403. *Some 5,8-Dialkoxy-1-tetralones.*

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5,8-Diethoxy-, 5-ethoxy-8-methoxy-, and 8-ethoxy-5-methoxy-1-tetralone have been prepared. Hydroxyl groups in *ortho*-position to carbonyl in these tetralones and the intermediates cannot readily be alkylated and alkoxyl *ortho* to carbonyl is very readily dealkylated. These reactions and ultraviolet absorption have been used to establish the structures of two series of compounds.

5,8-DIALKOXY-1-TETRALONES of types (IVa, c, f, g) were required for synthetic work. The dimethoxy-compound (IVc) was known [1] and there was no difficulty in preparing the diethoxy-analogue (IVa) by the route indicated in the chart. The main problem was the allocation of structures to the mixed ethers (IVf and g). This was done by preparing 5-hydroxy-8-methoxy- and 8-hydroxy-5-methoxy-1-tetralone and studying the alkylation and dealkylation of the tetralones and intermediates, as well as the ultraviolet absorption of the tetralones.

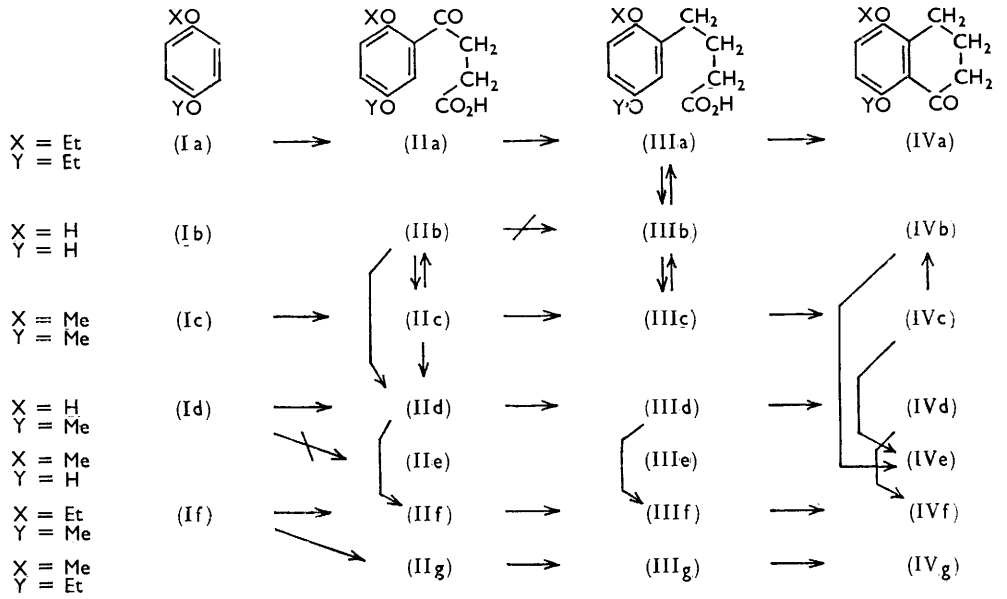
In preparing the tetralones the method of Fieser *et al.*[2] for γ-phenylbutyric acids was used, followed by cyclisation with polyphosphoric acid [3] which gave better yields more conveniently than did sulphuric acid, stannic chloride, or aluminium chloride. Quinol dimethyl and diethyl ether thus gave good yields of the tetralones (IVc and a). One exception, γ-(2-hydroxy-5-methoxyphenyl)butyric acid (IIId), which contains a free hydroxyl group, required sulphuric acid for cyclisation as polyphosphoric acid was ineffective.

It has been stated, but without proof, that quinol dimethyl ether at higher temperatures [4] affords γ-(2-hydroxy-5-methoxyphenyl)-γ-oxobutyric acid (IId) and not its isomer (IIe). Proof was obtained by comparison of the ultraviolet absorption spectra of the tetralone (IVd) with that of its isomer (IVe) obtained by methylation of the tetralone (IVb) and by demethylation of (IVc). Demethylation studies confirmed this.

