484. *Intramolecular Acylation. An Attempt to Cyclise β-(8-Oxo-2-tetralyl)propionic and γ-(8-Oxo-2-tetralyl)butyric Acids.*

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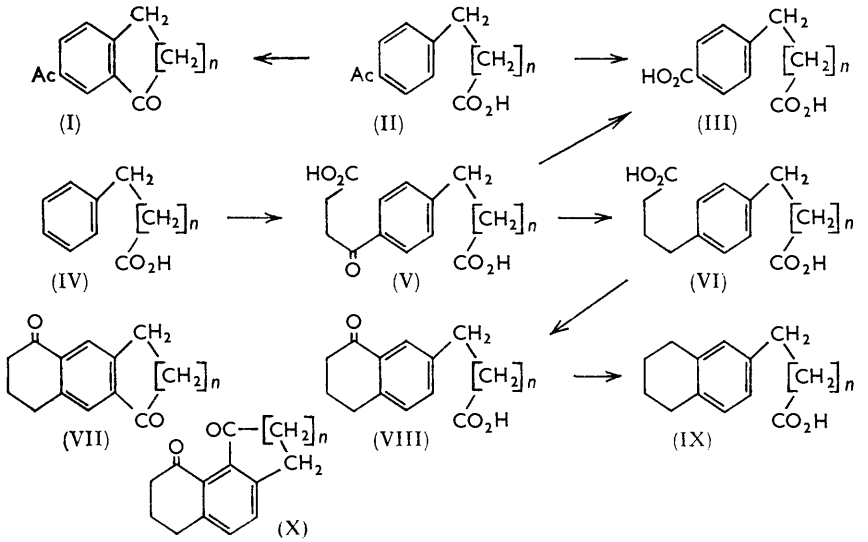
The novel keto-acids (VIII; $n = 1$ and 2) have been prepared and heated with an excess of aluminium chloride: the yields of the products of cyclisation, $C_{13}H_{12}O_2$ and $C_{14}H_{14}O_2$, respectively, were only about 5%. We conclude, therefore, that whereas β-4-acylphenylpropionic acid and γ-4-acylphenylbutyric acid are readily cyclised (see II ⟶ I; $n = 1$ and 2), the cyclisation of the analogues having the acyl group in the 3-position of the phenyl group is a very inefficient process of little preparative importance.

With an excess of Friedel–Crafts acylating agent, benzene and its monoalkyl derivatives can be acylated only once; further reaction, when it occurs, involves dehydrogenation of the alkyl group.[1] Diacylation is readily effected (i) when the benzene ring has a strong *op*-directing group, *e.g.*, *p*-ethylphenol can be acylated in both the 2- and the 6-position, and (ii) when the acyl group in the monoacyl derivative is sterically prevented from mesomerically deactivating the benzene ring towards further acylation by having bulky substituents in both *ortho*-positions; thus mesitylene and durene are easily diacylated. These limitations to the Friedel–Crafts acylation of aromatic ketones apply to inter- but not to



intra-molecular acylations, *e.g.*, whereas 1-tetralone cannot be acetylated, γ-*p*-acetylphenylbutyric acid (II; $n = 2$) in the presence of aluminium chloride readily gives 7-acetyl-1-tetralone (I; $n = 2$) by cyclisation.[2] There are numerous examples of intramolecular acylation providing aromatic diketones in which the carbonyl groups are oriented *ortho* to one another (*e.g.*, *o*-benzoylbenzoic acids ⟶ anthraquinones [3]) or *meta* [2] (*e.g.*, see II ⟶ I), but none in which the ring closure occurs in the position *para* to a carbonyl group. We now report an attempt to fill this gap: it involved the preparation of the oxo-acids (VIII; $n = 1$ and 2) and heating them with an excess of aluminium chloride.

