the action of boiling methyl-alcoholic hydrogen chloride on anethole. On treatment with potassium permanganate in acetone solution, it was oxidised almost quantitatively to anisic acid and a *ketone*, $C_{12}H_{16}O_2$, which was characterised by its crystalline *semicarbazone* and *oxime*. The production of anisic acid excluded structure (III), and a decision between (I) and (II) was made by comparing the ketone $C_{12}H_{16}O_2$ with the ketones (IV) and (V), which were synthesised.

In order to prepare the ketone (IV), *ethyl* p-*methoxybenzylacetoacetate* was prepared from *p*-methoxybenzyl bromide (Lapworth and Shoesmith, J., 1922, **121**, 1391) and ethyl sodioacetoacetate. The high-boiling fractions from this condensation contained *ethyl di*-p-*methoxybenzylacetoacetate*, which was hydrolysed by 10% potassium hydroxide solution to *di*-p-*methoxybenzylacetone*. Ethyl *p*-methoxybenzylacetoacetate, which was hydrolysed to p-*methoxybenzylacetone* by 10% potassium hydroxide solution, was treated with sodium methoxide and methyl iodide and converted into *ethyl* p-*methoxybenzylmethylacetoacetate* (VI).

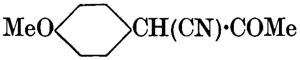
α-p-*Methoxybenzylethyl methyl ketone* (IV), obtained from the ester (VI) by hydrolysis with 10% potassium hydroxide solution, yielded a crystalline *semicarbazone*, which was not identical with the semicarbazone of the ketone produced by the oxidation of *iso*anethole.

The synthesis of the isomeric ketone (V) was first attempted from *p*-methoxyphenylacetonitrile, which we hoped would react with ethyl iodide and sodamide to give the ethyl derivative (compare Bodroux and Taboury, *Compt. rend.*, 1910, **150**, 531). The experiments, however, were unsuccessful and the following method was adopted.

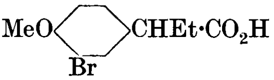
p-Methoxyphenylacetonitrile was condensed with ethyl acetate in the presence of sodium ethoxide (compare Beckh, *Ber.*, 1898, **31**,

3150) and a good yield of *acetyl-*p*-methoxyphenylacetonitrile* (VII) was obtained. This was boiled with 50% sulphuric acid and the p*-methoxybenzyl methyl ketone* (VIII) obtained was converted into α-p*-methoxyphenyl-*n*-propyl methyl ketone* (V) by the action of sodium ethoxide and ethyl iodide (compare Tiffeneau and Levy, *Bull. Soc. chim.*, 1923, **33**, 767). This ketone (V) could not be completely freed from the unchanged *p*-methoxybenzyl methyl ketone by distillation, but a pure specimen of the *semicarbazone* was easily obtained. This was identical with the semicarbazone of the ketone $C_{12}H_{16}O_2$ obtained from *iso*anethole. A pure specimen of α-*p*-methoxybenzyl-*n*-propyl methyl ketone (IV) was prepared by hydrolysing the semicarbazone with 30% sulphuric acid and converted into an *oxime* which was identical with the oxime of the ketone prepared from *iso*anethole. The identity of the ketones was also confirmed by their oxidation with sodium hypobromite to a bromo-acid which was probably α-3-*bromo-4-methoxyphenyl-*n*-butyric acid* (IX).

(VII.)



(VIII.)



(IX.)

EXPERIMENTAL.

iso*Anethole.*—Anethole (50 g.) and 5*N*-methyl-alcoholic hydrogen chloride (250 c.c.) were heated under reflux. The colour changed from orange to purple and an oil rapidly separated. After 12 hours, most of the alcohol was removed and the residue was diluted with water and extracted with ether. The extract was washed with dilute sodium hydroxide solution, dried with potassium carbonate, and distilled under reduced pressure; a viscous, pale yellow oil (45 g.), b. p. 205—210°/0·7 mm., was obtained (Found: C, 81·0; H, 8·3; *M*, 288. Calc. for $C_{20}H_{24}O_2$: C, 81·0; H, 8·1%; *M*, 296).

