891. *The Constitution and Synthesis of Anisoxide.*

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The structure (II) has, by degradation, been established for anisoxide. This conclusion has been confirmed by the synthesis of anisoxide and some of its degradation products.

THE substance, anisoxide, was first isolated by Jackson and Short,[1] from star anise oil (*Illicium verum*); they established for it the empirical formula $C_{14}H_{18}O$ and adduced evidence for its constitution which may be summarised as follows. The oxygen function was shown to be present in a cyclic ether, probably not 1 : 2 or 1 : 3, since it did not react with phenylmagnesium bromide at 100°. Of the remaining four double-bond equivalents one was shown to be present in an ethylidene grouping since ozonolysis produced acetaldehyde. Reduction with sodium and ethanol afforded dihydroanisoxide with loss of the ethylidene group. Energetic catalytic hydrogenation gave a saturated perhydroanisoxide, $C_{14}H_{26}O$, indicating that anisoxide was bicyclic. One further *C*-methyl group, probably attached to the carbon atom bearing the ethereal oxygen, was shown to be present by Kuhn–Roth determination and by fission of the oxide followed by oxidation to a ketone giving a positive iodoform test. Important results were also obtained by oxidation of anisoxide itself with potassium permanganate. The first product was an " acid A," $C_{12}H_{14}O_3$, produced by oxidation of the ethylidene group. Further oxidation of " acid A " gave " acid B," to which the formula $C_{11}H_{12}O_3$ was attributed and, finally, an " acid C,"

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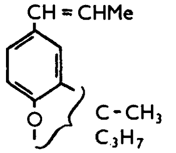
[1] Jackson and Short, *J.*, 1937, 513.

$C_{11}H_{10}O_4$. Through the kindness of the late Dr. W. F. Short, who provided us with his remaining material, we have been able to re-investigate the constitution of this interesting substance.

The ultraviolet spectrum of anisoxide [$\lambda_{max.}$ 265 (ε 18,740) and 302 mμ (ε 3700)] immediately suggested a close relationship with anethole[2] which was confirmed by the resemblance of the spectrum of dihydroanisoxide[1] [$\lambda_{max.}$ 231 (ε 6700) and 286 mμ (ε 3200)] to that of dihydroanethole. Further, these conclusions were confirmed by the infrared spectrum (see p. 4395) which also (bands at 741, 784, 826, 852, and 1000 cm.$^{-1}$) suggested a 1 : 3 : 4-trisubstituted benzene ring. This, together with Jackson and Short's findings,[1] suggested strongly the partial formula (I) for anisoxide. However none of the several possibilities implied by formula (I) was fully in accord with the degradative evidence previously obtained. In particular the loss of one carbon atom in " acid B " was not readily rationalised. For this reason the oxidative degradation of anisoxide was re-investigated.



(I)

The first product, obtained by oxidation with potassium permanganate in pyridine solution, was found to be a neutral glycol $C_{14}H_{20}O_3$, evidently formed by addition to the double bond. Further oxidation then gave " acid A " having $\lambda_{max.}$ 264 mμ (ε 12,000) and thus resembling anisic acid, corresponding, as suggested by Jackson and Short,[1] to the loss of the ethylidene chain. Further oxidation of " acid A" with alkaline potassium permanganate gave a hydroxy-acid, $C_{12}H_{14}O_4$, and *not* the " acid B " described by the earlier workers. This discrepancy was resolved when it was found that the hydroxy-acid was unstable to warm acetic acid in which it was dehydrated to " acid B." Since the " acid B " was originally crystallised from acetic acid it must be presumed that dehydration took place during purification. We now find that " acid B " has the empirical formula $C_{12}H_{12}O_3$ and, since it gives formaldehyde on ozonolysis together with " acid C," which has the spectral properties of an acetophenone, it must contain a methylidene group. Finally, " acid C," obtained in this manner and by potassium permanganate oxidation of " acid B," was reconverted, by reaction with methylmagnesium iodide, into the hydroxy-acid, now to be formulated as (V). On this basis anisoxide may be represented as (II), the glycol as (III), and acids A, B, and C as (IV), (IX), and (VIII) respectively. This relation was confirmed by hydrogenation of acid (IX) to give back " acid A" (IV). " Acid A" agrees in m. p. with a compound of the same structure synthesised by Lauer and Moe.[3]. The structure (II) accounts in a simple manner for all the available evidence. In particular, the adduct with maleic anhydride[1] is probably of the type described by Hudson and Robinson[4] for *p*-methoxylated β-alkylstyrenes.