Ethyl β-phenylpropionate and γ-phenylbutyrate (IV; $n = 1$ and 2, respectively), in ethylene chloride, dissolved a molecular proportion of aluminium chloride (as $AlCl_3$), and

[1] Baddeley and Wrench, *J.*, 1956, 4943.
[2] Baddeley and Williamson, *J.*, 1956, 4647.
[3] Baddeley, Holt, and Maker, *J.*, 1952, 2415.

when these solutions were added to a mixture of succinic anhydride and aluminium chloride (2 mol.) in ethylene chloride, vigorous reactions occurred at room temperature and gave the half esters of the oxo-dicarboxylic acids (V) in excellent yields. Additional evidence for their structure was obtained by oxidation with dilute nitric acid: the dicarboxylic acids (III) were thereby obtained for comparison with authentic samples. Clemmensen reduction of the compounds (V) and cyclisation of the resulting dicarboxylic acids (VI) with anhydrous hydrofluoric acid gave the novel oxo-acids (VIII; $n = 1$ and 2). Wolff–Kishner reduction of these oxo-acids gave the known acids (IX; $n = 1$ and 2), m. p. 81—82° and 47—49°, respectively.[4] The ring closure (VI ⟶ VIII; $n = 1$) is a further example of the preference for tetralone rather than indanone formation in hydrofluoric acid.

When a molten mixture of the oxo-acid (VIII; $n = 1$) with an excess of aluminium chloride and a little sodium chloride to lower the melting point was heated at 190—200° for 1 hr., subsequent decomposition with ice and hydrochloric acid gave mainly unchanged oxo-acid and an alkali-insoluble tar from which a crystalline compound $C_{13}H_{12}O_2$, m. p. 116—117°, with the properties of an aromatic diketone was isolated. It represents only about 5% of the oxo-acid, and its structure has not been determined. Attempts to improve the yield by heating the reaction mixture at 200° and above for longer than 1 hr. increased only the amount of intractable tar. The oxo-acid (VIII; $n = 2$) behaved similarly and gave a crystalline compound $C_{14}H_{14}O_2$, m. p. 132—133°, in about 5% yield. Apparently, the cyclisation of β-*m*-acylphenylpropionic and γ-*m*-acylphenylbutyric acids differs from that of the isomers having a *p*-acyl group in being a very inefficient process of little if any preparative importance.

Experimental

γ-(p-2-Carboxyethylphenyl)butyric Acid (VI; $n = 1$).—A solution of ethyl β-phenylpropionate (200 g.) and aluminium chloride (152 g.) in ethylene chloride (300 ml.) was gradually added to a cold mixture of succinic anhydride (112 g.) and aluminium chloride (304 g.) in ethylene chloride (600 ml.). A vigorous reaction occurred, and the mixture was kept at room temperature for several hours and was then poured on ice and dilute hydrochloric acid. An emulsion was obtained which was extracted with a large volume of ether. The ether extract was thoroughly washed with sodium hydrogen carbonate solution; acidification of the washings gave β-(*p*-2-ethoxycarbonylethylbenzoyl)propionic acid [5] which separated from dilute ethanol in plates (248 g.), m. p. 113—114° (Found: C, 64·6; H, 6·8. Calc. for $C_{15}H_{18}O_5$: C, 64·7; H, 6·5%). The *semicarbazone* crystallised from ethanol in needles, m. p. 199—200° (Found: C, 57·3; H, 6·6; N, 12·5. $C_{16}H_{21}O_5N_3$ requires C, 57·3; H, 6·3; N, 12·5%). After 8 hr. in a boiling mixture of water (750 ml.) and concentrated nitric acid (50 ml.), the oxodicarboxylic acid (V; $n = 1$) (4·0 g.), obtained by hydrolysis of the above half oxo-ester, gave β-*p*-carboxyphenylpropionic acid, m. p. and mixed m. p. 284—285°; dimethyl ester, m. p. and mixed m. p. 34—35°. After 3 hr. in boiling hydrochloric acid (2N; 2·2 l.), the half oxo-ester (200 g.) gave the oxo-dicarboxylic acid [5] (V; $n = 1$; 144 g.) as plates, m. p. 194—195°, from water (Found: C, 62·7; H, 5·7. Calc. for $C_{13}H_{14}O_5$: C, 62·4; H, 5·6%). This compound was obtained in very poor yield by the interaction of succinic anhydride and β-phenylpropionic acid in the presence of aluminium chloride. Clemmensen reduction of (V; $n = 1$; 140 g.) with amalgamated zinc (300 g.), water (200 ml.), and concentrated hydrochloric acid (700 ml.) required 20 hr. and gave the required *dicarboxylic acid* (VI; $n = 1$; 106 g.) as needles, m. p. 143—144°, from a large volume of water (Found: C, 66·1; H, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

