The Cyclisation of Some Substituted Phenylsuccinic Acids.

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[Reprint Order No. 5221.]

The cyclisation of derivatives of phenylsuccinic acid has been investigated as a route to the corresponding indane-1-carboxylic acids required in the synthesis of analogues of cortical hormones (see also Linnell, Mathieson, and Modi, *J.*, 1953, 3257).

Cyclisation by the Friedel–Crafts and the hydrogen fluoride method has been investigated and evidence is given of the sensitivity of anhydrous hydrogen fluoride to activating and deactivating influences in the cyclisation process.

Phenylsuccinic acid has been cyclised by sulphuric acid (Speight, Stevenson, and Thorpe, *J.*, 1924, 2185), by fluorosulphonic acid (Baker, Coates, and Glockling, *J.*, 1951, 1376), and by the Friedel–Crafts method (Baker and Leeds, *J.*, 1948, 974). *p*-Methoxyphenylsuccinic acid was reported resistant to cyclisation by sulphuric acid and by phosphoric oxide (Chatterjee and Barpujari, *J. Indian Chem. Soc.*, 1940, **17**, 292).

The derivatives of phenylsuccinic acid used in the present work were prepared by modifications of the original method of Baker and Lapworth (*J.*, 1925, 560). Nitrobenzene was used as solvent in cyclisations by the Friedel–Crafts method: intermediate acid chlorides or anhydrides were not isolated.

m-Methoxyphenylsuccinic acid when cyclised by the Friedel–Crafts method at 80° gave 6-methoxy-3-oxoindane-1-carboxylic acid, the constitution of which was verified by oxidation with alkaline potassium permanganate to 4-methoxyphthalic acid. In addition, a small amount of an isomer was produced, presumably 4-methoxy-3-oxoindane-1-carboxylic acid formed by cyclisation into the position *ortho* to the methoxy-group.

Under similar conditions, 3 : 4-dimethoxyphenylsuccinic acid gave 5 : 6-dimethoxy-3-oxoindane-1-carboxylic acid. The consitution of this compound was established by decarboxylation to the known 5 : 6-dimethoxyindanone.

Both of these phenylsuccinic acids were readily cyclised by anhydrous hydrogen fluoride, and quantitative determination of the products (see Table) showed that cyclisation had occurred almost to the theoretical extent.

In contrast, *p*-methoxyphenylsuccinic acid could not be cyclised under the Friedel–Crafts conditions adequate for the above acids. The product was mainly a tar from which no ketone could be isolated. When a temperature of 150° was used, only small amounts (less than 5%) of ketonic material were isolated in addition to tar. By a comparable procedure, β-*p*-methoxyphenylglutaric acid has been cyclised with simultaneous demethylation (Hey and Kohn, *J.*, 1949, 3177). Molten sodium chloride–aluminium chloride (Bruce, Sorrie, and Thompson, *J.*, 1953, 2403) also gave less than 5% of ketonic material. It appears that *p*-methoxyphenylsuccinic acid, having a carboxyl group nearer the aromatic ring, is far more resistant to cyclisation than β-*p*-methoxyphenylglutaric acid (see Badger, Campbell, and Cook, *J.*, 1949, 1084). *p*-Methoxy- and *p*-hydroxy-phenylsuccinic acid gave no detectable ketonic product by the action of anhydrous hydrogen fluoride (28 hours), and starting material was recovered.

p-Ethylphenylsuccinic anhydride was cyclised by the Friedel–Crafts method to 5-ethyl-3-oxoindane-1-carboxylic acid (isolated *via* the semicarbazone); yields from the acid chloride were inferior. Reaction of *p*-ethylphenylsuccinic acid with anhydrous hydrogen fluoride is slow, and a prolonged period of reaction (14 days) was necessary for the reaction to approach completion.

The results of the action of anhydrous hydrogen fluoride on derivatives of phenylsuccinic acid show this reagent to be peculiarly sensitive to activating and deactivating influences. A number of derivatives were cyclised by anhydrous hydrogen fluoride and the amounts of keto-acid in the crude products of the reaction determined as the 2 : 4-dinitrophenylhydrazones. In addition, since the products were clean and free from tar, in most cases it was possible to make an approximate determination by direct titration of the product, on the assumption that it consisted of a mixture of dibasic and monobasic (keto-)acid only. The

results, which are roughly parallel, are given in the Table below. Phenylsuccinic acid is largely unchanged by the action of anhydrous hydrogen fluoride (28 hours), which illustrates the deactivating effect of a carboxyl group α to a phenyl nucleus (Badger, Campbell, and Cook, *loc. cit.*; Ansell and Hey, *J.*, 1950, 2874). This effect is offset, to some extent, by *p*-alkyl groups. A *m*-methoxy-group, which specifically activates the position into which cyclisation occurs, entirely overcomes the deactivating effect. It appears that anhydrous hydrogen fluoride, being highly selective in operation, offers a more reliable means for comparing the relative ease of cyclisation of carboxylic acids than does anhydrous aluminium chloride.