In view of the unusual arrangement of the isoprenoid side chain, so far as we are aware unique in Nature, it was considered necessary to confirm the structure (II) by synthesis. 2-Hydroxy-5-methyl*iso*butyrophenone (X) was converted by reaction with methylmagnesium iodide into the alcohol (XI). This was dehydrated and cyclised by perchloric acid in acetic acid directly to the dihydrobenzofuran (XII). Oxidation with chromic acid then gave " acid C " (VIII). Oxidation with aqueous potassium permanganate followed by dehydration gave " acid B " (IX), the conversion of which into " acid A " (IV) has already been described.

" Acid A " was converted into the corresponding ethyl ketone (VII) by reaction of the acid chloride with diazoethane followed by reduction with hydriodic acid and with zinc in acetic acid. Reduction to the alcohol (VI) was easily effected with potassium borohydride, but dehydration of the latter to anisoxide presented initially some difficulty because of the ready polymerisation of anisoxide itself. Distillation from iodine gave anisoxide (II) in small yield, but the method of choice proved to be hot aqueous-ethanolic

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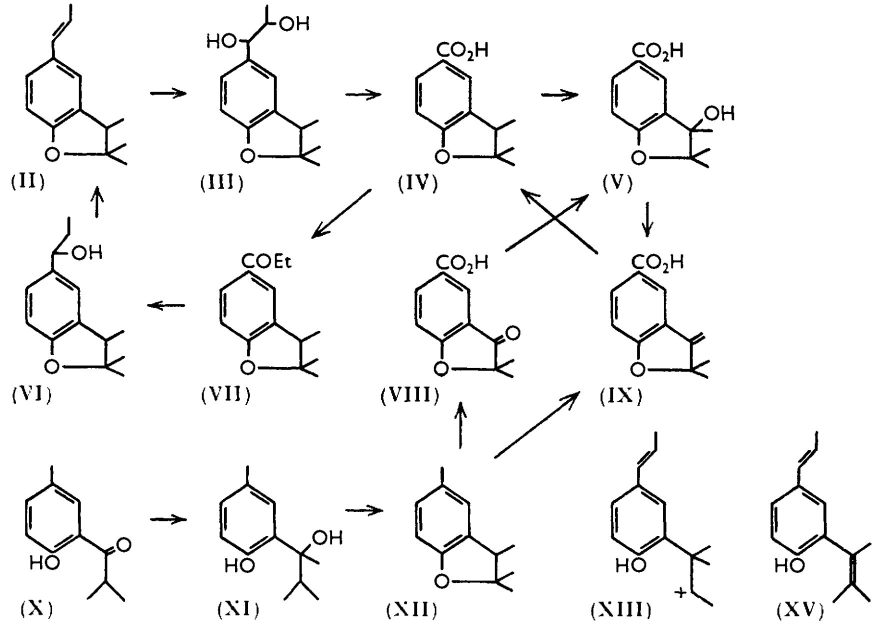
[2] Kharasch and Kleiman, *J. Amer. Chem. Soc.*, 1943, **65**, 11.
[3] Lauer and Moe, *ibid.*, 1943, **65**, 289.
[4] Hudson and Robinson, *J.*, 1941, 715.

hydrochloric acid, which gave a yield of about 20% of anisoxide, identical with the authentic material.

The unusual method of attachment of the isoprenoid residue of anisoxide has already been referred to above. It appears that isoprenoid residues are in general attached to aromatic rings at position 1 or 3 (of $\overset{1}{C}-\overset{2}{C}-\overset{3}{C}\begin{smallmatrix}/C\\ \backslash C\end{smallmatrix}$), corresponding to the electrophilic carbons of a postulated carbonium ion (XIV). The attachment at position 2 observed in anisoxide suggests either a new type of biogenetic mechanism or, more probably, a rearrangement of (say) the carbonium ion (XIII) at some stage in the biogenesis. Such a rearrangement is encountered, for instance, in the chemistry of dunnione.[5] Anisoxide is also peculiar in being optically inactive although containing an asymmetric centre. It is conceivable that the relatively drastic method of working up[1] the oil has caused racemisation. However, it is also possible that star anise oil really contains a readily cyclised unsaturated precursor of anisoxide, for example (XV), which lacks asymmetry.



$$\overset{+}{\overbrace{H_2C-CH-CMe_2}}$$
(XIV)

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions with the Unicam S.P. 500 Spectrophotometer. Infrared spectra are for liquid films unless otherwise stated. Light petroleum refers to the fraction of b. p. 40—60°. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their associates.

