243. *The Mechanism of Condensation of the Anhydrides of Mono- and Di-substituted Succinic Acids with Aromatic Hydrocarbons under the Conditions of the Friedel–Crafts Reaction.*

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The condensation of the mono- and di-substituted succinic anhydrides with aromatic hydrocarbons in presence of aluminium chloride is discussed. The monosubstituted anhydride always produces two isomers, *viz.*, β-aroyl-α- and -β-monosubstituted propionic acids, but the disubstituted anhydride produces one acid only, the β-aroyl-αα-disubstituted propionic acid. One or two contradictions in the literature are shown to be due to inaccuracy. An explanation is offered for the production of two isomeric acids from the monosubstituted anhydride and the production of one isomeric acid from the disubstituted anhydride.

WHEN a benzene solution of a monoalkylated succinic anhydride is treated with aluminium chloride the main product is the α-substituted benzoylpropionic acid, $\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}CHR{\cdot}CO_2H}$ (I) with a smaller proportion of the β-substituted acid, $\mathrm{Ph{\cdot}CO{\cdot}CHR{\cdot}CH_2{\cdot}CO_2H}$ (II). The αα-disubstituted benzoylpropionic acid,

$$\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}CR_2{\cdot}CO_2H}\ \text{(III)},$$

is the only product from an unsymmetrically disubstituted succinic anhydride (Rothstein and Saboor, *J.*, 1943, 425; *q.v.* for references to previous work in this field). An apparent exception to this rule is the observation of Sen-Gupta (*J. Indian Chem. Soc.*, 1934, **11**, 392) that *cyclo*pentane-1-carboxylic-1-acetic anhydride furnishes 1-benzoyl-*cyclo*pentane-1-acetic acid, $\mathrm{Ph{\cdot}CO{\cdot}C(\colon C_4H_8){\cdot}CH_2{\cdot}CO_2H}$ (IV). Sen-Gupta found that this acid was identical with that obtained in the Friedel–Crafts reaction using the half ester chloride,

$$\mathrm{ClCO{\cdot}C(\colon C_4H_8){\cdot}CH_2{\cdot}CO_2Me}\ \text{(V)}.$$

The reactions of the acid (IV) do not confirm its assigned structure. Both this acid and its isomeride (III; $\mathrm{R} = \mathrm{\colon C_4H_8}$) can be expected to behave similarly towards reduction and cyclisation. On the other hand, the easy formation of a semicarbazone is inconsistent with the structure, $\mathrm{C_4H_8\colon C(CO{\cdot}Ph)}$–, where steric hindrance might be expected to impede it (cf. *inter alia*, Haller and Bauer, *Compt. rend.*, 1909, **148**, 72; 1910, **150**, 1475; Kipping, *J.*, 1894, **65**, 497; Rothstein and Saboor, *loc. cit.*). Rothstein and Saboor showed that tertiary acid chlorides should eliminate carbon monoxide in the Friedel–Crafts reaction resulting in a β-phenyl derivative :

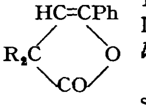
$$\text{(V)} \longrightarrow \mathrm{PhC(\colon C_4N_8){\cdot}CH_2{\cdot}CO_2Me + CO + HCl}$$

In the hands of these authors the half-ester chloride of *as*-dimethylsuccinic acid, $\mathrm{ClCO{\cdot}CMe_2{\cdot}CH_2{\cdot}CO_2Me}$, afforded β-benzoyl-αα-dimethylpropionic acid (III; R = Me). By the use of the more carefully controlled conditions described in the experimental portion of this paper, however, β-phenyl*iso*valeric acid,

$$\mathrm{PhCMe_2{\cdot}CH_2{\cdot}CO_2H}$$

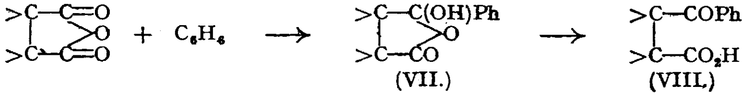
has been isolated, the expected loss of carbon monoxide taking place during the reaction. The foregoing considerations taken with the close analogy between the *gem*-dimethyl and the *cyclo*pentane groups (Vogel, *J.*, 1928, 2014) again suggests that (III; $\mathrm{R_2} = \mathrm{\colon C_4H_8}$) and not (IV) is the substance obtained from *cyclo*pentane-1-carboxylic-1-acetic anhydride.