Ultraviolet Absorption Spectra.—2-Hydroxyacetophenone absorbs at longer wavelength than its methyl ether,[5] owing presumably to resonance in its chelated form for there is very little difference in absorption between 3- and 4-hydroxyacetophenone and their

[1] Cocker, Cross, and McCormick, *J.*, 1952, 72; Thompson, *J.*, 1952, 1822; H. S. Blair, M.Sc. Thesis, Queen's University, Belfast, 1953.
[2] Fieser, Gates, and Kilmer, *J. Amer. Chem. Soc.*, 1940, **62**, 2966.
[3] Uhlig, *Angew. Chem.*, 1954, **66**, 435.
[4] Merck, B.P. 702,012; Momose, Oya, Ohkuta, and Iwasaki, *Pharm. Bull.* (*Japan*), 1954, **2**, 119 (*Chem. Abs.*, 1956, **50**, 911); Newhall, Harris, Holly, Johnston, Richter, Walton, Wilson, and Folkers, *J. Amer. Chem. Soc.*, 1955, **77**, 5646; U.S.P. 2,720,542; Coillard and Mentzer, *Bull. Soc. chim. France*, 1953, 168.
[5] Morton and Stubbs, *J.*, 1940, 1447; Dannenberg, *Z. Naturforsch.*, 1949, **46**, 327.

respective methyl ethers which all absorb similarly to 2-hydroxyacetophenone. 1-Tetralone resembles 2-hydroxyacetophenone structurally; indeed in it the carbonyl group is forced even more to take up the position co-planar with the benzene ring most suitable for chelation with the 8-hydroxy-group. Hence 8-hydroxy-1-tetralones will be expected



to absorb at longer wavelengths than their isomers. For the series of tetralones (IVb—e) the absorption bands are given in the Table. The deepest-coloured is the dihydroxy-compound (IVb) with band 3 at 364 mμ, closely followed by the yellow monomethyl ether (IVe) with band 3 at 356 mμ. There follows then a gap of 14 mμ before the pale yellow monomethyl isomer (IVd). Thereafter between it and the colourless dimethoxy-ketone (IVc) there is only a difference of 4 mμ. It is clear by analogy with the hydroxy- and methoxy-acetophenones that the first tetralone in the Table possesses a hydroxy-group *ortho* to the carbonyl group, as indeed is known. This applies also to the second, the yellow monomethyl ether of m. p. 93·5°, which therefore has structure (IVe). The other two with band 3 at shorter wavelength have 8-methoxyl groups, as is known for the last, the dimethoxy-compound. The third compound, the pale yellow monomethyl ether of m. p. 170°, has therefore the structure (IVd).

Ultraviolet absorption maxima (mμ) *of 1-tetralones.*

		Band 1		Band 2		Band 3	
		λ	ε	λ	ε	λ	ε
5,8-$(OH)_2$	(IVb)	234	14,250	264	9050	364	4175
8-OH-5-OMe	(IVe)	232	14,350	260	8333	356	3700
5-OH-8-OMe	(IVd)	229	15,750	259	8475	342	4050
5,8-$(OMe)_2$	(IVc)	228	19,900	253	7200	338	4140

Demethylation.—Partial demethylation of a dimethoxy-compound is normally difficult to achieve, the product being usually a mixture of dihydroxy- and unchanged material. However, boiling the dimethoxy-compounds (IIc and IVc) with constant-boiling hydriodic acid hydrolyses only the methoxy-group *ortho* to the carbonyl group, leading to the phenols (IId and IVe respectively). With longer boiling and more concentrated acid complete demethylation results. On the other hand, the dimethoxy-acid (IIIc), which does not possess a carbonyl group, was demethylated completely. The ready demethylation of the group *ortho* to the carbonyl group is attributable to stabilisation of the transition state

by resonance and hydrogen-bonding. Demethylation of n-alkyl aryl ethers is believed to proceed by an S_N2 mechanism,[6] but a change to S_N1 reaction owing to the different and more stable transition state cannot be excluded. An *ortho*-carbonyl interaction is not possible with the 5-methoxyl group, which consequently requires more severe conditions for demethylation. It is noteworthy that aluminium chloride also demethylates the 8-methoxyl group readily.[4]

The structures indicated by the light absorption of the tetralones (IVd and e) are thereby confirmed. The structure of the acid (IId), known from its conversion through (IIId) into (IVd), is also confirmed. Coillard and Mentzer [4] obtained the acid (IId) by partial hydrolysis of the dimethoxy-acid (IIc) but gave it the incorrect formula (IIe) on the grounds that the sterically least hindered methoxyl group would be hydrolysed first. Cocker, Cross, and McCormick [1] allocated the correct structure to the acid (IVe) because it gave a dark green ferric derivative soluble in ether and could not be methylated. The structures of the remaining compounds listed are derived as indicated below.