Anisoxide (II).—The material as received was partially resinified. It was purified by fractionation and the fraction of b. p. 142—143°/14 mm. was collected and crystallised from ice-cold methanol, to give pure anisoxide, m. p. (Kofler) 34—37° (Found: C, 82·95; H, 9·5. Calc. for $C_{14}H_{18}O$: C, 83·1; H, 8·95%), $\nu_{max.}$ 3005, 1610, 1488 (benzenoid), 963 (*trans*-disubstituted ethylenic linkage), 1254, 1138, and 1006 cm.$^{-1}$ (aryl ether).

Oxidation of Anisoxide (II).—To an ice-cold solution of anisoxide (2·02 g.) in pyridine (60 ml.)

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[5] Price and Robinson, *J.*, 1939, 1522; 1940, 1493.

was added with stirring during 1 hr. 2% aqueous potassium permanganate (128 ml.). After being stirred for a further three hours and kept overnight the manganese dioxide was removed by filtration and the neutral material isolated with ether. After evaporation the residual gum (1·3 g.) was dissolved in ether–light petroleum (5 : 2) and filtered through a short column of silica gel. Crystallisation of the product from light petroleum and from benzene–light petroleum gave the glycol, 5-(1 : 2-*dihydroxypropyl*)-2 : 2 : 3-*trimethylbenzofuran* (III), m. p. 78—80°, $\lambda_{max.}$ 233 (ε 8770) and 285 mμ (ε 3200) (Found: C, 71·25; H, 8·3. $C_{14}H_{20}O_3$ requires C, 71·15; H, 8·55%). Concentration of the aqueous alkaline phase, acidification, and isolation of the product with ether, and crystallisation from benzene, gave " acid A " (IV), m. p. 186° (Found: C, 69·9; H, 7·20. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·85%). The *methyl ester*, prepared with diazomethane, had n_D^{22} 1·5325 (Found: C, 70·55; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

Oxidation of the Glycol (III) *to " Acid A ".*—To the glycol (3·08 g.) in acetone (50 ml.) was added, with stirring, a 2% solution of potassium permanganate in the same solvent (230 ml.) during 30 min. After removal of the manganese dioxide the acidic material was isolated in the usual way and crystallised from benzene, to give " acid A " (IV) identical with material isolated by the direct oxidation of anisoxide.

2 : 3-*Dihydro-3-hydroxy-2* : 2 : 3-*trimethylbenzofuran-5-carboxylic Acid* (V).—(*a*) To " acid A " (228 mg.) in 1% aqueous sodium carbonate solution (25 ml.) was added 2% aqueous potassium permanganate solution (24·5 ml.) during 20 min. After removal of the manganese dioxide the alkaline solution was concentrated and the acidic material isolated with ether in the usual way. After being washed with ether the resultant solid crystallised from aqueous alcohol, to give the *hydroxy-acid* (V), m. p. 223·5—224·5°, $\lambda_{max.}$ 260 mμ (ε 12,900) (Found: C, 64·4; H, 6·15. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

(*b*) Anisoxide (4·0 g.) was heated on the steam-bath and 4% aqueous potassium permanganate (970 ml.) was added slowly. After 16 hr. the excess of potassium permanganate was destroyed with ethanol and, after cooling and concentration, the neutral material was extracted with ether. The alkaline solution was then carefully acidified at 0° and the product crystallised from aqueous alcohol, to give the hydroxy-acid described above.

Acidification of the alkaline oxidation mixture with an excess of hydrochloric acid gave, instead of the hydroxy-acid, " acid B " (IX), m. p. 214°, $\lambda_{max.}$ 240 (ε 24,600), 246 (ε 22,600), 272 (ε 7450), 316 (ε 6100), and 330 mμ (ε 6500) (Found: C, 70·15; H, 6·2. Calc. for $C_{12}H_{12}O_3$: C, 70·55; H, 5·9. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%). The same substance may be obtained by boiling the hydroxy-acid with acetic acid.