The matter has now been put beyond doubt by refluxing the product with acetyl chloride when *γ-phenyl-αα-tetramethylene-Δ^{β}-butenolactone*, *i.e.*, the lactone of *cyclo*pentane-1-(α-hydroxystyryl)-1-carboxylic acid (VI; $\mathrm{R_2} = \mathrm{\colon C_4H_8}$) is obtained analogously to the formation of γ-phenyl-αα-dimethyl-Δ^{β}-butenolactone (VI; R = Me) from β-benzoyl-αα-dimethylpropionic acid (Rothstein and Saboor, *loc. cit.*).


(VI.)

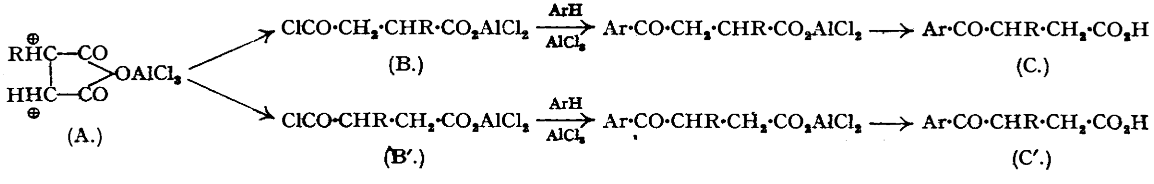
It is impossible to formulate the formation of an unsaturated lactone from the alternative structure (IV).

In Rothstein and Saboor's paper reasons were stated for rejecting the views of Haworth (*J.*, 1932, 1125) and of Desai and Wali (*Proc. Indian Acad. Sci.*, 1937, **6A**, 135) on the mechanism of the orientation of the phenyl group. A further point may now be considered. It is an essential part of these authors' formulation that the addition of benzene to the anhydride involves the α-carbonyl group with formation of the hydroxy-lactone (VII) which by a tautomeric change affords the ketone (VIII) :



It would appear unlikely, however, that (VII) could be formed without its undergoing further condensation yielding a lactone of a phthalide type. Furthermore, it does not appear that the activating influence of α-substituent groups on the carbonyl groups is a major factor in the orientation of the final product because ketonic groups do not generally undergo the Friedel–Crafts reaction; although they form addition complexes with aluminium chloride, a further molecule of the latter is needed before an acid anhydride will furnish the ketonic acid.

An alternative explanation is that the anhydride forms the complex through the ring oxygen and this results in the ionisation of the α-hydrogen atoms :



Ar = Ph or $\mathrm{C_6H_4Me}$. R = Alkyl or Aryl.

The formation of the complex A leads to the partial ionisation of the hydrogen atoms; a chlorine atom, separating as an anion, attaches itself to any available positive centre and results in the formation of the open-chain compounds B and B′. These in turn react with the aromatic hydrocarbon and *more* aluminium chloride producing the two isomeric ketonic acids. The chlorine ion attaches itself to the carbon with the greater number of ionisable hydrogen atoms, *i.e.*, C rather than C′ tends to be favoured. Solvents of high ionising power will also, therefore, increase the proportion of C. This is actually observed when phenylsuccinic anhydride is condensed in nitrobenzene solution (Desai and Wali, *loc. cit.*). It is evident that for asymmetrically disubstituted succinic anhydrides only one isomer should be formed, namely the β-aroyl-αα-disubstituted propionic acid.

The complex A has been isolated in the case of *as*-dimethylsuccinic anhydride by adding aluminium chloride to the anhydride dissolved in ligroin and distilling the mixture. The residue, on treatment with benzene, yielded β-benzoyl-αα-dimethylpropionic acid; when it was warmed with methanol, the methyl hydrogen ester, $CO_2Me{\cdot}CH_2{\cdot}CMe_2{\cdot}CO_2H$, was isolated, corresponding to the formation of the aluminium chloride complex, $ClCO{\cdot}CH_2{\cdot}CMe_2{\cdot}CO_2AlCl_2$, and thus affording evidence of the structure of the latter.

