65. *Condensation of* o-*Acetoxybenzaldehyde with Malonic Acid and Ethyl Malonate.*

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Condensation of *o*-acetoxybenzaldehyde with malonic acid or ethyl malonate, in presence of pyridine, involves partial ring-closure to coumarin derivatives. Some aryl esters of coumarin-3-carboxylic acid have been shown to have no insecticidal action on house-flies.

The pyridine-catalysed condensation of salicylaldehyde with malonic acid or ethyl malonate gives respectively coumarin-3-carboxylic acid and its ethyl ester (Knoevenagel, *Ber.*, 1898, **31**, 2596; Kurien, Pandya, and Surange, *J. Indian Chem. Soc.*, 1934, **11**, 823; Khan, Kurien, and Pandya, *Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 440; Knoevenagel and Hoffmann, *Ber.*, 1898, **31**, 2593; Kurien, Peter, and Pandya, *Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 775; Horning, Horning, and Dimmit, *Org. Synth.*, 1948, **28**, 24). We have now found that replacement of this aldehyde by its acetyl derivative leads, with malonic acid to coumarin-3-carboxylic acid (38·7%) and 2-acetoxycinnamic acid (28%), and with ethyl malonate to ethyl coumarin-3-carboxylate (45·1%) and ethyl salicylidenemalonate (37%). It is interesting that a molecule of ethyl alcohol is not eliminated from the malonic ester during the condensation.

Ethyl salicylidenemalonate yielded coumarin-3-carboxylic acid on hydrolysis with acid, and with concentrated aqueous ammonia, gave the ester-amide which is also hydrolysed to coumarin-3-carboxylic acid by mineral acid. Ethyl salicylidenemalonate with acetyl chloride and pyridine, or with acetic anhydride and anhydrous sodium acetate, gave ethyl coumarin-3-carboxylate. These reactions prove the structure assigned to the salicylidenemalonate.

During this work, some aryl esters of coumarin-3-carboxylic acid were prepared. These had no insecticidal action on house-flies.

Experimental

o-*Acetoxybenzaldehyde.*—This was prepared by Perkin's method (*Annalen*, 1868, **148**, 203) in 75% yield and had b. p. 110—112°/1 mm., m. p. 37°.

Condensation of o-*Acetoxybenzaldehyde with Malonic Acid.*—o-Acetoxybenzaldehyde (20·5 g., 0·125 mol.), malonic acid (13 g., 0·125 mol.) and dry pyridine (1·6 g., 0·02 mol.) were heated at 100° for 4 hours and then left overnight. The product was treated with 2% hydrochloric acid (80 c.c.); the oil that separated solidified at 0° to a colourless crystalline mass which was filtered off and extracted with ether. Coumarin-3-carboxylic acid (9·2 g., 38·7%) was insoluble; recrystallised from hot water, it had m. p. 189° alone or mixed with an authentic sample (Kurien, Pandya, and Surange, *loc. cit.*). The ethereal extract, after drying and evaporation of the ether, yielded 2-acetoxycinnamic acid (7·2 g., 28%) which was purified by extraction with 8% sodium carbonate solution, precipitation with hydrochloric acid, and recrystallisation twice from hot water; it had m. p. 152—153° and with 10% potassium hydroxide yielded 2-hydroxycinnamic acid, m. p. 210—211°, in quantitative yield.

Coumarin-3-carboxylic acid dissolves only slowly in cold dilute aqueous sodium carbonate, sodium hydrogen carbonate, or sodium hydroxide.

Coumarin-3-carboxylic Acid Derivatives.—Thionyl chloride (98·7 g., 3 mols.) was added dropwise, with ice-cooling, to coumarin-3-carboxylic acid (52·5 g.), and the mixture refluxed for 2 hours. Next morning the chloride (53 g., 92%) was filtered off and washed with dry ether (100—125 c.c.); though slightly coloured, the product was almost pure, m. p. 146—147°. Recrystallisation from dry acetone gave colourless crystals, m. p. 147—148° (cf. Boehm and Schumann, *Arch. Pharm.*, 1933, **271**, 490). The chloride is not affected appreciably by exposure to air for 24 hours, though completely hydrolysed by boiling water in 10 minutes.