p-*Bis*-3-*carboxypropylbenzene* (VI; $n = 2$).—A solution of ethyl γ-phenylbutyrate (60 g.) and aluminium chloride (42 g.) in ethylene chloride (100 ml.) was gradually added to a cold (0°) mixture of succinic anhydride (31·3 g.) and aluminium chloride (84 g.) in ethylene chloride (300 ml.); the mixture was then kept at 0° for 15 hr. It was poured on ice and hydrochloric acid, and the organic layer was separated and, together with the ethylene chloride (100 ml.)

[4] Newman and Zahn, *J. Amer. Chem. Soc.*, 1943, **65**, 1097; cf. Darzens, *Compt. rend.*, 1935, **201**, 902.

[5] Borsche and Barthenheier, *Annalen*, 1942, **553**, 250.

extract of the aqueous layer, distilled with steam. The residue gave a solid which was extracted with sodium carbonate solution. Acidification of the extract gave γ-*p*-succinylphenylbutyric acid (V; $n = 2$; 73 g.), m. p. 162—163° after recrystallisation from dilute acetic acid (Found: C, 63·4; H, 6·4. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%). Cram, Allinger, and Steinberg [6] give m. p. 164·5°. Oxidation of this compound with dilute nitric acid gave γ-*p*-carboxyphenylbutyric acid, m. p. and mixed m. p. 192—194°. When preparing an authentic sample of this compound by the previously described method,[2] we prepared also the 2,4-*dinitrophenylhydrazone* of ethyl γ-*p*-acetylphenylbutyrate; it separated from ethanol in orange plates, m. p. 136—137° (Found: C, 58·1; H, 5·4; N, 13·2. $C_{20}H_{22}N_4O_6$ requires C, 58·0; H, 5·3; N, 13·5%). Clemmensen reduction of the oxo-dicarboxylic acid (V; $n = 2$; 60 g.) with amalgamated zinc (150 g.), concentrated hydrochloric acid (650 ml.), and water (100 ml.) required 20 hr. and gave *p*-bis-3-carboxypropylbenzene (51 g.) as needles, m. p. 168—171°, from water (Found: C, 66·9; H, 7·4. Calc. for $C_{14}H_{18}O_4$: C, 67·2; H, 7·2%). Cram *et al.*[6] give m. p. 176—177°.

β-(8-*Oxo*-2-*tetralyl*)*propionic Acid* (VIII; $n = 1$).—γ-(*p*-2-Carboxyethylphenyl)butyric acid (VI; $n = 1$; 100 g.) was covered with anhydrous hydrofluoric acid (700 ml.). After several days, the mixture gave a solid residue which was extracted with sodium carbonate solution. The alkaline extract was separated from insoluble material and, when acidified, gave the required *compound* (77·0 g.) which separated from dilute ethanol in rods, m. p. 110—111° (Found: C, 71·2; H, 6·3%; equiv., 216. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%; equiv., 218). The *semicarbazone* crystallised from dilute ethanol in plates, m. p. 222—224° (decomp.) (Found: C, 60·7; H, 6·2; N, 15·5. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·2; N, 15·3%), and the *oxime* in needles, m. p. 201—202° (Found: C, 67·1; H, 6·5; N, 6·1. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). A mixture of the semicarbazone (1·0 g.) and sodium hydroxide (1·5 g.) in water (3 ml.) and ethylene glycol (30 ml.) was kept at 180—200° for 6 hr. The solvent was then removed under reduced pressure, the residue was dissolved in water, and the solution was acidified. The solid was crystallised from light petroleum and gave β-2-tetralylpropionic acid [4] (0·5 g.) as plates, m. p. 81—82° (Found: C, 76·3; H, 8·0. Calc. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·8%). This acid was obtained in lower yield by Clemmensen reduction of compound (VIII; $n = 1$).

