THE STOBBE CONDENSATION OF ANISALDEHYDE AND DIMETHYL SUCCINATE

Synthesis of the Lactone of 2-Carboxy-4-Hydroxy-6-Methoxytetralone-1*

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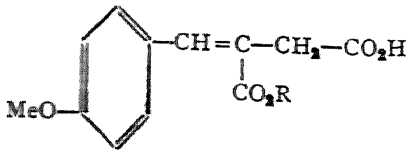
THE Stobbe condensation between *p*-methoxybenzaldehyde and diethyl succinate had been reported to yield only the dialkylidenesuccinic acid,[1] but Campbell, Cella and Campbell[2] adopting the procedure of Cornforth, Hughes and Lions[3] have obtained *p*-methoxyphenylitaconic acid. During the course of a scheme of work, we obtained methyl hydrogen *p*-methoxyphenylitaconate (I *a*) by condensing *p*-methoxybenzaldehyde with dimethyl succinate in the presence of potassium *tert.*-butoxide; and in view of the recent publication of El-Abbady and El-Assal[4] we are reporting our experiments.

The unsaturated half ester (I *a*) on reduction with 10% palladium on carbon yielded methyl hydrogen α-*p*-methoxybenzylsuccinate (II *a*) which on cyclisation with polyphosphoric acid gave a mixture of the tetralone compounds (IV *a* and IV *b*), the acid (IV *b*) being evidently formed by hydrolysis of the ester (IV *a*). The structures of these were proved by comparison with authentic specimens.[2]



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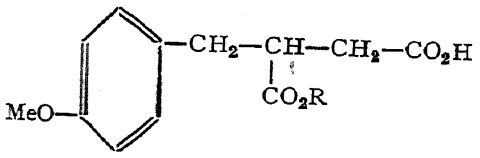
b R=H



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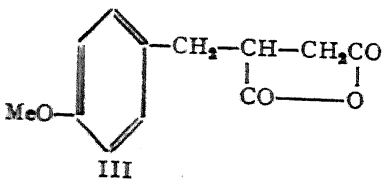
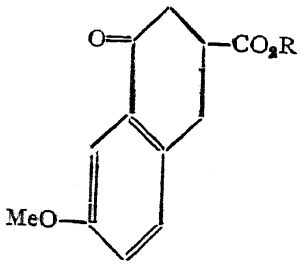
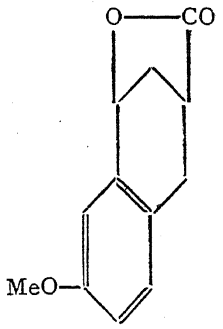


III

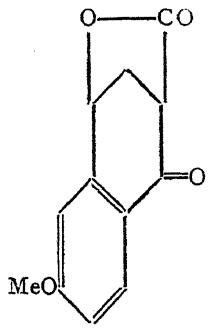


IV *a* R=Me
b R=H

* Presented at the Forty-fifth Session of the Indian Science Congress held at Madras in 1958.



V



VI

However, it was found that 3-carboxy-7-methoxytetralone-1 (IV *b*) could be most conveniently prepared by condensing *p*-methoxybenzaldehyde and dimethyl succinate in methanolic sodium methoxide,[3] followed by reduction of an alkaline solution of the *p*-methoxyphenylitaconic acid (I *b*) with nickel-aluminium alloy[5 a,b] when the saturated acid (II *b*) was obtained (there being no loss of the methoxyl group[5 c]) in 95% yield. The anhydride of the diacid (II *b*) was cyclised with anhydrous aluminium chloride in nitrobenzene to give 3-carboxy-7-methoxytetralone-1 (IV *b*) in 70% yield.

An aqueous solution of the sodium salt of 3-carboxy-7-methoxytetralone-1 on reduction with sodium borohydride followed by lactonisation of the hydroxy acid gave a poor yield of the lactone (V). 3-Methoxycarbonyl-7-methoxytetralone-1 (IV *a*) on reduction with aluminium isopropoxide gave in the neutral fraction the lactone (V) as one of the products. Oxidation of this lactone (V) with chromium trioxide in acetic acid yielded the lactone of 2-carboxy-4-hydroxy-6-methoxytetralone-1 (VI).

