Cyclisations in Anhydrous Hydrogen Fluoride; Derivatives of Diethyl Phenylmalonate

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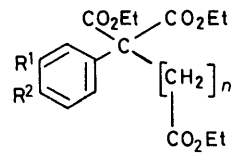
A number of ethoxycarbonylalkyl derivatives of diethyl phenylmalonate cyclise in anhydrous hydrogen fluoride giving derivatives of indanone and of tetralone. An ethoxycarbonylpropyl derivative gave a novel 9,10-dioxo-5,8-methanobenzocycloheptene (16).

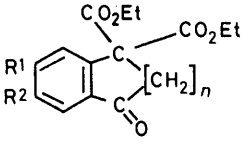
We required derivatives of indanone and tetralone having two ethoxycarbonyl groups on the carbon atom adjacent to the aromatic ring. Cyclisation of appropriate derivatives of diethyl phenylmalonate was considered to be a possible route, and a reagent was needed which would not cause hydrolysis and decarboxylation of the malonic ester residue. Anhydrous hydrogen fluoride converted diethyl 2-ethoxycarbonylethyl-(3-methoxyphenyl)-malonate (1) into the tetralone (8) in good yield; the malonic ester residue remained intact while the ethoxycarbonyl group of the side chain was lost during cyclisation. Other derivatives were similarly cyclised; the results are summarised in the Table. N.m.r. spectra of the products isolated from derivatives bearing methoxy-groups showed that cyclisation had occurred *para* and not *ortho* to a methoxy-group. Five-membered rings were formed more slowly than six-membered rings and extended reaction times (probably longer than absolutely necessary) were used in preparing indanones in order to secure maximum conversion. Cyclisation of the malonic ester derivative (5) which lacked activating groups was particularly slow: formation of a 2,4-dinitrophenylhydrazone from the product indicated that less than 5% of the indanone had been produced over 14 days at room temperature. The corresponding tetralone (12) was formed in good yield in 21 days. In the foregoing work, esters were used for cyclisation rather than the usual carboxylic acids. It is of interest that in

a cyclisation of ethyl hydrogen β-*m*-methoxyphenylglutarate by anhydrous hydrogen fluoride the product was the ester (13), indicating that the carboxy-function of the glutarate reacts preferentially.[1]

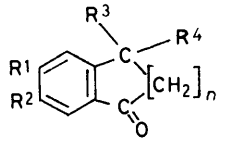
The triester (7) in anhydrous hydrogen fluoride for 5 days at room temperature gave not the expected benzocycloheptene derivative (14) but the tricyclic β-diketone (16). The n.m.r. spectrum of this compound showed the presence of two aromatic protons and only one ethoxycarbonyl group: an acid-catalysed Claisen condensation adjacent to the carbonyl group in compound (14) had



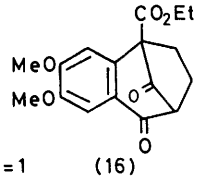
(1) R^1 = MeO, R^2 = H, n = 2
(2) R^1 = R^2 = MeO, n = 2
(3) R^1 = MeO, R^2 = H, n = 1
(4) R^1 = R^2 = MeO, n = 1
(5) R^1 = R^2 = H, n = 1
(6) R^1 = R^2 = H, n = 2
(7) R^1 = R^2 = MeO, n = 3



(8) R^1 = MeO, R^2 = H, n = 2
(9) R^1 = R^2 = MeO, n = 2
(10) R^1 = MeO, R^2 = H, n = 1
(11) R^1 = R^2 = MeO, n = 1
(12) R^1 = R^2 = H, n = 2



(13) R^1 = MeO, R^2 = H, R^3 = CH_2CO_2Et, R^4 = H, n = 1
(14) R^1 = R^2 = MeO, R^3 = R^4 = CO_2Et, n = 3
(15) R^1 = R^2 = MeO, R^3 = CO_2H, R^4 = H, n = 3



(16)

evidently occurred. The tricyclic compound (16), being both a β-diketone and a β-oxo-ester, was cleaved on heating with sodium hydroxide solution, and the benzocycloheptene derivative (15) was precipitated when the solution was acidified. This reaction was accompanied by the disappearance of i.r. bands at 1 785 and 1 755 cm^{-1}. There are few methods reported for the direct synthesis of bridged β-diketones [2] and the above reaction (briefly reported earlier [3]) represents a method whereby this may be achieved under mild conditions.