Oxidation. A slight excess of finely powdered potassium permanganate was added to a stirred, cooled solution of *iso*anethole (25 g.) in acetone (500 c.c.), to which solid sodium bicarbonate (25 g.) was then added. The liquid was filtered, the residue extracted several times with boiling water, and the extract concentrated and acidified; anisic acid (11 g.) was precipitated, m. p. 180° after crystallisation from dilute acetic acid. The acetone filtrate was evaporated, and the residual oil distilled in a vacuum; a colourless oil (13 g.), b. p. 120—125°/0·5 mm., was obtained (Found: C, 74·9; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). This ketone, *α-*p*-methoxyphenyl-*n*-propyl methyl ketone* (V), which had a faint odour resembling that of liquorice, gave a *semicarbazone* which crystallised from ethyl alcohol in rhombic plates, m. p. 189° (Found: C, 62·4; H, 7·8. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·6%). The *oxime* separated from aqueous ethyl alcohol in colourless prisms, m. p. 84—85° (Found: C, 69·6; H, 8·4. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2%).

Ethyl p*-Methoxybenzylacetoacetate.*—*p*-Methoxybenzyl bromide (40 g.) was gradually added to a cold suspension of ethyl sodioacetoacetate (from pulverised sodium, 4·6 g., and ethyl acetoacetate, 26 g.) in dry benzene (100 c.c.) and after 12 hours the mixture was refluxed for 1 hour and treated with water. The benzene layer was dried with calcium chloride, the solvent removed, and the residue distilled in a good vacuum; a colourless oil (27 g.), b. p. 165—170°/0·2 mm., was collected and redistilled at 172°/0·25 mm. (Found: C, 67·0; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). A higher-boiling fraction (A) contained ethyl di-*p*-methoxybenzylacetoacetate, which was hydrolysed as described below.

p*-Methoxybenzylacetone* was prepared by boiling the above ester (5 g.) with 10% potassium hydroxide solution (125 c.c.) for 3 hours. The ketone was extracted with ether, dried, and distilled, giving a colourless oil (3·5 g.), b. p. 177°/25 mm. (Found: C, 74·0; H, 7·8. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%). The *semicarbazone* crystallised from methyl alcohol, in which it was sparingly soluble, in irregular prisms, m. p. 172—173° (Found: C, 61·3; H, 7·4. $C_{12}H_{17}O_2N_3$ requires C, 61·3; H, 7·2%). The *oxime* separated from aqueous ethyl alcohol in slender felted needles, m. p. 77° (Found: C, 68·4; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%).

*Di-*p*-methoxybenzylacetone* was obtained by boiling the high-boiling fraction (A) with 10% potassium hydroxide solution for 6 hours. The ketone was extracted with ether and dried, and the solvent removed. The residue, which solidified on cooling, crystallised from ether in feathery needles, m. p. 96—97° (Found: C, 76·6; H, 7·3. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·3%).

Ethyl p*-Methoxybenzylmethylacetoacetate* (VI).—Ethyl *p*-methoxybenzylacetoacetate (10 g.) was added to a solution of sodium (1 g.) in dry methyl alcohol (20 c.c.) and refluxed with methyl iodide (6·2 g.) for 12 hours. The mixture was then dried, the solvent removed, and the residue distilled in a good vacuum; a colourless oil (7 g.), b. p. 180°/0·5 mm., was obtained (Found: C, 68·0; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

*α-*p*-Methoxybenzylethyl methyl ketone* (IV) was obtained as a colourless oil, b. p. 175°/20 mm., by hydrolysing the above ester (VI) with 10% potassium hydroxide (Found: C, 74·8; H, 8·4.

$C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The *semicarbazone* separated from ethyl alcohol, in which it was moderately easily soluble, in small irregular plates, m. p. 135° (Found: C, 62·6; H, 7·8. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·6%); a mixture of it and the semicarbazone of the ketone obtained from *iso*anethole melted at 120—135°. The oxime was obtained as an oil.

p-*Hydroxyphenylacetonitrile*.—This was prepared from phenylacetonitrile as described in Cohen's "Practical Organic Chemistry," 3rd edition, 1924, p. 356, with the following modification in the reduction of *p*-nitro- to *p*-amino-phenylacetonitrile: *p*-Nitrophenylacetonitrile (100 g.), zinc dust (120 g.), and methylated spirits (100 c.c.) were stirred during the gradual addition of dilute sulphuric acid until most of the zinc had dissolved. The liquid was filtered, the residue thoroughly extracted with hot water, and the combined extracts and filtrate made strongly alkaline with ammonia and extracted with chloroform. The extract was dried, and the solvent removed; the residue (45—50 g.), consisting of *p*-aminophenylacetonitrile, was used without further purification for conversion into *p*-hydroxyphenylacetonitrile.

