826. *Structural and Stereochemical Correlation of Metanethole with Other Dimerides of Aryl Propenyl Compounds.*

By Wilson Baker, C. N. Haksar, J. F. W. McOmie, and T. L. V. Ulbricht.

Metanethole (II) reacts with acetyl chloride and aluminium chloride to give a dihydroxy-diketone (IV), which is oxidised by alkaline hydrogen peroxide to a tetrahydric phenol (III; R = R′ = H). Methylation of the latter gives the known dimeride of *iso*eugenol methyl ether (III; R = R′ = Me). The saturated dimerides of 4-methoxy-, 4-hydroxy-3-methoxy-, 3 : 4-dimethoxy-, 4-ethoxy-3-methoxy-, 3 : 4-dibenzyloxy-, and (probably) 3-hydroxy-4-methoxy- and 3 : 4-methylenedioxy-propenylbenzenes are all now known to be derived from the one stereoisomeride of 1-ethyl-2-methyl-3-phenylindane.

Aromatic propenyl compounds, *e.g.*, anethole, *p*-MeO·C_6H_4·CH:CHMe, sometimes occur naturally, but are usually obtained from the allyl isomerides, *e.g.*, eugenol and safrole, by treatment with alkali. They give stable dimerides under the influence of acid reagents, and the first of these substances whose structure was established was an unsaturated dimeride of anethole, *iso*anethole, which was proved by Goodall and Haworth (*J.*, 1930, 2482) to possess structure (I); *cis*- and *trans*-forms of *iso*anethole have been obtained by Baker and Flemons (*J.*, 1948, 1984). Pailer (*Monatsh.*, 1947, **77**, 45) showed that a dimeric liquid form of *iso*safrole (3 : 4-methylenedioxypropenylbenzene) possesses a structure similar to that of *iso*anethole (I).

The more commonly formed dimeric propenyl compounds are saturated, *e.g.*, metanethole, di*iso*eugenol, and the dimeride of *iso*eugenol methyl ether, and these substances were for long thought to be derivatives of either *cyclo*butane or 9 : 10-dihydroanthracene.* It was shown first by Baker and Enderby (*J.*, 1940, 1094) that metanethole was, beyond reasonable doubt, 1-ethyl-5-methoxy-2-methyl-3-*p*-methoxyphenylindane (II), and subsequent investigations mainly by A. Müller and his collaborators (*Ber.*, 1942, **75**, 692, 891; 1943, **76**, 855, 1061, 1119; 1944, **77**, 6, 12, 159, 325, 343; *J. Org. Chem.*, 1947, **12**, 815; 1951, **16**, 481, 1003; van der Zanden and de Vries, *Rec. Trav. chim.*, 1949, **68**, 261, 407) have provided additional evidence of the accuracy of this formula. Attempted stepwise

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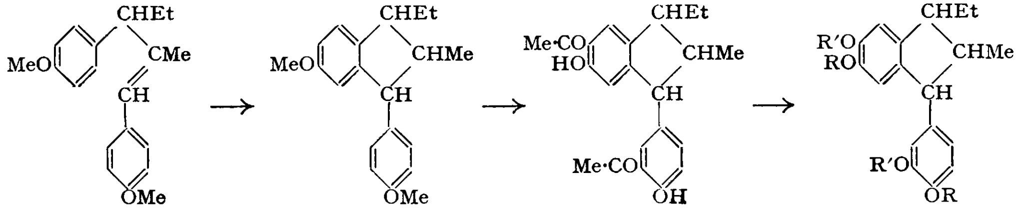
* The only established case of this type appears to be 9 : 10-diethyl-9 : 10-dihydro-2 : 3 : 6 : 7-tetramethoxyanthracene obtained in 0·07% yield by dimerisation of *iso*eugenol methyl ether (Pailer, *loc. cit.*).

