199. *The Structure of Metanethole.*

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Metanethole, the crystalline dimeride of anethole, is readily prepared in 24% yield by heating anethole with 43% sulphuric acid, *iso*anethole, the liquid dimeride of anethole, being produced simultaneously in 70% yield. Metanethole is also formed by treating *iso*anethole with stannic chloride in chloroform, and is degraded to 2-anisoylanisic acid by chromic acid. It must, therefore, be the hydrindene derivative (V).

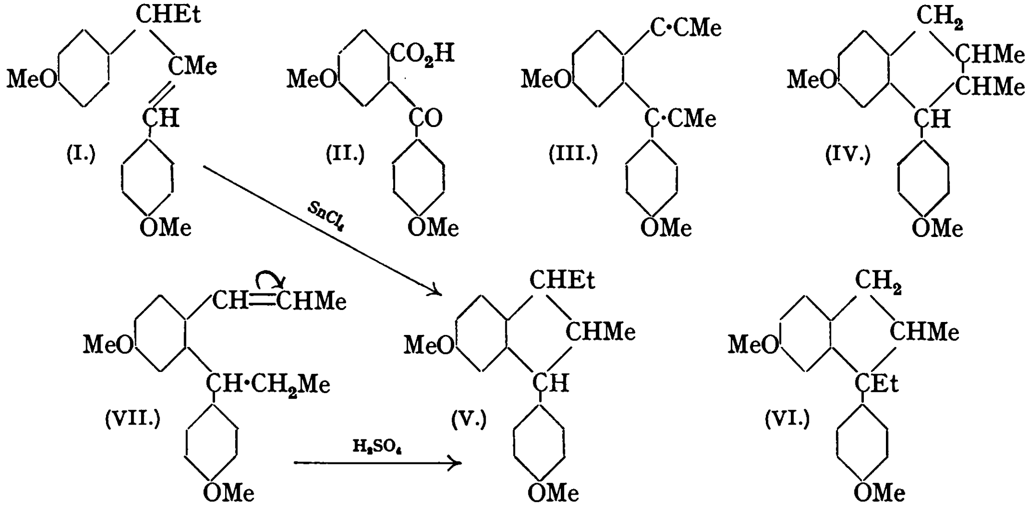
Two dimeric forms of anethole are known. The unsaturated, liquid *iso*anethole has the structure (I) (Goodall and Haworth, J., 1930, 2482), but very little is recorded about the crystalline dimeride, metanethole, which has hitherto been available only in small quantity. It is possible that the substance "photoanethoïl", m. p. 207°, prepared by De Varda (*Gazzetta*, 1891, **21**, 183) in 0·5% yield by exposing anethole to sunlight, is a dimeric anethole, and may be a *cyclo*butane derivative.

Metanethole was first prepared by Gerhardt (*J. pr. Chem.*, 1845, **36**, 273) by the action of stannic chloride or antimony trichloride on anethoïl. It was stated to melt above 100°, and its analysis agreed with the formula $C_{10}H_{12}O$.

Perrenoud (*Annalen*, 1877, **187**, 68) prepared metanethole, m. p. 132°, in 5·5—10% yield by heating anethole with anhydrous zinc chloride; analysis established the empirical formula $C_{10}H_{12}O$, and the author mentions a nitro-derivative, a bromo-substitution product (neither described), and a sulphonic acid convertible into a sulphonyl chloride. Chromic acid oxidation yielded only acetic acid. Grimaux (*Bull. Soc. chim.*, 1896, **15**, 778) isolated a trace of metanethole from the product obtained by distilling anethole saturated with hydrogen chloride. Orndorff, Terasse, and Morton (*Amer. Chem. J.*, 1897, **19**, 860) prepared it in 6·7% yield by Perrenoud's method; they record m. p. 133—133·5°, proved by analysis and molecular weight determination that it was a dimeric anethole, $C_{20}H_{24}O_2$, and, as it behaved as a saturated compound, suggested that it might be a *cyclo*butane derivative. Traces of metanethole were prepared by Puxeddu (*Gazzetta*, 1920, **50**, i, 149) by the action of anhydrous ferric chloride on an ethereal solution of anethole, and by Staudinger and Brunner (*Helv. Chim. Acta*, 1929, **12**, 972) by the action of stannic chloride on a solution of anethole in toluene at 100°. The most promising method (yield unstated) appeared to be that described by Glichitch (*Bull. Soc. chim.*, 1924, **35**, 1160), who boiled anethole with 90% formic acid; we have obtained only a 5% yield, however, under these conditions, but have raised the yield to 7% by using 80% formic acid for 1 hour; in either case the acid-free product was distilled in a vacuum, and the metanethole separated from the *iso*anethole by the addition of alcohol to the lower-boiling fraction.