Ozonolysis of " Acid B " (IX).—" Acid B " (IX) (148 mg.) in chloroform (10 ml.) was ozonised at 17° until the characteristic spectrum of the acid was replaced by new maxima at 255 and 325 mμ (10 min.). Decomposition of the ozonide with water and isolation of the acidic material in the usual way gave, after filtration in ether through a column of silica gel and crystallisation from benzene, " acid C " (VIII), identical with the acid obtained in the following experiment. In a parallel experiment steam-distillation of the ozonised solution gave formaldehyde (11%), isolated as the dimedone derivative.

Oxidation of " Acid B " (IX).—This was performed as described by Jackson and Short.[1] After crystallisation from benzene the product " acid C " (VIII) had m. p. 181·5—182·5°, $\lambda_{max.}$ 229 (ε 35,600), 251 (ε 9500), and 325 mμ (ε 4200) (Found: C, 64·15; H, 5·2. Calc. for $C_{11}H_{10}O_4$: C, 64·05; H, 4·85%).

Conversion of " Acid C " (VIII) *into the Hydroxy-acid* (V).—The acid (107 mg.) was refluxed for 4 hr. with a solution (25 ml.) of methylmagnesium iodide (prepared from 197 mg. of magnesium), after which the mixture was decomposed with ice-water and hydrochloric acid. Isolation of the product and its crystallisation from benzene gave the hydroxy-acid identical with the material previously described (Found: C, 65·3; H, 6·1%).

Conversion of " Acid B " (IX) *into " Acid A "* (IV).—" Acid B " (43 mg.) was hydrogenated in acetic acid (5 ml.) in the presence of platinum oxide. After the uptake of 1·02 mol. of hydrogen the product was isolated to give, after crystallisation from benzene, " acid A " (IV), identified by m. p., mixed m. p., and spectra.

Synthesis of Anisoxide.—2-Hydroxy-5-methyl*iso*butyrophenone (X), $\lambda_{max.}$ 217 (ε 17,200), 256 (ε 11,250), and 334 mμ (ε 3600), was prepared as described by von Auwers *et al.*[6] The

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[6] von Auwers, Baum, and Lorenz, *J. prakt. Chem.*, 1927, **115**, 98; von Auwers, *Ber.*, 1914, **47**, 2334; cf. also von Auwers and Lämmerhirt, *Annalen*, 1920, **421**, 1.

3 : 5-dinitrobenzoate, crystallised from benzene–light petroleum, had m. p. (Kofler) 190—193° (Found: C, 58·1; H, 4·55; N, 7·2. $C_{18}H_{16}O_7N_2$ requires C, 58·05; H, 4·35; N, 7·5%). The butyrophenone (21 g.) in dry ether (50 ml.) was added with stirring to an ethereal solution (300 ml.) of methylmagnesium iodide prepared from methyl iodide (100 g.) and magnesium (12 g.). After decomposition the product was isolated with ether and washed with sodium hydrogen carbonate solution, and the phenolic material was then extracted with sodium hydroxide. After isolation in the usual way the phenolic material was fractionated, the material of b. p. 142—146°/25 mm. being collected. Vapour-phase chromatography showed this fraction to be homogeneous 2-(2-hydroxy-5-methylphenyl)-3-methylbutan-2-ol (XI). The 3 : 5-*dinitrobenzoate*, after crystallisation from aqueous methanol, had m. p. 116—117° (Found: C, 58·5; H, 5·4; N, 7·6. $C_{19}H_{20}O_7N_2$ requires C, 58·75; H, 5·2; N, 7·2%).

The alcohol (10·3 g.) was added to a solution of 60% perchloric acid (310 ml.) in acetic acid (105 ml.) containing acetic anhydride (35·5 ml.). After being set aside for 16 hr. the mixture was poured into water, and the neutral material isolated in the usual way. This was fractionated and the fraction of b. p. 132—133°/25 mm. collected, to give 2 : 3-*dihydro*-2 : 2 : 3 : 5-*tetramethylbenzofuran* (XII), n_D^{28} 1·5100, $\lambda_{max.}$ 228—230 (ε 5700) and 287 mμ (ε 3100) (Found: C, 81·6; H, 9·2. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%).