synthesis of metanethole involving final catalytic reduction of 1-ethyl-5-methoxy-3-*p*-methoxyphenyl-2-methylindene gave a stereoisomer of (II) (four racemates are possible), m. p. 99° (metanethole, m. p. 135°) (van der Zanden and de Vries, *loc. cit.*; A. Müller, Toldy, Halmi, and Mészáros, *J. Org. Chem.*, 1951, **16**, 481), but reduction of the indene with sodium and ethanol gave metanethole itself, m. p. 134—134·5° (van der Zanden and de Vries, *Rec. Trav. chim.*, 1952, **71**, 733). The simultaneous production of *iso*anethole (I) and metanethole from the ketone $MeO{\cdot}C_6H_4{\cdot}CHEt{\cdot}CHMe{\cdot}CO{\cdot}C_6H_4{\cdot}OMe$ by treatment with aluminium *iso*propoxide (A. Müller, Toldy, Halmi, and Mészáros, *loc. cit.*) does not provide proof of the structure of metanethole, as it may have been formed *via iso*anethole; the change *iso*anethole to metanethole has been effected by stannic chloride (Baker and Enderby, *loc. cit.*), aluminium chloride, and titanium tetrachloride (A. Müller, Mészáros, Lempert-Sréter, and Szára, *J. Org. Chem.*, 1951, **16**, 1003) and it may take place slowly at room temperature, probably under the influence of traces of acid (Polak and Hixon, *J. Amer. Pharm. Assoc.*, 1945, **34**, 240; Baker, unpublished observation). Again, the metanethole isolated from a species of sponge by Bergmann and McAleer (*J. Amer. Chem. Soc.*, 1951, **73**, 4969) may be an artifact derived from anethole.

Di*iso*eugenol and its dimethyl ether (di*iso*homogenol) are now known to be phenylindanes (III; R = H, R′ = Me; and R = R′ = Me, respectively) analogous to metanethole (A. Müller and Horváth, *Ber.*, 1943, **76**, 855; Cartwright and Haworth, *J.*, 1947, 1094; von Doering and Berson, *J. Amer. Chem. Soc.*, 1950, **72**, 1118), the identity of the fundamental structures being proved by the fact that the dimethyl ether of di*iso*eugenol is identical with the dimeride of *iso*eugenol methyl ether (Haworth and Mavin, *J.*, 1931, 1363; Kovács, *J. Org. Chem.*, 1950, **15**, 15). The same structure (III; $RR' = CH_2$) has been established beyond reasonable doubt by Pailer (*loc. cit.*; Pailer, U. Müller, and Porschinski, *Monatsh.*, 1948, **79**, 620) for the solid dimerides of *iso*safrole [m. p.s 95° and 146°; these are possibly dimorphic forms as the former was stated to be converted into the latter at 150° (Mayer, *Atti R. Accad. Lincei*, 1914, **231**, 358), although we have been unable to confirm this observation], and Pailer, U. Müller, and Porschinski (*loc. cit.*) have also obtained a partial correlation between the di*iso*safrole, m. p. 146°, and di*iso*eugenol dimethyl ether by degrading them both to the same 1-ethyl-5 : 6-dihydroxy-2-methylindane. Moreover, we have been able to oxidise the lower-melting di*iso*safrole to 2-methyl-5 : 6-methylenedioxy-3-(3 : 4-methylenedioxyphenyl)inden-1-one, a compound previously obtained (Pailer, Müller, and Porschinski, *loc. cit.*) by similar oxidation of the higher-melting di*iso*safrole, thus providing strong evidence that the two di*iso*safroles are either dimorphic or stereoisomeric forms. Stepwise syntheses of the indane (III; R = R′ = Me) (by A. Müller and Gál, *Ber.*, 1944, **77**, 343; A. Müller, Toldy, Halmi, and Mészáros, *loc. cit.*; Cartwright and Haworth, *J.*, 1947, 948; Horning and Parker, *J. Amer. Chem. Soc.*, 1952, **74**, 3870) gave products differing slightly in melting point from di*iso*eugenol dimethyl ether, of which they were regarded as stereoisomerides (mixed m.p.s showed depressions).