p-Methoxyphenylacetonitrile was prepared by gradually adding methyl sulphate (12·6 g.) to a solution of *p*-hydroxyphenylacetonitrile (13 g.) in 10% methyl-alcoholic potassium hydroxide (50 c.c.). After 12 hours, the mixture was diluted with water and extracted with ether and the *p*-methoxyphenylacetonitrile was distilled, a colourless oil (12 g.), b. p. 170°, being obtained.

p-Methoxyphenylacetonitrile was heated with sodamide and ethyl iodide in ethereal or benzene solution, but *p*-methoxyphenylacetic acid, m. p. 86°, was the only crystalline substance isolated after hydrolysis.

Benzylidene-p-*methoxyphenylacetonitrile*, prepared by the action of a few drops of methyl-alcoholic potassium hydroxide on an equimolecular mixture of benzaldehyde and *p*-methoxyphenylacetonitrile, crystallised from ethyl alcohol in colourless plates, m. p. 96° (Found: N, 5·7. $C_{16}H_{13}ON$ requires N, 5·7%).

Acetyl-p-*methoxyphenylacetonitrile* (VII).—*p*-Methoxyphenylacetonitrile (6 g.) in a solution of sodium (1·2 g.) in absolute ethyl alcohol (16 c.c.) was refluxed with ethyl acetate (5·3 g.) for 3 hours. The mixture was poured into water and after acidification with dilute sulphuric acid the solid was collected and crystallised from aqueous ethyl alcohol; pale yellow needles (7 g.), m. p. 80°, were obtained (Found: C, 70·0; H, 6·1. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%). Several attempts were made to condense this nitrile with ethyl iodide in the presence of sodium ethoxide, but the product isolated after hydrolysis was *p*-methoxybenzyl methyl ketone, which was identified by means of its semicarbazone (see below).

p-*Methoxybenzyl methyl ketone* was prepared by refluxing acetyl-*p*-methoxyphenylacetonitrile with 5 vols. of 50% sulphuric acid for 12 hours. The mixture was extracted with ether and traces of acid were removed from the extract by washing it with dilute sodium hydroxide solution. After drying and removal of the ether, the residue was distilled; a colourless oil, b. p. 150°/20 mm., was obtained (Found: C, 73·0; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·3%). The *semicarbazone* crystallised from ethyl alcohol in small prisms, m. p. 173° (Found: C, 59·9; H, 6·9. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8%).

α-p-*Methoxyphenyl*-n-*propyl Methyl Ketone* (V).—*p*-Methoxybenzyl methyl ketone (5 g.) in a solution of sodium (0·86 g.) in ethyl alcohol (25 c.c.) was refluxed with ethyl iodide (5 g.) for 12 hours. The mixture was poured into water and extracted with ether. The residue, b. p. 145—152°/20 mm., obtained after evaporation of the dried solvent was converted into the semicarbazone, m. p. 173—182°. After several recrystallisations from ethyl alcohol, this melted at 189°, alone and when mixed with the semicarbazone of the ketone prepared from *iso*anethole. The pure semicarbazone, m. p. 189°, was boiled with 30% sulphuric acid for 6 hours and the α-*p*-methoxyphenyl-*n*-propyl methyl ketone (V) produced was distilled in steam, extracted, and distilled. It boiled at 125—128°/0·7 mm. and yielded an oxime, m. p. 84—85°, which was identical with the oxime described on p. 2485.

α-3-*Bromo*-4-*methoxyphenyl*-n-*butyric Acid* (IX).—The ketone (V) (5 g.) was shaken for 24 hours with a solution of bromine (18 g.) in 5% aqueous sodium hydroxide (180 c.c.). Non-acidic impurities were extracted with ether, the aqueous layer was saturated with sulphur dioxide, and the acid extracted with ether. The extract was dried and concentrated and the residue, which solidified on cooling, was crystallised from ether–light petroleum (b. p. 40—60°); colourless prisms, m. p. 123—125°, were obtained (Found: C, 47·9; H, 4·9. $C_{11}H_{13}O_3Br$ requires C, 48·3; H, 4·8%).

If the amount of oxidising agent is reduced, a large quantity of unchanged ketone (V) is recovered. The bromo-acid (IX) was recovered after refluxing with 10% sodium hydroxide solution for 3 hours.

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[*Received, September 25th,* 1930.]