To the crude chloride (from 0·6 g. of acid) in acetone (10 c.c.), freshly-distilled aniline (1 c.c.) was added dropwise, with ice-cooling, followed by 10% sodium hydroxide (30 c.c.). The mixture was shaken for 10 minutes, left in a refrigerator for some time, and then treated

with ether. Fine yellow crystals of the pure anilide separated (0·8 g.), which were filtered off and washed with ether; it had m. p. 249—250° (cf. Merck, *Chem. Zent.*, 1906, II, 724).

Aqueous ammonia (10 c.c.) was added dropwise to crude coumarin-3-carboxyl chloride (from 0·6 g. of acid) at 0°. After an hour, the amide formed in quantitative yield was filtered off, washed with water, and recrystallised from methyl–ethyl alcohol (1 : 1), yielding flaky needles, m. p. 267—268° (cf. Merck, *loc. cit.*).

Coumarin-3-carboxyl chloride and the appropriate phenol (equimol. quantities) were heated at 100° for 2—6 hours. The mixture darkened, solidifying later in some cases. It was left overnight, then treated with water (75—125 c.c.), and again left overnight in a refrigerator. The solid product was either filtered off or washed by decantation. The crude ester thus obtained was recrystallised from hot alochol, except in the case of the *p*-nitrophenyl ester which was sparingly soluble in alcohol, benzene, toluene, xylene, acetone, ethyl acetate, or acetic acid. This ester was purified by leaving the finely powdered crude product covered with sodium hydroxide for 48 hours, filtering, and washing the residue with water and then with a little alcohol; the whole process was subsequently repeated.

The *esters* prepared are described in the Table.

				Found, %		Required, %	
Ester	Form	M. p.	Formula	C	H	C	H
Phenyl	Plates	156°	$C_{16}H_{10}O_4$	72·0	3·9	72·2	3·8
o-Tolyl	Needles	131—132	$C_{17}H_{12}O_4$	73·1	4·6	72·9	4·3
m-Tolyl	—	164—165	$C_{17}H_{12}O_4$	72·9	4·3		
m-Methoxyphenyl	Needles	121—122	$C_{17}H_{12}O_5$	68·7	4·1	68·95	4·05
p-Methoxyphenyl	—	167—168	$C_{17}H_{12}O_5$	68·8	4·1		
p-Ethoxyphenyl	Needles	169	$C_{18}H_{14}O_5$	69·6	4·2	69·7	4·5
p-Nitrophenyl	—	274—276	$C_{16}H_9O_6N$ *	61·3	2·9	61·7	2·9

* Found : N, 4·3. Required : N, 4·5%.

Condensation of o-*Acetoxybenzaldehyde with Ethyl Malonate.*—o-Acetoxybenzaldehyde (24·6 g., 0·15 mol.), ethyl malonate (24 g., 0·15 mol.), and pyridine (2·37 g., 0·03 mol.) were heated in an oil-bath at 105—110° for 15 hours. After cooling, the product was treated with water (70 c.c.) and 18% hydrochloric acid (15 c.c.), then shaken with ether (50 c.c.), after which it was left in a refrigerator overnight. Ethyl coumarin-3-carboxylate which crystallised was filtered off and recrystallised from hot alcohol; it had m. p. 93—94° (4·71 g., 45%). With 10% potassium hydroxide solution (3—4 hours), it yielded coumarin-3-carboxylic acid, m. p. 189°, in quantitative yield. The ester was converted quantitatively into coumarin-3-carboxyamide, m. p. 267—268°, by keeping it in aqueous ammonia (5 c.c.) at room temperature for 48 hours. The ethereal layer from the filtrate obtained after the separation of ethyl coumarin-3-carboxylate, was washed with water and dried (Na_2SO_4). After evaporation, the residue was distilled in a vacuum, giving *ethyl salicylidenemalonate* as a sweet-smelling liquid (13·3 g., 33·6%) which was purified by redistillation (b. p. 74—76°/1·2 mm.) (Found: C, 63·05; H, 6·3. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). During the first distillation, a small residue (*ca.* 2 g.) proved to be ethyl coumarin-3-carboxylate. Ethyl salicylidenemalonate gives a deep violet colour with 1% ferric chloride, decolorises acidic potassium permanganate and bromine water, and is very slightly soluble in water, the aqueous extract being faintly acid to litmus. It dissolves in dilute aqueous sodium hydroxide to yield a deep yellow solution from which it is reprecipitated unchanged by dilute hydrochloric acid.