(I) (II) (IV) (III)

It is probable that dimerisation of aryl propenyl derivatives to give saturated compounds will give in all cases the same stereoisomeride of 1-ethyl-2-methyl-3-phenylindane (as II) bearing the appropriate nuclear substituents. It therefore became of importance to attempt the conversion of metanethole (II) into di*iso*eugenol dimethyl ether (dimeride of eugenol methyl ether; di*iso*homogenol) (III; R = R′ = Me) by introducing two methoxyl groups into the molecule, and this has now been achieved in the following manner.

Metanethole reacted with acetyl chloride in ether in presence of a very large excess of aluminium chloride (conditions critical) to give a diphenolic diketone, 6-acetyl-3-(3-acetyl-4-hydroxyphenyl)-1-ethyl-5-hydroxy-2-methylindane (IV) arising by a double Friedel–Crafts reaction and simultaneous demethylation (cf. reaction of acetyl chloride–ether upon 1 : 2 : 3 : 5-tetramethoxybenzene and upon pentamethoxybenzene, Baker, *J.*, 1941, 662). When less aluminium chloride was used 6(?)-acetylmetanethole was isolated. Reaction of the diketone (IV) with alkaline hydrogen peroxide (Dakin reaction) gave the tetrahydric phenol, 1-ethyl-5 : 6-dihydroxy-3-(3 : 4-dihydroxyphenyl)-2-methylindane (III; R = R′ = H), which was easily oxidised and could not be successfully purified. When treated with methyl sulphate and alkali, this phenol gave its tetramethyl ether, 1-ethyl-5 : 6-dimethoxy-3-(3 : 4-dimethoxyphenyl)-2-methylindane (III; R = R′ = Me), m. p. 94—96°, undepressed when mixed with an authentic specimen of di*iso*eugenol dimethyl ether, m. p. 95—96°; the identity was further proved by *X*-ray powder photographs, which showed exact correspondence of all lines (over twenty) in both position and intensity. It has not previously been clearly recognised that this racemic di*iso*eugenol dimethyl ether is dimorphic. Slow crystallisation from methanol gives a product, m. p. 105-106°; the m. p. falls after several weeks to 95-96°, and this lower-melting form is also obtained by rapid crystallisation from concentrated solutions (see Experimental; A. Müller, Mészáros, Körmendy, and Kucsman, *J. Org. Chem.*, 1952, **17**, 787; Ciamician and Silber, *Atti R. Accad. Lincei*, 1909, **18**, 1216).

Attempts to extend this correlation to di*iso*safrole by small-scale methylenation of the tetrahydric phenol (III; R = R′ = H) derived from metanethole did not succeed. In order to render the tetrahydric phenol (III; R = R′ = H) more available we unsuccessfully attempted, under a variety of conditions, both the demethylation of di*iso*eugenol and the demethylenation of di*iso*safrole, and finally reinvestigated a substance, supposed to be (III; R = R′ = H) (Kovács, *loc. cit.*). Kovács dimerised 3 : 4-dibenzyloxypropenylbenzene by treating its dibromide with sodium iodide in acetone, and reduced the dimeride catalytically to remove the benzyl groups; the crude product (not obtained solid or analysed) was then treated with diazomethane, giving a substance (not analysed), m. p. 106°, which differed from di*iso*eugenol dimethyl ether, of which it was supposed to be a stereoisomeride. We find that the dimeride of 3 : 4-dibenzyloxypropenylbenzene has m. p. 104—105° (Kovács records m. p. 114—116°), and that catalytic reduction gives either (*a*) the uncharacterised tetrahydric phenol (III; R = R′ = H) which with diazomethane gives a dimorphic compound indistinguishable from di*iso*eugenol dimethyl ether, or (*b*) unchanged material and a product which has lost only two benzyl groups and which when methylated with diazomethane gives a dibenzyl dimethyl ether of (III; R = R′ = H), m. p. 103—105°, of unknown orientation. It is possible that Kovács's compound, m. p. 106° (above), may have been this dibenzyl dimethyl ether of (III; R = R′ = H).