Acid	Time of reaction	Keto-acid (%) as dinitrophenylhydrazone	Keto-acid (%) by titration
Phenylsuccinic	28 hr.	4	6
Phenylsuccinic	48 ,,	6	11
Phenylsuccinic (anhydride)	28 ,,	11	15
p-Methoxyphenylsuccinic	28 ,,	0	—
p-Hydroxyphenylsuccinic	28 ,,	0	—
p-Ethylphenylsuccinic	28 ,,	21	25
p-Ethylphenylsuccinic	14 days	83	89
m-Methoxyphenylsuccinic	28 hr.	100	102
3 : 4-Dimethoxyphenylsuccinic	28 ,,	96	100

Experimental

Preparation of Acids.—m-*Methoxyphenylsuccinic acid.* (*a*) *m*-Hydroxybenzaldehyde (110 g.) was dissolved in a solution from sodium (21 g.) in alcohol (700 ml.). Methyl iodide (141 g.) was added to the cool solution and the mixture set aside for 3 days. Alcohol (approx. 500 ml.) was then removed by distillation, the residue was poured into water, and the mixture extracted with ether. The extract was dried (Na_2SO_4) and fractionally distilled, to give *m*-methoxybenzaldehyde (86 g., 70%), b. p. 103—105°/8 mm., n_D^{25} 1·5508. (*b*) Piperidine (1 ml.) was added to a mixture of *m*-methoxybenzaldehyde (34 g.) and ethyl cyanoacetate (29 g.); heat was evolved and water separated. The mixture was set aside for 2 hr., with occasional shaking, after which alcohol (40 ml.) was added followed by sodium cyanide (16 g.) in water (20 ml.). A solid was deposited overnight and was removed and freed, as far as possible, from dark liquid by pressure; it was then hydrolysed by 4 hours' refluxing with concentrated hydrochloric acid (450 ml.). The cooled solution was filtered and the crude product crystallised, with constant stirring, from water (300 ml.). The yield was 28 g. (45% from *m*-methoxybenzaldehyde) and the m. p. 174—175° (Found: C, 59·0; H, 5·4; MeO, 13·8%; equiv., 112·6. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4; MeO, 13·85%; equiv., 113·1).

p-*Methoxyphenylsuccinic acid.* By method (*b*), *p*-anisaldehyde (41 g.) gave a crude product (47·5 g.) which, when crystallised from water (1500 ml.), gave *p*-methoxyphenylsuccinic acid (39·4 g., 59%), m. p. 203—203·5°.

p-*Ethylphenylsuccinic acid.* *p*-Ethylbenzaldehyde (29 g.), ethyl cyanoacetate (24·5 g.), piperidine (1 ml.), and benzene (50 ml.) were refluxed together in a Dean–Stark apparatus. When the theoretical amount of water had been evolved, ether was added, and the mixture shaken with 5% hydrochloric acid, and then with water until the washings were neutral to litmus. The ethereal solution was dried (Na_2SO_4) and fractionally distilled. The separation of a sharp fraction was difficult owing to decomposition or chemical change which occurred on distillation. The fraction distilling at 130—140°/0·05 mm. (22·9 g.) was mixed with alcohol (15 ml.), and sodium cyanide (6·2 g.) in water (11 ml.) was added. The mixture was set aside overnight, then diluted with water (400 ml.) and acidified with concentrated hydrochloric acid (30 ml.). A heavy yellow oil was precipitated from which the supernatant liquid was decanted. The oil was heated under reflux for 6 hr. with concentrated hydrochloric acid (350 ml.), and the crude product removed by filtration from the cooled mixture. Crystallisation from water (1200 ml.) gave pale yellow p-*ethylphenylsuccinic acid* (12·75 g., 27% from *p*-ethylbenzaldehyde), m. p. 188—189°. Recrystallisation from alcohol (30 ml.) gave a colourless product (8·5 g.) of the same m. p. (Found: C, 64·9; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). The *dimethyl ester* is a colourless liquid, b. p. 155°/8 mm. (Found: C, 67·1; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·25%).