We have now found that metanethole is available very simply from anethole in 24% yield by refluxing with 43% sulphuric acid with vigorous mechanical stirring, and is readily separated from the *iso*anethole produced simultaneously in some 70% yield by taking advantage of the fact that, whilst *iso*anethole is totally miscible with alcohol, the solubility of metanethole is only 0·09 g. in 100 g. of alcohol at 15°. *iso*Anethole, which forms no simple crystalline derivative, is best characterised by catalytic reduction to dihydro*iso*anethole, followed by demethylation with hydrobromic acid in acetic acid to the crystalline 1 : 3-di-*p*-hydroxyphenyl-2-methyl-*n*-pentane (cf. Campbell, Dodds, and Lawson, *Proc. Roy. Soc.*, 1940, *B*, **128**, 253). Metanethole and *iso*anethole are produced in almost similar proportions by the action of 43% sulphuric acid upon *p*-methoxy-α-methylcinnamic acid, the mechanism of the reaction being undoubtedly decarboxylation to anthole (see Perkin, J., 1877, **31**, 411; Moureu and Chauvet, *Compt. rend.*, 1897, **124**, 404), followed by dimerisation.

Metanethole readily yields crystalline *dibromo*- and *dinitro*-derivatives, and is demethylated by hydrobromic acid in acetic acid to the dihydric phenol, which may be termed "*metanethol*". Treatment of metanethol with alkali and methyl sulphate regenerates metanethole. Metanethole proved remarkably resistant towards oxidation with potassium permanganate, but dinitrometanethole was attacked, yielding 3-nitroanisic acid, and a smaller quantity of another acid, whose formation was capricious and which was not subjected to detailed examination. There can, however, be little doubt that this second acid is 5(or 3)-*nitro*-2-(3'-*nitroanisoyl*)*anisic acid*. Chromic acid in acetic acid readily attacks metanethole, giving anisic acid under vigorous conditions, but under milder conditions a 24% yield of 2-*anisoylanisic acid* (II) is obtained, thus proving the presence of the partial structure (III). It is assumed that the propenyl group of anethole does not undergo isomeric change to the allyl group; such a reaction is unknown, and is extremely unlikely in view of the ease with which the reverse reaction occurs. The formation of 2-anisoylanisic acid excludes the possibility of metanethole being a dimethoxy-9 : 10-diethyl-9 : 10-dihydroanthracene (cf. structure of di*iso*eugenol; Haworth and Mavin, J., 1931, 1363), since, although it possesses the necessary carbon skeleton, such compounds do not in fact yield 2-aroylbenzoic acids on oxidation, nor could they be expected to do so. A specimen of 2-anisoylanisic acid was prepared synthetically from 4-methoxyphthalic anhydride and anisole, and proved identical with that prepared by the degradation of metanethole. The formation of this acid and not the other possible isomeride, 2-anisoyl-5-methoxybenzoic acid, was expected on theoretical grounds; it may be noted that the latter acid could not arise by the degradation of any possible dimeride of anethole.



The partial structure (III) leads to three possible formulæ for metanethole, (IV), (V), and (VI). The tetrahydronaphthalene structure (IV) is attractive owing to its relation to the natural lignans, but it involves the $\beta\beta'$-linking of the side chains, a type of reaction which, we believe, has not yet been observed *in vitro* (it may be noted that the $\alpha\alpha'$-linking of side chains occurs in the formation of traces of 4 : 4'-dihydroxy-$\gamma\delta$-diphenyl-*n*-hexane during the demethylation of anethole; see Campbell, Dodds, and Lawson, *loc. cit.*). Moreover we have been unable to dehydrogenate metanethole to a naphthalene derivative by the use of sulphur, palladised charcoal, Hübl's iodine solution (see Schroeter, Lichtenstadt, and Irineu, *Ber.*, 1918, **51**, 1609), lead tetra-acetate (see Erdtmann, *Annalen*, 1934, **513**, 238), or an eccess of bromine, and this fact, coupled with further evidence given below, enables formula (IV) to be rejected.