Two further correlations between dimeric arylpropenyl compounds may be noted. (1) A. Müller, Toldy, Halmi, and Mészáros (*loc. cit.*) showed that the diethyl ether of di*iso*eugenol is identical with the dimeride of 4-ethoxy-3-methoxypropenylbenzene obtained from 4-ethoxy-3-methoxy-α-methylcinnamic acid by heating it with sulphuric acid (cf. *p*-methoxy-α-methylcinnamic acid which is similarly converted into metanethole and also *iso*anethole, Baker and Enderby, *loc. cit.*; these reactions undoubtedly proceed by loss of carbon dioxide followed by dimerisation of the propenyl compound). (2) The saturated dimeride of 3-hydroxy-4-methoxypropenylbenzene (*iso*chavibetol) gives a dimethyl ether which exists in two forms, m. p. 94—96° and 105·5—106·5° [Funakubo, Kawasaki, and Hoshimoto, *J. Chem. Soc. Japan*, 1941, **63**, 1555 (see *Chem. Abs.*, 1947, **41**, 3442)] and is without doubt identical with di*iso*eugenol methyl ether (also dimorphic, see above), although it is not known if mixed melting points were carried out.

To summarise, it has now been established (with possibility of slight doubt in cases marked with *) that the saturated dimerides of the following aryl propenyl compounds are all derived from the one stereoisomeride of 1-ethyl-2-methyl-3-phenylindane: 4-methoxypropenylbenzene (anethole), 3 : 4-dimethoxypropenylbenzene (*iso*eugenol methyl ether), and 3 : 4-dibenzyloxypropenylbenzene (this paper); 4-hydroxy-3-methoxypropenylbenzene (*iso*eugenol) (Haworth and Mavin; Kovács); 4-ethoxy-3-methoxypropenylbenzene

(A. Müller, Toldy, Halmi, and Mészáros); 3-hydroxy-4-methoxypropenylbenzene* (Funakubo, Kawasaki, and Hoshimoto); 3 : 4-methylenedioxypropenylbenzene* (*iso*safrole) (Pailer, U. Müller, and Porschinski). The parent substance, 1-ethyl-2-methyl-3-phenylindane, is with little doubt the compound " methronol " (for references, etc., see Baker and Enderby, *loc. cit.*) obtained by decarboxylation and dimerisation of α-methylcinnamic acid under the influence of sulphuric acid (see above); it yields benzoylbenzoic acid on oxidation.

Saturated dimerides of other arylethylene derivatives are, in addition, known to be substituted phenylindanes, *e.g.*, dimeric styrene (Spoerri and Rosen, *J. Amer. Chem. Soc.*, 1950, **72**, 4918) and dimeric *p*-*iso*propenyltoluene (Hukki, *Acta Chem. Scand.*, 1945, **3**, 279.) (for a summary of earlier work on dimerides of substituted ethylenes, see Bergmann and Weiss, *Annalen*, 1930, **480**, 49).

EXPERIMENTAL

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

6-Acetyl-3-(3-acetyl-4-hydroxyphenyl)-1-ethyl-5-hydroxy-2-methylindane (IV) *and 6(?)-Acetylmetanethole.*—Anhydrous ether (100 c.c.) was added slowly, with cooling in ice, to anhydrous aluminium chloride (137 g., 50 mols.). Metanethole (Baker and Enderby, *loc. cit.*) (6 g., 1 mol.) was then added in portions to the viscous solution followed by the dropwise addition of redistilled acetyl chloride (8·0 c.c., 5·6 mols.). After being stirred for 1 hour the mixture was heated at 50—60° for 2 hours, the dark red product poured into ice (400 g.) and concentrated hydrochloric acid (150 c.c.), and after being heated for 1 hour on the water-bath the liquid was extracted with ether (2 × 200 c.c.). The extracts (see * below) were shaken with 10% aqueous sodium hydroxide (100 c.c.), the alkaline layer acidified with dilute hydrochloric acid, and the liberated oil taken up in ether (200 c.c.). The dried ethereal extract yielded an oil which later solidified, and was crystallised 3 times from ethanol (charcoal). This *6-acetyl-3-(3-acetyl-4-hydroxyphenyl)-1-ethyl-5-hydroxy-2-methylindane* (IV) formed needles, m. p. 115—116° (1·0—2·5 g., 15—35%) (Found : C, 75·3; H, 6·9. $C_{22}H_{24}O_4$ requires C, 75·0 ; H, 6·8%). It gives a purple colour with alcoholic ferric chloride. The 2 : *4-dinitrophenylhydrazone* crystallised from ethanol–ethyl acetate in minute, red needles, m. p. 260° (decomp.) (Found : N, 15·5. $C_{34}H_{32}O_{10}N_8$ requires N, 15·7%).