Other derivatives of phenylsuccinic acid were prepared by methods previously described in the literature, *viz.*, phenylsuccinic acid (*Org. Synth.*, Coll. Vol. I, 1st Edn., p. 440): *p*-hydroxyphenylsuccinic acid [Chrzaszezewska, *Roczn. Chem.*, 1925, **5**(1—3), 33]: 3 : 4-dimethoxyphenyl-

succinic acid (Richardson, Robinson, and Seijo, *J.*, 1937, 835): phenylsuccinic anhydride (Robinson and Young, *J.*, 1935, 1414).

Cyclisation Experiments.—Reactions involving anhydrous hydrogen fluoride were conducted in " Polythene " screw-cap bottles. For the quantitative determinations (see Table), the solution of the acid (3 g.) in anhydrous hydrogen fluoride (approx. 30 ml.) was set aside for the required time, after which it was poured into a " Polythene " beaker and allowed to evaporate in a good draught in the fume cupboard. The residue was air-dried at 40°. Titrations of the residue were performed in aqueous alcohol. Quantitative determinations by 2 : 4-dinitrophenylhydrazine were conducted by Sharp's method (*Analyst*, 1951, **76**, 215, method *h*). Hot water (40 ml.) was used for the final washing of each precipitate.

m-*Methoxyphenylsuccinic Acid.*—(*a*) The acid (10 g.) and pure thionyl chloride (15 ml.) were refluxed together and, when the reaction was complete, the excess of chloride was removed at the water-pump. The residue was added (with the aid of 15 ml. of nitrobenzene) to a solution of anhydrous aluminium chloride (6·25 g.) in nitrobenzene (75 ml.). The mixture was heated for 30 min. in an oil-bath at 80—85° and then poured on crushed ice and dilute hydrochloric acid. Nitrobenzene was removed in steam, conditions being adjusted so that the volume of solution remaining was approx. 350 ml. The crude product (5·4 g.) deposited from this solution on cooling was recrystallised from alcohol (30 ml.) to give *6-methoxy-3-oxoindane-1-carboxylic acid* as colourless needles (4·3 g., 47%), m. p. 186·5—187·5°, unchanged on further crystallisation (Found: C, 64·0; H, 4·7; MeO, 15·1%; equiv., 208·2. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9; MeO, 15·05%; equiv., 206·2). The *semicarbazone* crystallised from aqueous alcohol in colourless felted needles, m. p. 227° (decomp.) (Found: C, 54·7; H, 5·0; N, 15·7. $C_{12}H_{13}O_4N_3$ requires C, 54·75; H, 4·95; N, 16·0%). The combined aqueous mother-liquors from three experiments as above were evaporated to low volume; a dark brown solid (4·7 g.) separated from the cooled solution. Two crystallisations from alcohol gave colourless needles (1 g.), m. p. 216° (decomp.), presumably *4-methoxy-3-oxoindane-1-carboxylic acid* (Found C, 64·3; H, 4·7; MeO, 15·0%; equiv., 208·2).

(*b*) *m*-Methoxyphenylsuccinic acid (20 g.) was dissolved in anhydrous hydrogen fluoride (approx. 100 ml.). After 7 days, the solution was allowed to evaporate to dryness and the residue crystallised from water (1000 ml.) to give 6-methoxy-3-oxoindane-1-carboxylic acid (9 g., 49%). By evaporation of the mother-liquors and crystallisation of the product as above, the isomeric keto-acid (1·5 g.) was obtained in addition to mixtures of the two isomers. The products of the reaction are apparently volatile in steam as only two-thirds of the total solids was recovered when the solution was evaporated to low volume. 6-Methoxy-3-oxoindane-1-carboxylic acid (1 g.) was oxidised by alkaline potassium permangantae (Hey and Kohn, *J.*, 1949, 3177). The crude product (0·85 g.) when crystallised from water gave 4-methoxyphthalic acid, m. p. and mixed m. p. 163·5° (authentic sample, 164°). The anhydride prepared by vacuum sublimation had m. p. 89·5—90·5° with shrinking at 87°.