Experimental

Stobbe Condensation of p-*Methoxybenzaldehyde and Dimethyl Succinate*

(*a*) *With Potassium* tert.-*butoxide*.—To a stirred solution of potassium *tert*.-butoxide, from potassium (10·80 g.) and *tert*.-butanol (270 ml.), under nitrogen was added dimethyl succinate (73·4 g.) which was washed down with *tert*.-butanol (15 ml.). To this was added with vigorous stirring during 1·5 hour freshly distilled *p*-methoxybenzaldehyde (32·64 g.) in *tert*.-butanol (30 ml.). After stirring for 10 hr. at room temperature (*ca.* 23°) it was cooled and dilute hydrochloric acid (25·3 ml. of conc. hydrochloric acid in 168 ml. of water) was added gradually with stirring. Most of the butanol was distilled off under reduced pressure, the residue was taken up in ether, and the ethereal solution extracted with saturated sodium bicarbonate solution at 0°. The alkaline solution was run into an excess of cold hydrochloric acid, and the acid solution extracted with ether, the ethereal phase was washed

with cold water, and dried, and the ether was distilled off. On cooling, a solid (59·3 g.) melting at 87–96° was obtained. After two crystallisations from benzene-light petroleum (40–60°) *methyl hydrogen* p-*methoxyphenylitaconate* (I *a*) (35·7 g.; m.p. 118–19°, lit.[4] 119–20°; U.V.: $\lambda_{max.}^{alc.}$ 294 mμ log ε 4·42) was obtained (Found: C, 62·58; H, 5·52. $C_{13}H_{14}O_5$ requires C, 62·40; H, 5·64%. Equivalent weight: Found, 249·4; $C_{13}H_{14}O_5$ requires 250·2).

(*b*) *With sodium methoxide.*[3]—To a stirred solution of methanolic sodium methoxide, from sodium (57·5 g.) and methanol (450 ml.), was gradually added under reflux a mixture of *p*-methoxybenzaldehyde (136 g.) and dimethylsuccinate (160 g.) over a period of 0·5 hr. The stirred yellow reaction mixture was refluxed for 2·5 hr. and then water (500 ml.) was added cautiously with simultaneous distillation of methanol. When methanol had ceased to distil, the reaction mixture was diluted with a further 750 ml. of water, extracted twice with ether (300 ml.) and then the alkaline phase was slowly run in with stirring to an excess of ice-cold hydrochloric acid. The precipitated acid on repeated crystallisations from aqueous ethanol yielded *p*-methoxyphenylitaconic acid (I *b*) (172 g.; m.p. 192–94°, recorded 188–91°,[2] 202–03°[4]; U.V.: $\lambda_{max.}^{alc.}$ 294 mμ log ε 4·36).

Methyl hydrogen α-p-*methoxybenzylsuccinate* (*II* a).—The unsaturated half-ester (I *a*) (2·1 g.) in dioxane (30 ml.) containing 60% perchloric acid (1 ml.) was hydrogenated at room temperature over 10% palladium on carbon. After filtering off the catalyst, the reduced material was taken up in a large quantity of ether and repeatedly washed with ice-cold water till the aqueous phase was free of acid. On drying the ethereal phase and on complete removal of the solvent *methyl hydrogen* α-*p-methoxybenzylsuccinate* (II *a*) (1·91 g.; U.V.: $\lambda_{max.}^{alc.}$ 226 mμ log ε 4·06, 277·5 mμ log ε 3·25) was obtained as a semi-solid. A sample was purified by molecular distillation for analysis (Found: C, 61·75; H, 6·34. $C_{13}H_{16}O_5$ requires C, 61·87; H, 6·35%).

p-*Methoxybenzylsuccinic acid* (*II* b).—*p*-Methoxyphenylitaconic acid (I *b*) (42·5 g.) was dissolved in 1 l. of 12% aqueous sodium hydroxide. A few drops of octyl alcohol was introduced and then to the stirred solution at 90° was gradually added 1 : 1-nickel-aluminium alloy (85 g.) over 1·75 hr. After stirring for a further 0·75 hr. at 90°, the hot solution was cautiously filtered under suction[5 a] and the catalyst washed well with water. The warm alkaline solution was then added slowly with stirring to a large excess of hydrochloric acid. The reduced acid was either filtered (if solid), or extracted with ether (if oily) and the solvent removed, when *p*-methoxy-

benzylsuccinic acid (42·0 g.; m.p. 95–98° or 106–09°) was obtained. Recrystallisation from dilute alcohol or dilute acetic acid yielded either of the polymorphs m.p. 101° or 114° showing no depression with samples prepared by the procedure of Campbell *et al.*[2]