EXPERIMENTAL

The following instruments and conditions were used unless otherwise specified. I.r. spectra: Perkin-Elmer 237 spectrophotometer (Nujol mulls); u.v. spectra: Unicam SP 800 spectrophotometer; n.m.r. spectra: Perkin-Elmer R32 spectrometer (by courtesy of Professor A. H. Jackson, University College, Cardiff; solutions in deuteriochloroform with tetramethylsilane as standard). Mass spectra were produced by the Physico-chemical Measurements Unit, Harwell, and microanalyses were performed by Mr. G. S. Crouch, School of Pharmacy, London, and by Dr. F. B. Strauss, Oxford.

Diethyl 3-Methoxyphenylmalonate.—Diethyl oxalate (73 g, 0.5 mol) was added dropwise to a stirred solution of sodium ethoxide [from sodium (11.5 g, 0.5 mol)] in 'super dry' ethanol [4] (200 ml); external cooling maintained the temperature of the mixture below 60 °C. Ethyl 3-methoxyphenylacetate [5] (97 g, 0.5 mol) was added in one portion; the mixture was stirred at 60 °C for 4 h and then set aside at room temperature for 24 h. A solid was filtered off and a further crop was obtained by evaporating the filtrate. The combined solids were dissolved in water (250 ml); the solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 × 200 ml). Evaporation of the extract gave a thick brown oil which was heated in a distillation apparatus fitted with an air leak at 165—170 °C and at 15 mmHg until evolution of carbon monoxide ceased. Distillation then gave a viscous light yellow oil (106 g, 80%), b.p. 148—150° at 1.5 mmHg (lit.,[5] yield 44.8%, b.p. 150—152° at 2 mmHg).

Derivatives of Diethyl Phenylmalonate.—Preparative method A: Michael addition of ethyl acrylate. Ethyl acrylate (0.1 mol) was added dropwise to a stirred solution of the derivative of diethyl phenylmalonate (0.1 mol), methanolic Triton B (40%; 4 ml), and hydroquinone (4 mg) in dioxan (100 ml). The mixture was stirred at room temperature for 0.5 h, then heated under reflux for 5 h, cooled, diluted with iced water, and three times extracted with chloroform. The combined extracts were washed, dried (Na_2SO_4), and evaporated; the residue was distilled under reduced pressure.

Preparative method B: reaction of bromo-esters with derivatives of diethyl phenylmalonate. The derivative of diethyl phenylmalonate (0.1 mol) was added to a stirred mixture of dimethylformamide (120 ml) and sodium hydride (0.1 mol as a 50% suspension in oil). Stirring was continued at room temperature for 0.5 h, then at 60 °C for 0.5 h. Ethyl bromoacetate (0.1 mol) was added dropwise and the mixture then heated at 70 °C for 6 h. Iced water was added and the product was isolated as in method A.

Cyclisations in Anhydrous Hydrogen Fluoride.—Anhydrous hydrogen fluoride (about ten times the weight of triester used) was poured on to the triester in a polythene bottle fitted with a screw cap. The mixture was gently swirled to give a clear solution, and the bottle was then capped and set aside for the period shown in the Table. The hydrogen fluoride was then evaporated off in a polythene beaker, and the residue was neutralised with sodium hydrogen carbonate solution and extracted with chloroform. The extract was washed, dried (Na_2SO_4), and evaporated to give a viscous residue which solidified and was crystallised from ethanol.

Ethyl 6,7,8,9-Tetrahydro-2,3-dimethoxy-9,10-dioxo-5,8-methano-5H-benzocycloheptene-5-carboxylate (16). Data in addition to those given in the Table are as follows; $\nu_{max.}$ (Nujol) 1 785 and 1 755 [C(10) : O] and 1 721 and 1 662 cm^{-1} (ester and ArC : O); $\lambda_{max.}$ (EtOH) 212, 237, 276, and 317 nm (log, ε 4.19, 4.28, 3.99, and 3.93), τ 2.5 and 3.2 (each 1 H, s, aromatic), 5.6 and 8.5 (2 H, distorted q, and 3 H, t, OEt), 6.1 (6 H, s, OCH_3), and 6.2—8.5 (m, $[CH_2]_2$·CH).