As mentioned above, the higher alkylated succinic anhydrides give entirely different products with elimination of carbon monoxide. Some explanation of this has already been given by Rothstein and Saboor (*loc. cit.*). A number of unsolved problems remain, however, and the work is being continued.

EXPERIMENTAL.

Lactone of cyclo*Pentane-*1-(α*-hydroxystyryl*)-1-*carboxylic Acid* (VI; $R_2 = {:}C_4H_8$).—The anhydride of 1-carboxy-*cyclo*pentane-1-acetic acid (10 g.) (Bardhan, *J.*, 1928, 2599) was dissolved in benzene (65 g.) and treated with anhydrous aluminium chloride (23 g.) and the keto acid formed was separated and recrystallised from ethyl acetate. The acid (5 g.) was gently refluxed with excess acetyl chloride and, after removal of the solvent, the fragrant residue solidified on standing over potassium hydroxide in an evacuated desiccator. It crystallised from ligroin in plates having m. p. 50—51° (Found: C, 78·4; H, 6·5. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

Reaction between the acid chloride of methyl 1-*carboxy*cyclo*pentane-*1-*acetic acid and benzene.* The acid chloride (10 g.) was dissolved in benzene (70 g.) and pulverised aluminium chloride (25 g.) was added gradually with cooling and shaking. After being at room temperature for a few hours, the mixture was warmed and finally refluxed for an hour on a water-bath. It was decomposed with water at 0°, acidified with dilute hydrochloride acid and extracted with ether. The ether extract was washed with water, dried and the ether distilled away. The residue was fractionally distilled under reduced pressure, two fractions being obtained: (1) having b. p. 125°/11 mm. (11 g.) was methyl 1-phenyl*cyclo*pentane-1-acetate (Found: C, 76·8; H, 8·5. Calc. for $C_{14}H_{18}O_2$: C, 77·4; H, 8·3%); (2) having b. p. 190°/11 mm. was 1-benzoyl-*cyclo*pentane-1-acetic acid (Found: C, 73·4; H, 7·2. Calc. for $C_{15}H_{18}O_3$: C, 73·2; H, 7·3%). A semicarbazone or 2 : 4-dinitrophenylhydrazone could not be prepared from the latter compound. Hydrolysis of these esters by alcoholic potash gave, respectively, 1-phenyl*cyclo*pentane-1-acetic acid in shining prisms from ethyl acetate, m. p. 120° (Found: C, 76·3; H, 7·9. Calc. for $C_{13}H_{16}O_2$: C, 76·5; H, 7·8%) and 1-benzoyl*cyclo*pentane-1-acetic acid in plates from rectified spirit, m. p. 161° (Found: C, 72·1; H, 7·1. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·9%).

Reaction between as.-*dimethylsuccinic anhydride and aluminium chloride in presence of ligroin.* The anhydride (17 g.) was dissolved in ligroin (b. p. 60—80°; 100 c.c.) and powdered aluminium chloride (40 g.) was added with cooling and shaking. The mixture was warmed and refluxed on the water-bath for 15 minutes. The ligroin was distilled away. Attempts to obtain the residual aluminium complex in pure state were unsuccessful. The aluminium complex was treated with benzene (72 g.) and warmed on a water-bath for two hours and the product separated and crystallised as usual. There were evidences of the formation of other compounds besides β-benzoyl-αα-dimethylpropionic acid. But the larger quantity, on repeated crystallisation, had m. p. 173°, the same as that of the acid obtained by the direct action of benzene on the anhydride under the conditions of the Friedel–Crafts reaction (Found: C, 69·8; H, 6·7. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8%).