Cyclisation of Methyl Hydrogen α-p-Methoxybenzylsuccinate (II a)

(*a*) *With polyphosphoric acid.*—To a stirred solution of phosphorous pentoxide (30 g.) in syrupy phosphoric acid (sp. gr. 1·75; 15 ml.) was added the half-ester (II *a*) (4·9 g.) under anhydrous conditions. It was heated for 40 min. on a steam-bath, and then to the reaction mixture was added crushed ice (100 g.) and water (100 ml.). It was extracted with ether (there was a considerable quantity of tar formed), and the ethereal solution washed with ice-cold 5% alkali, then with brine and dried. On removal of the solvent, the neutral phase deposited 3-methoxycarbonyl-7-methoxytetralone-1 (IV *a*) (0·6 g.). On crystallisation from ether-light petroleum (40–60°) the ester melted at 80–81° (recorded 78–79·5°[2]); U.V.: $\lambda_{max.}^{alc.}$ 253 mμ log ε 3·98, 323 mμ log ε 3·19 (Found: C, 67·08; H, 6·09. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·02%).

The alkaline wash on running into ice-cold hydrochloric acid yielded 3-carboxy-7-methoxytetralone-1 (IV *b*) (1·8 g.). After crystallisation from acetone-benzene it melted at 152–53° (recorded 149–51°[2]); U.V.: $\lambda_{max.}^{alc.}$ 253 mμ log ε 3·99, 322 mμ log ε 3·21 (Found: C, 65·65; H, 5·35. $C_{12}H_{12}O_4$ requires C, 65·46; H, 5·50%).

(*b*) *With aluminium chloride.*—To a suspension of the half-ester (II *a*) (7·15 g.) in dry benzene (100 ml.) was added dropwise a solution of thionyl chloride (5 ml.) in dry benzene (15 ml.) with swirling. After refluxing gently for 2·75 hr. the excess thionyl chloride and all the benzene were removed completely under suction. To a stirred solution of the crude acid chloride in benzene (100 ml.) kept at 0° was added a solution of aluminium chloride (9·5 g.) in dry benzene (20 ml.). After leaving it overnight at room temperature, it was decomposed with ice-cold 2 N-hydrochloric acid, and extracted with ether. After removal of the solvent the crude oily material was dried thoroughly and saponified with 10% aqueous potassium hydroxide. On working up, 3-carboxy-7-methoxytetralone-1 (IV *b*) (1·2 g.; m.p. 151–52°) was obtained.

3-*Carboxy-7-methoxytetralone*-1 (*IV* b) *from* p-*methoxybenzylsuccinic acid* (*II* b).—*p*-Methoxybenzylsuccinic acid (72·3 g.) was converted to the anhydride (III) by treatment with an excess of acetyl chloride at room temperature for 6 hours. (A sample crystallised from benzene-hexane melted at 91–92°, lit.[2] 90–92°.) A suspension of the crude anhydride (64·8 g.; m.p.

87–90°) in nitrobenzene (150 ml.) was added portionwise over a period of 20 mins. at room temperature to a vigorously stirred solution of aluminium chloride (125 g.) in nitrobenzene (400 ml.); the temperature rose to about 40°. It was left overnight (15 hr.) with stirring under anhydrous conditions. The reaction mixture was decomposed with ice and hydrochloric acid and the nitrobenzene removed by steam-distillation. The solid product on repeated crystallisations from hot water (charcoal) yielded 3-carboxy-7-methoxytetralone-1 (IV *b*) (46·2 g.; yield 71%; m.p. 151–53°).

To an ethereal suspension of 3-carboxy-7-methoxytetralone-1 (IV *b*) (2·0 g.) kept at 0°, was added a solution of diazomethane (from 3·0 g. of nitrosomethylurea) in ether in small portions. The resulting pale yellow solution after standing for 5 min., was treated with a little acetic acid and then washed with ice-cold potassium carbonate solution and water. After drying, on removal of the solvent, the residue (2·1 g.) melted at 70–75° which on crystallisation from ether-light petroleum (40–60°) furnished 3-methoxycarbonyl-7-methoxytetralone-1 (IV *a*), m.p. 80°.