[1] V. Askam and S. S. Mody, unpublished work.
[2] (*a*) W. Herz and G. Caple, *J. Amer. Chem. Soc.*, 1962, **84**, 3517; (*b*) H. J. E. Loewanthal and Z. Neuwirth, *J. Org. Chem.*, 1967, **32**, 517; (*c*) P. W. Hickmott and J. R. Hargreaves, *Tetrahedron*, 1967, **23**, 3151.
[3] V. Askam and T. U. Qazi, *J.C.S. Chem. Comm.*, 1975, 798.
[4] A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, 3rd edn., p. 168.
[5] H. Tsukamoto, H. Yashimura, and S. Toki, *Chem. and Pharm. Bull. (Japan)*, 1955, **3**, 239.

Properties of diethyl phenylmalonates and their cyclisation products *

Derivative of diethyl phenyl-malonate	Preparative method	B.p. (°C) [mmHg]	Analyses (%) Found	Reqd.	Time of cyclisation	Product	Yield %	B.p. (°C) [mmHg]	M.p. (°C)	† Analyses % and M^+ Found	Reqd.
(1)	A	186—188 [1.5]	C, 62.6 H, 7.24	62.3 7.15	18 h	(8)	95	196—198 [2]	48	C, 64.1 H, 6.15 M^+, 320	63.75 6.3 320
(2)	A	210—211 [1.8]	C, 60.8 H, 6.75	60.6 7.12	20 h	(9)	86	224—225 (3)	56	C, 60.7 H, 6.25 N, 4.15 C, 61.4 H, 6.2 M^+, 350	60.8 6.25 4.2 61.7 6.35 350
(3)	B	180—182 [1.5] (m.p. 55 °C) †	C, 61.0 H, 6.6	61.35 6.85	16 days	(10)	77	172—173 [0.4]	62	C, 62.5 H, 5.9 M^+, 306	62.75 5.9 306
(4) ‡	B	184—185 [0.5] (m.p. 54.5 °C) †	C, 59.9 H, 6.74	59.7 6.8	14 days	(11)	83	210—212 [4]	112	C, 60.4 H, 6.1 M^+, 336	60.7 6.0 336
(5)					14 days	<5% of cyclised product determined as 2,4-dinitrophenyl-hydrazone					
(6)	A	160—162 [1.0]	C, 64.2 H, 6.8	64.25 7.2	21 days	(12)	93	165—166 [1.0]	65—66	C, 66.0 H, 6.4 M^+, 290	66.2 6.25 290
(7)	B	220—222 [2.2]	C, 61.2 H, 7.15	61.45 7.25	5 days	(16)	80	196—200 [1.0]	151—152	C, 66.25 H, 5.55 M^+, 318.111 5	66.15 5.65 318.110 3

* N.m.r. spectra of derivatives of diethyl phenylmalonate and of the cyclised products showed expected peaks. Details of the spectrum of compound (16) are recorded in the Experimental section. I.r. spectra of compounds (8)—(12) showed, in comparison with spectra of starting materials, new peaks below 1 700 cm^{-1} (ArC:O). † From ethanol. ‡ A. Burger and W. E. Coyne, *J. Org. Chem.*, 1964, **29**, 3079.

6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-5-*oxo*-5 H-*benzocycloheptene*-9-*carboxylic Acid*.—Compound (16) (1.0 g) was heated under reflux with 10% sodium hydroxide (4 ml) for 1.5 h and the solution was then acidified with dilute hydrochloric acid (vigorous effervescence occurred) and seeded. The resulting solid (0.85 g) was crystallised from chloroform and then from light petroleum (b.p. 60—80 °C) giving *crystals*, m.p. 164—165° (Found: C, 63.9; H, 6.2%; Equiv. 261.7. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%; Equiv. 264.3), $\nu_{max.}$ 1 717 and 1 648 cm^{-1} (ester and ArC : O).

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