Alkylation.—Methylation of γ-(2,5-dihydroxyphenyl)-γ-oxobutyric acid (IIb) gives both mono- and di-methoxy-products (IId and c). The corresponding dihydroxytetralone (IVb), however, gives only the monomethoxy-product (IVe). Further alkylation could not be achieved, as Thompson [1] also noted. Presumably the resonance-stabilised *o*-hydroxy-keto-system is again responsible for this. In the tetralone (IVb) the stability of this system prevents alkylation of the 8-hydroxy-group; in the acid (IIb) alkylation of the 2-hydroxy-group occurs but only after the more reactive 5-hydroxy-group has been alkylated. That alkylation of this 2-hydroxy-group occurs at all is due to the greater flexibility of the side-chain containing the carbonyl group. Further alkylation of 5-hydroxy-8-methoxy-1-tetralone (IVd), the isomeric monomethyl derivative obtained directly, proceeded readily.

Dihydroxy-series.—The normal preparative methods are less satisfactory if free hydroxyl is present; *e.g.*, quinol monomethyl ether gave γ-(2-hydroxy-5-methoxyphenyl)-γ-oxobutyric acid (IId) in low yield. It was readily prepared from the dimethoxy-acid (IIc) by way of the dihydroxy-acid (IId). The dihydroxybutyric acid (IIIb) was not obtained by reduction of the keto-acid (IIb), but by demethylation of the dimethoxy-acid (IIIc) (which Fieser *et al.*[2] were unable to achieve), and its structure was confirmed by ethylation to give acid (IIIa). It was also obtained by de-ethylation of this acid (IIIa). Similarly the dihydroxytetralone (IVb) was prepared by complete demethylation of the tetralone (IVc).

Isomeric Ethoxy-methoxy-derivatives.—Quinol ethyl methyl ether (If), as starting material, leads to two keto-acids (IIf and IIg), which were found difficult to separate. First attempts using crystallisation and chromatography were unsuccessful. The mixture was reduced but the acids (IIIf and g) were also inseparable. These finally gave the mixed tetralones (IVf and g) which were readily separated by fractional crystallisation of their sodium bisulphite compounds. It was then found that the keto-acids (IIf and g) could be separated with care in the same way, and this led to preparation of the butyric acids (IIIf and g) separately. Thus both sets of isomers (f and g) were obtained pure. Their structures were proved by ethylation of compounds (IId, IIId, and IVd), whose structures were known (see above), to the corresponding compounds (IIf, IIIf, and IVf). Compounds (IIe and IIIe) could not be prepared.

Experimental

γ-Aryl-γ-oxobutyric Acids (IIa, c, d, f, g).—The method of Fieser *et al.*[2] was used. *γ-(2,5-Diethoxyphenyl)-γ-oxobutyric acid* (IIa) formed needles (from ethanol), m. p. 151° (Found: C, 63·3; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·4; H, 6·8%). The γ-2,5-dimethoxy-acid (IIc) had m. p. 103°. The mixed ethoxymethoxy-acids (IIf and g) prepared in this way in good yield were separated as described below. The 2-hydroxy-5-methoxy-acid (IId) was obtained impure in low yield. Quinol monoethyl ether gave none of the expected keto-acid.

[6] Burwell, *Chem. Rev.*, 1954, **54**, 615; Hughes and Ingold, *J.*, 1935, 244.

γ-Arylbutyric Acids (IIIa, c, d, f, g).—Reduction was carried out as described by Fieser *et al.*,[2] with minor modifications. *γ-(2,5-Diethoxyphenyl)butyric acid* (IIIa) did not require distillation as it separated in crystalline form. When recrystallised five times alternately from ethanol and benzene, it had m. p. 119° (Found: C, 66·6; H, 8·1. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%). The *2-ethoxy-5-methoxy-acid* (IIIf) formed needles (from alcohol), m. p. 82° (Found: C, 65·3; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The *5-ethoxy-2-methoxy-acid* (IIIg) had m. p. 72° (from alcohol) (Found: C, 66·0; H, 7·2%).

Tetralones (IVa, c, d, f, g).—The arylbutyric acid (10 g.) and polyphosphoric acid [3] (100 g.) were stirred together at 60° for 75 min., then poured into ice-water (200 ml.). Extraction with ether, washing, drying, and removal of solvent gave the tetralone (8·5 g.), which was recrystallised from benzene–ligroin (b. p. 60—80°). *5,8-Diethoxy-1-tetralone* (IVa) formed pale yellow needles, m. p. 79·5° (Found: C, 72·1; H, 7·8. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The ethoxymethoxytetralones (IVf and g) described below were also obtained by this method in good yield. 5-Hydroxy-8-methoxy-1-tetralone (IVd) was not obtained with polyphosphoric acid, but in good yield by using sulphuric acid.