Both the hydrindene structures (V) and (VI) are equally probable in so far as they involve the $\alpha\beta'$-linking of the side chains as in *iso*anethole (I) and the polymeric forms of styrene, etc., but it is doubtful if (VI) would easily yield 2-anisoylanisic acid on oxidation, whereas (V) would readily give this acid. Formula (V), as distinct from (VI), further represents a molecule which might be derived by a simple process of ring-closure from *iso*anethole (I). Attempts were, therefore, made to convert *iso*anethole into metanethole; this is not brought about either by the action of methyl-alcoholic hydrogen chloride (usual method of preparing *iso*anethole from anethole, whereby no metanethole is produced), or by boiling with 43% sulphuric acid, since in the simultaneous preparation of metanethole and *iso*anethole described in this paper the yield of metanethole rises to a maximum of 24%, and no further metanethole is produced however long the experiment is continued. It has now been found that a 10% yield of metanethole can be obtained from *iso*anethole by treatment in chloroform solution with stannic chloride, conditions which convert anethole into high molecular weight polymers without the formation of metanethole. Hence a direct conversion of *iso*anethole into metanethole must have occurred without preliminary depolymerisation to anethole, thus proving that the two substances possess the same arrangement of the side-chain carbon atoms, and, therefore, excluding formula (IV). Two reasons for preferring (V) to (VI) have already been given, but a further reason is the following. In the conversion of anethole into metanethole and *iso*anethole by sulphuric acid, the former does not arise from the latter, but probably from the intermediate (VII), and in the subsequent ring closure to metanethole that required by formula (VI) involves the unlikely addition of a proton to the more weakly anionoid of the two ethylenic carbon atoms, whereas ring closure to formula (V) is in accordance with theoretical expectations. We, therefore, conclude that metanethole must be one of the four possible racemic forms of structure (V), which contains three dissimilar asymmetrical carbon atoms, and is *6-methoxy-1-p-methoxyphenyl-2-methyl-3-ethylhydrindene.* Liquid stereoisomerides of (V) are probably produced simultaneously with metanethole by the action of stannic chloride upon *iso*anethole (see experimental section).

The structure now assigned to metanethole has a bearing on the structure of " methronol ", a saturated liquid hydrocarbon, $C_{18}H_{20}$, prepared by Erdmann (*Annalen*, 1885, **227**, 249) by boiling α-methylcinnamic acid with dilute sulphuric acid. " Methronol " gave *o*-benzoylbenzoic acid on oxidation with chromic acid, and structures corresponding to formulæ (IV) and (V) were considered. Of these, Erdmann preferred to regard it as 1-phenyl-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene, but it is much more probable that " methronol " is 1-phenyl-2-methyl-3-ethylhydrindene, corresponding to structure (V) for metanethole.

EXPERIMENTAL.

Metanethole (V) *and* iso*Anethole* (I).—(a) *From anethole.* A mixture of anethole (100 g.), water (600 c.c.), and concentrated sulphuric acid (250 c.c.) was boiled under reflux on a sand-bath with vigorous mechanical stirring for 7 hours (the odour of anethole had then disappeared, and the top organic layer, on cooling, became semi-solid with metanethole). While hot, the lower acid layer was carefully syphoned off, the top layer heated on the water-bath with alcohol (400 c.c.) and thoroughly cooled, and after several hours the colourless, crystalline metanethole collected, washed with cold alcohol, and dried (yield, 24 g.). This product was almost pure, and had m. p. 131—132° (Found in material crystallised several times from alcohol, m. p. 134° : C, 80·8; H, 8·3. Calc. for $C_{20}H_{24}O_2$: C 81·0; H, 8·1%).