The dihydrobenzofuran (XII) (255 mg.) in acetic acid (5 ml.) was oxidised with a 0·1N-solution of chromic acid in acetic acid (50 ml.). After 3·5 hr. the uptake was equivalent to 6·25 atoms of oxygen, no further uptake occurring during the next hour. Reduction of the excess of oxidant with sodium metabisulphite and isolation of the product in the usual way gave " acid C " (VIII), identical with the material obtained by oxidation of anisoxide.

Oxidation of the Dihydrobenzofuran (XII) *to " Acid B "* (IX).—The dihydrobenzofuran (163 mg.) was heated on the steam-bath and a 4% solution of potassium permanganate (30 ml.) was added slowly. After 8·5 hr. the mixture was cooled, excess of oxidant destroyed with sulphur dioxide, and the product isolated in the usual way. After crystallisation from chloroform–light petroleum " acid B " (IX) was obtained, identical in every respect with the material from the oxidation of anisoxide. Its identity was confirmed by hydrogenation with palladised charcoal in ethyl acetate to " acid A " (IV).

2 : 3-*Dihydro*-2 : 2 : 3-*trimethyl*-5-*propionylbenzofuran* (VII).—" Acid A " (IV) (2·15 g.) was suspended in benzene (6 ml.), oxalyl chloride (4·5 ml.) added, and the mixture set aside overnight. Excess of oxalyl chloride was removed from the now homogeneous solution by evaporation under reduced pressure, and the product dissolved in benzene (7 ml.) and added to a solution of diazoethane (1 g.) in ether (700 ml.). After 2 hr. the solution was evaporated to dryness, and the residual oil taken up in chloroform, shaken for 5 min. with 60% hydriodic acid (2 ml.), washed with aqueous sodium thiosulphate and saturated aqueous sodium hydrogen carbonate, and recovered. This red oil was dissolved in acetic acid and shaken with zinc dust for 1 hr. The product, isolated in the usual way, showed an infrared band at 1715 cm.$^{-1}$ due to a small amount of the ethyl ester of " acid A ". This was removed by dissolving the product in 3 : 7 aqueous dioxan (120 ml.), adding N-sodium hydroxide (20 ml.), and setting the whole aside for 40 hr. Isolation of the neutral material in the usual way and distillation gave 2 : 3-*dihydro*-2 : 2 : 3-*trimethyl*-5-*propionylbenzofuran* (VII), b. p. 128—132°/0·4 mm., n_D^{29} 1·5363 (Found: C, 76·7; H, 8·4. $C_{14}H_{18}O_2$ requires C, 77·05; H, 8·3%). The *semicarbazone*, crystallised from chloroform–light petroleum, had m. p. (Kofler) 179—180° (Found: N, 15·6. $C_{15}H_{21}O_2N_3$ requires N, 15·25%). The ketone (VII) (590 mg.) in 1 : 1 aqueous methanol (60 ml.) containing potassium borohydride was set aside overnight. Isolation of the product gave after distillation (bath-temperature 180°) at 0·5 mm. the 2 : 3-*dihydro*-5-1′-*hydroxypropyl*-2 : 2 : 3-*trimethylbenzofuran* (VI), n_D^{25} 1·5223, $\lambda_{max.}$ 231 (ε 5850) and 284 (ε 2440) mμ (Found: C, 76·35; H, 8·95. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

Dehydration of the Alcohol (VI) *to Anisoxide* (II).—(*a*) The alcohol (200 mg.) was distilled under reduced pressure from a small crystal of iodine. The product (23 mg.) was filtered in light petroleum solution through a column of alumina (Grade III; 700 mg.). Sublimation of the product gave a colourless oil which crystallised, then having m. p. 34—37° (Kofler) undepressed on admixture with authentic anisoxide.

(*b*) Optimum conditions were determined in preliminary experiments taking advantage of the maximum in the ultraviolet spectrum at 265 mμ. The alcohol (100 mg.) in ethanol (100 ml.) was treated with 6N-hydrochloric acid (70 drops), then refluxed for 20 min. The product was isolated with chloroform after neutralisation of the acid with sodium hydrogen carbonate.

After evaporation of the chloroform the residual oil (90 mg.) was filtered in light petroleum (b. p. 60—80°) through alumina (Grade III). Crystallisation of the product gave anisoxide (20 mg.) identified by m. p., mixed m. p., and infrared (chloroform solution) and ultraviolet spectra.

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