The yield of the diketoindane (IV) is apt to vary considerably in this preparation. When the amount of aluminium chloride was reduced to 20 mols., a non-phenolic product was isolated from the ethereal solution (* above) as an oil which slowly solidified. This was crystallised three times from ethanol (charcoal), giving *6(?)-acetylmetanethole* as colourless needles, m. p. 122° (1·2 g.) (Found : C, 78·0; H, 7·6. $C_{22}H_{26}O_3$ requires C, 78·1; H, 7·7%). The 2 : *4-dinitrophenylhydrazone* separated from ethanol–ethyl acetate as an orange-red, microcrystalline powder, m. p. 225° (decomp.) (Found : N, 11·2. $C_{28}H_{30}O_6N_4$ requires N, 10·8%).

1-Ethyl-5 : 6-dihydroxy-3-(3 : 4-dihydroxyphenyl)-2-methylindane (III; R = R′ = H).—Aqueous hydrogen peroxide (3%; 30 c.c., 3 mols.) was added to a solution of the diketone (IV) (3 g.) in N-sodium hydroxide (67·5 c.c., 6 mols.) in an atmosphere of nitrogen. The temperature rose from 19° to 36° in ½ hour, and the yellow solution became deep red. After a further 2 hours, the mixture was kept at about 50° for 10 minutes, then cooled, and a little sodium dithionite (hydrosulphite) added to decolorise the solution, which was then poured into water (200 c.c.) and acidified with dilute sulphuric acid. After ½ hour, the solid was collected, washed, and dried (yield 2·4 g.; m. p. 90—105°). This tetrahydroxy-compound could not be satisfactorily recrystallised and did not yield a crystalline tetra-acetate.

*Diiso*eugenol *Dimethyl Ether* (III; R = R′ = Me).—(*a*) *From the tetrahydroxy-compound* (III; R = R′ = H). Aqueous sodium hydroxide (20%; 10 c.c., 6 mols.) was slowly added to a stirred solution of the crude tetrahydroxy-compound (2·4 g.) in methanol (15 c.c.) and methyl sulphate (5 c.c., *ca.* 7 mols.) in an atmosphere of nitrogen, and the vigorous reaction was moderated by cooling in water. Similar quantities of methyl sulphate and alkali were then added alternately in portions, and the mixture was finally heated on a water-bath for 3 hours. The solution, made slightly alkaline, was extracted with ether (200 c.c.), and the extract washed with water, dried (K_2CO_3), and distilled, leaving a brown oil which solidified. Crystallisation from methanol (charcoal) yielded di*iso*eugenol dimethyl ether as microcrystalline needles (0·12 g.), m. p. 85—90°, raised to 94—96° by 3 further crystallisations from methanol. A mixed m. p.

with an authentic specimen of di*iso*eugenol dimethyl ether (m. p. 95—96°) was undepressed, and with the polymorphic form (m. p. 105—106°; see next two paragraphs) the mixed m. p. was 103—104° (Found: C, 74·2; H, 7·7; OMe, 34·5. Calc. for $C_{22}H_{28}O_4$: C, 74·2; H, 7·9; OMe, 34·8%).