Lactone of 1-Hydroxy-3-carboxy-7-methoxytetralin (V)

(*a*) *Reduction with sodium borohydride.*—To a solution of 3-carboxy-7-methoxytetralone-1 (IV *b*) (5·0 g.) in 1 N-sodium hydroxide (22·8 ml.) was added sodium borohydride (0·65 g.) with swirling at room temperature. The reaction mixture after standing overnight was cooled and acidified with dilute sulphuric acid (6·5 ml. of conc. acid in 125 ml. water). It was then warmed for 15 min. on a steam-bath, cooled and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, water and dried. On removal of the ether, a solid residue (1·9 g.; m.p. 101°) was obtained. Crystallisation from benzene-hexane yielded the *lactone of 1-hydroxy-3-carboxy-7-methoxytetralin* (1·8 g.); m.p. 103°; U.V.: $\lambda_{max.}^{alc.}$ 232 mμ log ε 4·00, 280 mμ log ε 3·36; I.R.: 1792 cm.$^{-1}$ (γ-lactone) (Found: C, 70·31; H, 6·01. $C_{12}H_{12}O_3$ requires C, 70·58, H, 5·93%).

(*b*) *Reduction with aluminium isopropoxide.*—From 3-methoxycarbonyl-7-methoxytetralone-1 (IV *a*) (2·32 g.), aluminium isopropoxide (2·1 g.) and dry isopropanol (30 ml.), acetone was distilled off using a Hahn condenser containing methanol under anhydrous conditions. After complete removal of the acetone much of the isopropanol was removed under suction and the residue was decomposed at 0° with ice-cold hydrochloric acid (3·5 ml. conc. acid and 17·5 ml. water). The product was extracted with ether and the ethereal solution was washed with ice-cold sodium bicarbonate solution, brine and dried (Na_2SO_4). Most of the ether was removed and light petroleum (40–60°) was added to it, and then the material was left in the

refrigerator. The precipitated solid was filtered and washed with a little dry ether (yield 0·09 g.; m.p. 102–03°). The lactone was recrystallised from ether-light petroleum (40–60°), m.p. 103°.

Lactone of 2-carboxy-4-hydroxy-6-methoxytetralone-1 (VI).—To a solution of the lactone of 1-hydroxy-3-carboxy-7-methoxytetralin (V) (0·2 g.) in acetic acid (2·1 ml.) and propionic acid (0·4 ml.) at 0° was added with swirling, in the course of 8 min., a solution of chromium trioxide (0·2 g.) in water (0·2 ml.) and acetic acid (1·1 ml.). After keeping at 0° for a further 40 min. it was left at room temperature for 24 hr. After addition of a small quantity of methanol, the deep violet product was poured into water (50 ml.) and extracted with ether. The combined ether extract was washed with ice-cold potassium carbonate solution, water and dried. On distillation of the ether a white precipitate was obtained (0·14 g.; m.p. 134–36°). *The lactone of 2-carboxy-4-hydroxy-6-methoxytetralone-1* (VI) was recrystallised from ether-light petroleum (40–60°), m.p. 136°; U.V.: $\lambda_{max}^{alc.}$ 228 mμ log ε 4·31, 292·5 mμ log ε 4·31; I.R.: 1790 cm.$^{-1}$ (γ-lactone), 1700 cm.$^{-1}$ (aryl conjugated carbonyl) (Found: C, 65·72; H, 4·57. $C_{12}H_{10}O_4$ requires C, 66·04; H, 4·62%).

Summary

Condensation of anisaldehyde and dimethyl succinate in presence of potassium *tert.*-butoxide yielded methyl hydrogen *p*-methoxyphenylitaconate. Reduction followed by cyclisation with polyphosphoric acid furnished 3-methoxycarbonyl-7-methoxytetralone-1 and 3-carboxy-7-methoxytetralone-1. The lactone of 1-hydroxy-3-carboxy-7-methoxy-tetralin was obtained as a product in the aluminium isopropoxide reduction of 3-methoxycarbonyl-7-methoxytetralone-1; or by reducing the sodium salt of 3-carboxy-7-methoxytetralone-1 with sodium borohydride followed by lactonisation with dilute sulphuric acid. Oxidation of this lactone yielded the lactone of 2-carboxy-4-hydroxy-6-methoxytetralone-1.

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