γ-(8-*Oxo*-2-*tetralyl*)*butyric Acid* (VIII; $n = 2$).—This *oxo-acid* (26 g.) was obtained from *p*-bis-3-carboxypropylbenzene (30 g.) by the action of anhydrous hydrofluoric acid; it crystallised from dilute ethanol or dilute acetic acid in flat needles, m. p. 86—87° (Found: C, 72·2; H, 7·1%; equiv., 230. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%; equiv., 232). The *semicarbazone* crystallised from dilute ethanol in small needles, m. p. 208—210° (decomp.) (Found: C, 62·7; H, 6·8; N, 14·5. $C_{15}H_{19}N_3O_3$ requires C, 62·3; H, 6·6; N, 14·5%), and the *oxime* in needles, m. p. 124—125° (Found: C, 67·9; H, 6·9; N, 5·9. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%). The semicarbazone with alkali at 180—200° gave γ-2-tetralylbutyric acid, m. p. 48—49° (Found: C, 76·9; H, 8·3. Calc. for $C_{14}H_{18}O_2$: C, 77·0; H, 8·2%).

γ-(8-*Oxo*-2-*tetralyl*)*butyric Acid* (VIII; $n = 2$) *and Aluminium Chloride*.—An intimate mixture of these reactants (2·0 and 7·0 g., respectively) and sodium chloride (0·5 g.) was heated in an oil bath at 190—200° for 1 hr. When decomposed with ice and hydrochloric acid, it gave a solid which was taken up in benzene or chloroform, washed with water, and then extracted with sodium hydrogen carbonate solution. Acidification of this extract gave the unchanged oxo-acid (VIII; $n = 2$), m. p. and mixed m. p. 85—87°. Removal of the solvent from the organic layer gave a red viscous residue which was extracted repeatedly with boiling light petroleum (b. p. 60—80°). These extracts gave yellow plates (0·15 g.), m. p. 132—133° (Found: C, 78·7; H, 6·3. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). This compound has strong infrared absorption bands at 1687 and 1695 cm.$^{-1}$, indicative of conjugated carbonyl groups, and gave a 2,4-*dinitrophenylhydrazone*, m. p. 218—219° (Found: C, 60·6; H, 4·4; N, 14·5. $C_{20}H_{18}N_4O_5$ requires C, 60·9; H, 4·6; N, 14·2%), and *semicarbazone*, m. p. 234—236° (Found: C, 66·7; H, 6·2; N, 15·7. $C_{15}H_{17}N_3O_2$ requires C, 66·4; H, 6·3; N, 15·5%).

β-(8-*Oxo*-2-*tetralyl*)*propionic Acid* (VIII; $n = 1$) *and Aluminium Chloride*.—The procedure was the same as that above and gave the unchanged propionic acid and pale orange needles (0·15 g.), m. p. 116—117° (Found: C, 78·0; H, 6·0. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%). These have strong infrared absorption bands at 1678 and 1718 cm.$^{-1}$ and gave a 2,4-*dinitrophenylhydrazone*, m. p. 233—234° (Found: C, 59·9; H, 4·1; N, 14·3. $C_{19}H_{16}N_4O_5$ requires

[6] Cram, Allinger, and Steinberg, *J. Amer. Chem. Soc.*, 1954, **76**, 6132.

C, 60·0; H, 4·2; N, 14·7%), and a *disemicarbazone*, m. p. 200—201° (Found: C, 57·3; H, 5·8; N, 26·5. $C_{15}H_{18}N_6O_2$ requires C, 57·3; H, 5·7; N, 26·75%).

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