Demethylations.—The milder of the two methods used consisted of boiling the substance with excess of hydriodic acid (*d* 1·7) for 2 hr., cooling, addition of ice-water, filtration, washing, drying, and recrystallisation from alcohol. Yields were good. In this way the keto-acid (IIc) was partially demethylated to (IId), the tetralone (IVc) to (IVe), m. p. 93·5°, and the butyric acid (IIIc) completely demethylated to (IIIb), m. p. 139—140°. When boiled with hydriodic acid (*d* 1·9) for 3 hr. the keto-acid (IIc) was completely demethylated to (IIb), m. p. 186·5° (lit.,[4,7] 181·2°, 177°) and the tetralone (IVc) to (IVb), m. p. 185°, in good yields. *γ-(2,5-Dihydroxyphenyl)butyric acid* was prepared by demethylation of the acid (IIIc), m. p. 139—140° (Fieser *et al.*[2] give m. p. 132°). This compound was also obtained by de-ethylation of acid (IIIa). On methylation it gave (IIIc) and on ethylation (IIIa).

Alkylations.—The following ethylations were carried out in good yield by using diethyl sulphate: the 2-hydroxy-5-methoxy-keto-acid (IId) to the 2-ethoxy-5-methoxy-keto-acid (IIf), m. p. 137·5°, the 2,5-dihydroxybutyric acid (IIIb) to the diethoxybutyric acid (IIIa), m. p. 119°, the 2-hydroxy-5-methoxybutyric acid (IIId) to the 2-ethoxy-5-methoxybutyric acid (IIIf), m. p. 82°, and the 5-hydroxy-8-methoxytetralone (IVd) to the 5-ethoxy-8-methoxytetralone (IVf), m. p. 100°. Dimethyl sulphate converted 5,8-dihydroxytetralone (IVb) into the 8-hydroxy-5-methoxytetralone (IVe), m. p. 93·5°. Further alkylation of (IVe) could not be achieved. In methylating the dihydroxy-keto-acid (IIb) the main product was the dimethoxy-acid (IIc), m. p. 103°, with a smaller amount of the 5-monomethoxy-acid (IId), m. p. 145°.

Separation of Isomeric Tetralones.—The mixed tetralones (IVf and g) (10 g.), dissolved in alcohol (15 ml.), were stirred for 4 hr. with sodium hydrogen sulphite solution (800 ml.), prepared from saturated sodium carbonate solution and sulphur dioxide. A small amount of water was added and the whole kept at 0° overnight and then filtered. The residue crystallised from water as needles. Decomposition by boiling 20% sodium hydroxide solution gave *5-ethoxy-8-methoxy-1-tetralone* (IVf), plates (from benzene–ligroin), m. p. 100° (Found: C, 70·7; H, 6·8. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). On addition of more sodium hydroxide solution to the filtrate *8-ethoxy-5-methoxy-1-tetralone* (IVg) separated which, after extraction and several recrystallisations from benzene–ligroin, formed prisms, m. p. 55·5° (Found: C, 70·9; H, 7·0%).

Separation of Isomeric γ-(Ethoxy-methoxyphenyl)-γ-oxobutyric Acids.—The mixed keto-acids (130 g.), dissolved in an excess of saturated sodium carbonate solution, were treated with sulphur dioxide until no more bisulphite compound was precipitated. This compound was filtered off and recrystallised three times from water. It was decomposed by boiling dilute hydrochloric acid. On cooling, *γ-(2-ethoxy-5-methoxyphenyl)-γ-oxobutyric acid* (IIf) (42 g.) separated; it formed needles, m. p. 137·5°, from alcohol (Found: C, 62·1; H, 6·2. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). Passing more sulphur dioxide into the main mother-liquor produced a bisulphite compound which, on recrystallisation from water and decomposition, gave an acid. To this was added the acid obtained by boiling the mother-liquor from the first recrystallisation above with dilute hydrochloric acid (total, 56 g.). On recrystallisation from alcohol, *γ-(5-ethoxy-2-methoxyphenyl)-γ-oxobutyric acid* (IIg) was obtained as needles, m. p. 105·5° (Found: C, 61·8; H, 6·0%).

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[7] Rosenmund, Zymalkowski, and Engels, *Chem. Ber.*, 1951, **84**, 711.