After the addition of water (200 c.c.) the alcohol was distilled from the filtrate and washings under slightly diminished pressure, and the residual mixture made alkaline with sodium hydroxide and extracted with carbon tetrachloride. The extracts were dried and distilled, finally under diminished pressure. The following fractions were collected : (1) b. p. up to 190°/0·1 mm. (3·5 g.); this contained a little anethole and a trace of metanethole which crystallised on the addition of alcohol; (2) b. p. 190—200°/0·1 mm. (62 g.); nearly all this fraction boiled at 192—193°/0·1 mm. and consisted of almost pure *iso*anethole, which, however, deposited a trace of crystalline metanethole on long standing; (3) b. p. 200—220°/0·1 mm. (6 g.), mainly *iso*anethole; the residue (4 g.) was dark brown and very viscous. Redistillation of fraction (2) gave pure *iso*anethole as a faintly yellow oil, b. p. 192—193°/0·1 mm., $n_D^{20°}$ 1·5867 (Found : C, 81·0; H, 8·1. Calc. for $C_{20}H_{24}O_2$: C, 81·0 ; H, 8·1%). A specimen of *iso*anethole prepared by the method of Goodall and Haworth (*loc. cit.*) had b. p. 192—193°/0·1 mm., $n_D^{20°}$ 1·5863. The product was further recognised as *iso*anethole by oxidation with potassium permanganate in acetone, giving anisic acid and α-*p*-methoxyphenyl-*n*-propyl methyl ketone (semicarbazone, m. p. 189°; oxime, m. p. 84°; anisylidene derivative, m. p. 76°—Campbell, Dodds, and Lawson, *loc. cit.*) in the proportions recorded by Goodall and Haworth.

(b) *From* p-*methoxy-α-methylcinnamic acid.* A mixture of the acid (10 g.), water (60 c.c.), and concentrated sulphuric acid (25 c.c.) was vigorously stirred at the b. p. for 16 hours, giving a semi-solid product resembling that obtained under (a). Its solution in carbon tetrachloride yielded the unchanged acid (1 g.) to aqueous sodium carbonate; removal of the solvent and addition of alcohol gave metanethole (2 g.), and distillation of the filtrate gave *iso*anethole (4 g.).

1 : 3-*Di*-p-*hydroxyphenyl*-2-*methyl*-1-*ethylpropane*.—*iso*Anethole prepared as described above was reduced to the dihydro-compound with hydrogen in presence of a palladium–strontium carbonate catalyst (Campbell, Dodds, and Lawson). The dihydro*iso*anethole, b. p. 187—188°/0·06 mm. (lit., b. p. 167°/0·08—0·09 mm.) (5 g.) was refluxed for 8 hours with acetic acid (20 c.c.) and hydrobromic acid (20 c.c.; *d* 1·5), the mixture diluted and extracted with ether, the extracts shaken with aqueous sodium bicarbonate and then with sodium hydroxide solution, and the latter solution acidified and extracted with ether. The extract yielded an oil which solidified in contact with chloroform, and separated from the same solvent as a crystalline powder, m. p. 126—127° (Campbell, Dodds, and Lawson record m. p. 128° for the product crystallised from *cyclo*hexane).

Dibromometanethole.—Metanethole (3 g.), suspended in glacial acetic acid (20 c.c.), when treated at room temperature with a solution of bromine (4 g.) in acetic acid (40 c.c.), rapidly dissolved. After standing overnight, the crystalline *dibromometanethole* was collected (3·4 g.) and washed with and crystallised from acetic acid, from which it separated in colourless, quartz-like prisms, m. p. 135° (Found: C, 52·6; H, 4·8; Br, 32·1. $C_{20}H_{22}O_2Br_2$ requires C, 52·8; H, 4·9; Br, 35·2%). A further small quantity of the compound was obtained by diluting the first acetic acid filtrate.

Metanethol.—Pure metanethole (2 g.) was refluxed (oil-bath for 4½ hours) with acetic acid (20 c.c.) and hydrobromic acid (12 c.c.; *d* 1·5), the mixture poured into water, and the solid collected and washed. It separated from dilute alcohol in thin, colourless, prismatic needles containing water of crystallisation, m. p. *ca.* 83°, but was best crystallised from light petroleum (b. p. 100—120°), from which it separated in the anhydrous form, m. p. 156—157° (Found: C, 80·3; H, 7·4. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·4%). The *compound* is difficult to purify, and loss of crystalline material always occurs during recrystallisation; the m. p. is, moreover, greatly lowered if the compound is not completely dry.

Dinitrometanethole.—Metanethole (5 g.) was dissolved in hot glacial acetic acid (75 c.c.), the solution cooled rapidly to obtain a fine crystalline suspension, and concentrated nitric acid (25 c.c.; *d* 1·42) added. The metanethole dissolved (½ hour) to an orange solution, and, after standing overnight, the crystalline product (3·5 g.) was collected, washed with cold acetic acid, and crystallised from hot alcohol (600 c.c.). *Dinitrometanethole* separated in pale yellow, fern-like, crystalline growths, m. p. 190° (Found: C, 62·1; H, 5·8; N, 7·3. $C_{20}H_{22}O_6N_2$ requires C, 62·2; H, 5·7; N, 7·2%).