Action of absolute methanol on the aluminium complex formed by the action of aluminium chloride on as.-*dimethylsuccinic anhydride.* *as*-Dimethylsuccinic anhydride (18 g.) was treated with aluminium chloride (40 g.) in ligroin (b. p. 60—80°; 68 g.) and finally heated on the water-bath till a homogeneous dark-coloured liquid was obtained. Excess of ligroin was distilled away under reduced pressure, the residue treated with absolute methanol (15 g.) and refluxed for about 2 hours; excess alcohol was distilled away and the residue decomposed with water at 0°, acidified and extracted with ether. The ether extract was dried and the ether distilled away; the residual oil solidified when kept under reduced pressure. It was crystallised twice from ligroin. It was methyl hydrogen *as*-dimethylsuccinate (β-form), m. p. 51°.

β-*Phenyl*iso*valeric acid.* The half ester prepared by gently refluxing *as*-dimethylsuccinic anhydride and sodium methoxide in equivalent proportions was treated with slight excess of thionyl chloride. Excess of thionyl chloride was distilled away. Benzene (7 g. for each 2 g. of the anhydride) was added. Aluminium chloride (4 g. for each 2 g. of the anhydride) was next gradually added with cooling and shaking. The mixture was kept at room temperature and then refluxed on a water-bath for an hour. The issuing gas was chiefly carbon monoxide. The product was decomposed by water at 0° and acidified with hydrochloric acid. It was then extracted with ether; the ether extract was washed with dilute sodium carbonate solution and water and dried. The ether was distilled away at the ordinary pressure and the residue collected at 122°/10 mm. This was refluxed with alcoholic potash for 9 hours. After acidification an oil, which solidified on cooling, slowly precipitated. It was separated, pressed on porous plate and crystallised from ligroin (b. p. 60—80°) giving colourless prisms, m. p. 59°. This was the acid prepared by Hoffman (*J. Amer. Chem. Soc.*, 1929, **51**, 2545) in a different way (Found: C, 74·4; H, 8·1. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%).

Reaction between as.-*dimethylsuccinic anhydride and benzene.* Experiments, using widely different conditions, carried out with the object of obtaining the β-isomeride were unsuccessful. Employment of rigorous conditions increased the amount of tar and decreased the yield of the α-isomer already reported (*J.*, 1943, 428). The reaction, finally carried out as described by Rothstein and Saboor (*J.*, 1943, 428), consisted in adding pulverised aluminium chloride (72 g.) to a solution of the anhydride (34 g.) in benzene (70 g.) and nitrobenzene (70 g.) with cooling and shaking. The mixture was allowed to stand at the room temperature for two hours then gently warmed and, finally, heated on the water-bath for an hour. It was decomposed by water at 0°, acidified with hydrochloric acid and extracted with ether. The ether extract was dried and the ether distilled away at ordinary pressure and the nitrobenzene removed under reduced pressure. The residue was steam distilled until free from oily material. It was treated with aqueous sodium hydroxide till alkaline, filtered, and the filtrate concentrated to a small volume and acidified. The precipitate was dried and crystallised fractionally from ethyl acetate. All the fractions had m. p. 173° and were β-benzoyl-αα-dimethylpropionic acid. The yield was 47 g., 90% of the theoretical amount.

β-Benzoyl-α-phenylpropionic acid and β-benzoyl-β-phenylpropionic acid. Phenylsuccinic anhydride was prepared according to the method of Lapworth and McRae (*J.*, 1922, 2741). It was converted into the anhydride by refluxing with acetic anhydride. The anhydride (18 g.) was dissolved in benzene (78 g.). Powdered aluminium chloride (30 g.) was gradually added to the mixture with shaking and cooling. After standing for some hours at room temperature, the mixture was warmed and finally heated on the water-bath for two hours. The dark-coloured product was decomposed by being poured into water at 0° and acidification with hydrochloric acid. It was extracted with ether and the ether extract dried and the ether removed. The sodium carbonate extract of the residual oil was acidified and the crude acids (17 g.) separated. This mixture was fractionally crystallised from benzene–alcohol. The first fraction, m. p. 169°, was the β-acid. The other fractions melted indefinitely from 140°. These, on further crystallisation, gave β-benzoyl-α-phenylpropionic acid, m. p. 154°.

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