3 : 4-*Dimethoxyphenylsuccinic Acid.*—(*a*) The acid (38·2 g.) was refluxed with pure thionyl chloride (60 ml.), and the reaction completed as described above, with anhydrous aluminium chloride (21 g.) and nitrobenzene (280 ml.), the reaction time being 40 min. After the nitrobenzene had been removed, a dark brown solid (17 g.) was deposited from the cooled residual solution (830 ml.), and a further crop (8·7 g.) was collected after evaporation of the solution to 290 ml. Further evaporation gave tars. The two crops were combined and crystallised from methanol (150 ml.) and from water, to give *5 : 6-dimethoxy-3-oxoindane-1-carboxylic acid* as colourless needles (13·5 g., 38%), m. p. 190—190·5° with softening at 184° (Found: C, 60·9; H, 4·95; MeO, 26·4%; equiv., 238·0. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1; MeO, 26·3%; equiv., 236·2). The *oxime* crystallised from aqueous alcohol as colourless needles, m. p. indefinite (darkens above 200°, almost black at 217°) (Found: C, 57·5; H, 5·4; N, 5·7. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6%).

(*b*) The acid (5 g.) was dissolved in anhydrous hydrogen fluoride (50 ml.). After 28 hr., the solution was allowed to evaporate and the residue crystallised from water (170 ml.), to give pale buff needles (3·4 g., 73%), m. p. 185—186° (with softening at 183°) unchanged on further crystallisations from methanol and from ethanol. Since the crude product of this cyclisation contains almost 100% of keto-acid (see Table), the low m. p. must be ascribed to the presence of an isomer. 5 : 6-Dimethoxy-3-oxoindane-1-carboxylic acid (1 g.), quinoline (10 ml.), and copper bronze (1 g.) were heated together at 220—230°. After 10 min., the vigorous reaction had subsided. Ether was added to the cooled mixture and the copper bronze removed by filtration. Quinoline was removed by 15% hydrochloric acid. The acid solution was repeatedly extracted with ether, then all the ethereal solutions were combined, washed with sodium hydrogen

carbonate solution, and dried (Na_2SO_4). Evaporation of the ether gave pale yellow prisms (0·4 g.) which, when crystallised from toluene–light petroleum (b. p. 80—100°), gave 5 : 6-dimethoxyindanone as large yellow prisms, m. p. 114—116°. The 2-*m*-methoxybenzylidene derivative (Perkin, Ray, and Robinson, *J.*, 1926, 941) had m. p. 162·5—163°.

p-*Ethylphenylsuccinic Acid.*—(*a*) The acid (4·4 g.) was refluxed with acetyl chloride (25 ml.) : when the reaction was complete, the excess of acetyl chloride was removed at the water-pump. The general procedure used in the cyclisation of *m*-methoxyphenylsuccinic acid was then followed, with anhydrous aluminium chloride (5·6 g.) and nitrobenzene (50 ml.). After the nitrobenzene had been removed, an oil was separated from the aqueous solution by extraction with ether. Removal of the ether gave a viscous residue which was dissolved in alcohol (12 ml.). The alcoholic solution was heated, under reflux, for 15 min. with semicarbazide hydrochloride (3 g.) and sodium acetate (6 g.) in water (20 ml.). The mixture was cooled and filtered, and the residue washed with boiling alcohol (10 ml.) to remove unchanged *p*-ethylphenylsuccinic acid : the crude semicarbazone remained as a pale yellow powder (4·1 g., 79%), which crystallised from ethoxyethanol as colourless needles, m. p. 242° (decomp.). The crude semicarbazone (0·7 g.) was decomposed by refluxing it for 20 min. with concentrated hydrochloric acid (25 ml.). Water (10 ml.) was added, and the hot solution filtered. The filtrate was extracted with ether, and the washed and dried ethereal solution evaporated to a viscous residue (0·35 g.). Crystallisation from water (approx. 70 ml.) with seeding gave *5-ethyl-3-oxoindane-1-carboxylic acid* as colourless needles, m. p. 87—88° (Found : C, 70·7; H, 5·9. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone*, crystallised from alcohol–xylene, melts partly at 211° (Found : C, 56·6; H, 4·4; N, 14·2. $C_{18}H_{16}O_6N_4$ requires C, 56·2; H, 4·2; N, 14·6%).

(*b*) *p*-Ethylphenylsuccinic acid (4·4 g.) was dissolved in anhydrous hydrogen fluoride (approx. 40 ml.). After 14 days, the hydrogen fluoride was allowed to evaporate, and the residue was converted into the semicarbazone as above. The yield was 3·7 g., corresponding to 71% of 5-ethyl-3-oxoindane-1-carboxylic acid.

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[*Received, March 20th*, 1954.]