Oxidation of Dinitrometanethole to 3-*Nitroanisic Acid and* 5(or 3)-*Nitro*-2-(3′-*nitroanisoyl*)-*anisic Acid*.—Dinitrometanethole (3·2 g.) was dissolved on the water-bath in a mixture of acetic acid (250 c.c.) and water (50 c.c.), and oxidised by the addition, in portions of several grams, of powdered potassium permanganate (50 g.), the heat of the reaction being sufficient to keep the solution gently boiling without further heating. The reaction mixture was cooled, diluted, acidified with sulphuric acid, and, after sulphur dioxide had been passed in slight excess, extracted twice with warm ethyl acetate. The ethyl acetate solution was shaken with water, and then with successive small quantities of dilute sodium hydroxide solution until a yellow aqueous alkaline layer was obtained. On acidification this deposited a crystalline product (0·28 g.), which largely dissolved in boiling water; the hot filtered solution after treatment with charcoal deposited 3-nitroanisic acid in small crystals, m. p. 187°; the mixed m. p. with authentic 3-nitroanisic acid (m. p. 188—189°) was 187—189°. The water-insoluble *acid*, the amount of which varied considerably in different experiments, separated from dilute alcohol in bunches of minute needles, m. p. 221—222° (Found: C, 50·2; H, 3·5; N, 7·7. $C_{16}H_{12}O_9N_2$ requires C, 51·1; H, 3·2; N, 7·4%).

Oxidation of Metanethole to 2-*Anisoylanisic Acid* (II) *and Anisic Acid*.—Metanethole (4 g.), suspended in acetic acid (40 c.c.) containing concentrated sulphuric acid (8 c.c.), was oxidised by the addition in portions of a solution of chromic acid (10 g.) in acetic acid (50 c.c.) and water (4 c.c.), the temperature being kept at about 40° by occasional cooling. After dilution, the solution was extracted twice with warm ethyl acetate, and the extracts shaken with water and then with aqueous sodium hydroxide; the alkaline layer yielded a pale brown, crystalline acid, which was washed and dried (0·75 g.), and crystallised twice from 50% alcohol (charcoal). 2-*Anisoylanisic acid* separated in faintly brownish, fern-like crystals, m. p. 208° (Found: C, 67·1; H, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The m. p. was not depressed on admixture with 2-anisoylanisic acid synthesised as described below. The ethyl acetate layer, when distilled and treated with alcohol, gave unchanged metanethole (0·8 g.), and the motherliquors contained a trace of a bright yellow organic substance which could not be isolated. More vigorous oxidation of metanethole with a large excess of chromic acid at the b. p. of acetic acid gave anisic acid, m. p. and mixed m. p. 180—181°.

2-Anisoylanisic Acid.—A mixture of 4-methoxyphthalic anhydride (3·2 g.), anisole (13 g.), and powdered anhydrous aluminium chloride (4 g.) was heated at 80° for 4 hours, the mixture poured into dilute hydrochloric acid and ice, and the insoluble material collected and treated with sodium carbonate solution. The alkaline filtrate yielded a solid product on acidification, from which the 4-methoxyphthalic acid was removed by conversion into the anhydride by heating for ½ hour at 170° and extraction with hot benzene, in which the anhydride was readily soluble but the 2-anisoylanisic acid was insoluble. The colourless residue was crystallised from 50% alcohol, giving 2-anisoylanisic acid, m. p. and mixed m. p. 207—208°.

Conversion of iso*Anethole into Metanethole.*—To a solution of *iso*anethole (5 g.) in chloroform (10 c.c.), anhydrous stannic chloride (2 g.) was added; the red solution was kept for 2 hours at 25° and then shaken with dilute hydrochloric acid. The chloroform layer was washed with aqueous sodium hydroxide, dried, and distilled, leaving a pale yellow oil, which was dissolved in warm alcohol (50 c.c.) and kept overnight at 0°. Metanethole (0·5 g.; m. p. *ca.* 128°) crystallised, and was obtained pure after one recrystallisation from alcohol. If the reaction is continued for a longer period, the thick oily product obtained after removal of the metanethole is incompletely soluble in alcohol, and probably contains stereoisomerides of metanethole.

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