(*b*) *From di*iso*eugenol.* Methylation of di*iso*eugenol (Haworth and Mavin, *J.*, 1931, 1364) with methyl sulphate and sodium hydroxide gave, after crystallisation from methanol, di*iso*eugenol dimethyl ether, m. p. 105—106°. After several weeks the material had m. p. 95—96°. Slow recrystallisation from a dilute solution in methanol gave the higher-melting form, whereas concentrated solutions deposited the lower-melting form; thus the two forms are clearly polymorphic modifications.

(*c*) *From* 3 : 4-*dibenzyloxypropenylbenzene.* A mixture of the dibromide of 3 : 4-dibenzyloxypropenylbenzene (3·8 g.; Kovács, *loc. cit.*) and sodium iodide (3 g.) in pure, dry acetone (30 c.c.) was kept for 9 days, a solution of sodium thiosulphate (4·2 g.) in water (160 c.c.) added, and the solid collected and crystallised from ethanol, giving 5 : 6-dibenzyloxy-3-(3 : 4-dibenzyloxyphenyl)-1-ethyl-2-methylindane (III; R = R′ = CH_2Ph) (0·9 g., 70%), m. p. 101—103°, raised by further recrystallisation to 104—105° (Kovács gives m. p. 114—116°, and yield 33%) (Found: C, 83·5; H, 6·4. Calc. for $C_{46}H_{41}O_4$: C, 83·7; H, 6·7%). Palladium black (0·1 g.), suspended in ethanol (5 c.c.), was saturated with hydrogen, a solution of the tetrabenzyl ether (0·2 g.) in absolute ethanol (100 c.c.) added, and the mixture shaken in hydrogen (1 atm.) till uptake of hydrogen ceased. The filtered solution was treated with excess of diazomethane, and yielded a product which separated from methanol in crystals, m. p. 93—95° (rapid heating). When heated slowly it partially melted at 93—95°, then solidified, and remelted at 104—105°. The same behaviour was shown on admixture with di*iso*eugenol dimethyl ether.

Dibenzyl Dimethyl Ether of 1-*Ethyl*-5 : 6-*dihydroxy*-3-(3 : 4-*dihydroxyphenyl*)-2-*methylindane.*—When the reduction of the benzyl ether (III; R = R′ = CH_2Ph) was carried out in presence of one-fifth of the amount of catalyst previously used, and the product treated with diazomethane as above, unchanged starting material (0·2 g.) was recovered, together with a solid *ether* (0·1 g.), m. p. 103—105° after crystallisation from methanol (Found: C, 80·9; H, 6·5. $C_{34}H_{36}O_4$ requires C, 80·3; H, 7·1%).

*Oxidation of Di*iso*safrole, m. p.* 95°. 2-*Methyl*-5 : 6-*methylenedioxy*-3-(3 : 4-*methylenedioxyphenyl*)*inden*-1-*one.*—Chromic acid (3·5 g.) in water (5 c.c.) and acetic acid (25 c.c.) was added (½ hour) to a stirred, cooled solution of di*iso*safrole (m. p. 95°; 5 g.) in acetic acid (100 c.c.). After 2 hours, benzene (15 c.c.) and light petroleum (35 c.c.; b. p. 60—80°) were added, and next day stirring was continued for 4 hours, water added, and the mixture extracted with benzene. The extract, after being washed with alkali and water, was distilled, and the residue sublimed several times at 170—190°/0·4 mm., and finally crystallised from ethanol, giving 2-methyl-5 : 6-methylenedioxy-3-(3 : 4-methylenedioxyphenyl)inden-1-one as red plates, m. p. 229—231° (Found: C, 70·4; H, 3·9. Calc. for $C_{18}H_{12}O_5$: C, 70·1; H, 3·9%) (Pailer, Müller, and Porschinski, *loc. cit.*, record m. p. 231—232°). The compound gave a reddish-brown 2 : 4-*dinitrophenylhydrazone*, m. p. 288—290° (decomp.), which crystallised from benzene–alcohol (Found: N, 11·0. $C_{24}H_{16}O_8N_4$ requires N, 11·5%).

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THE UNIVERSITY, BRISTOL.

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