Hydrolysis of Ethyl Salicylidenemalonate.—The ester (4 g.) was refluxed with 50% sulphuric acid (50 c.c.) for 3 hours and then left in a refrigerator overnight. The coumarin-3-carboxylic acid (2·5 g., 83%) was filtered off and recrystallised, and had m. p. 189° alone or mixed with an authentic sample.

Hydrolysis of the ester (1·5 g.) could also be effected with acetic (6 c.c.) and 10% sulphuric (15 c.c.) acids; the yield of coumarin-3-carboxylic acid in this case was, however, much lower (0·4 g., 30%).

Ethyl α-Carbamyl-2-hydroxycinnamate.—Ethyl salicylidenemalonate (7 g.) was treated propwise with excess of cold aqueous ammonia (20 c.c.). A brisk reaction took place accompanied by profuse separation of a yellow solid. The mixture was left for 0·5 hour and then filtered. The *amide-ester* (5 g., 80·2%) was washed well with water and recrystallised from hot alcohol, to yield yellow crystals, m. p. 136—137° (Found : C, 61·8; H, 5·8; N, 5·75. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%). The product gives ammonia when heated with dilute sodium hydroxide solution, in which it is soluble in the cold, being reprecipitated unchanged by dilute hydrochloric acid. It slowly gives a deep violet colour with ferric chloride.

When the amide (0·4 g.) was heated with 50% sulphuric acid (9 c.c.) for 15 minutes, it dissolved. On cooling in ice, coumarin-3-carboxylic acid, m. p. 189° (after recrystallisation), separated out in quantitative yield.

Attempts to Acetylate Ethyl Salicylidenemalonate.—(*a*) Acetyl chloride (9 g.) was added dropwise, with stirring, to an ice-cooled solution of the hydroxy-compound (10 g.) in pyridine (6 c.c.). After the brisk reaction had subsided, the mixture was set aside at room temperature for a day, then poured into dilute hydrochloric acid containing lumps of ice, and left in a refrigerator overnight. The separating ethyl coumarin-3-carboxylate (5 g., 60·5%) was filtered off and recrystallised; it had m. p. (and mixed m. p. with an authentic sample) 93—94°.

(*b*) Ethyl salicylidenemalonate (15 g.), acetic anhydride (12 g.), and anhydrous sodium acetate (6·9 g.) were refluxed for 4 hours. After cooling, addition of ice-water (125 c.c.) precipitated an oil which solidified at 0° overnight. Ethyl coumarin-3-carboxylate thus obtained (10·5 g., 84·8%) was filtered off and recrystallised; it had m. p. (and mixed m. p.) 93—94°.

(*c*) The hydroxy-compound was not acetylated by refluxing it with 3 times the required amount of acetyl chloride for 2 hours, the original substance being recovered unchanged.

Toxicity Tests with Esters of Coumarin-3-carboxylic Acid.—The esters (see table) were tested on adult house-flies, at a concentration of 2·5% in benzene, by means of a modified Potter's spraying apparatus (*Ann. Appl. Biol.*, 1941, **28**, 142); three were also tested at a concentration of 5%. Twenty flies were used and 2 c.c. of the benzene solution sprayed in each experiment, which was conducted in duplicate. None of the esters exhibited lethal activity, except *p*-methoxyphenyl coumarin-3-carboxylate where a 15% mortality was observed against none in the control.

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