433. *Synthesis of some 2-Benzoylcoumaran-3-ones and some related ω-(2-Methoxycarbonylphenoxy)acetophenones*

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A number of substituted ω-(2-methoxycarbonylphenoxy)acetophenones have been synthesised by the Hoesch reaction. Some of these compounds have been correlated with 2-benzoylcoumaran-3-ones, prepared from ω-halogenoacetophenones by an improved method.

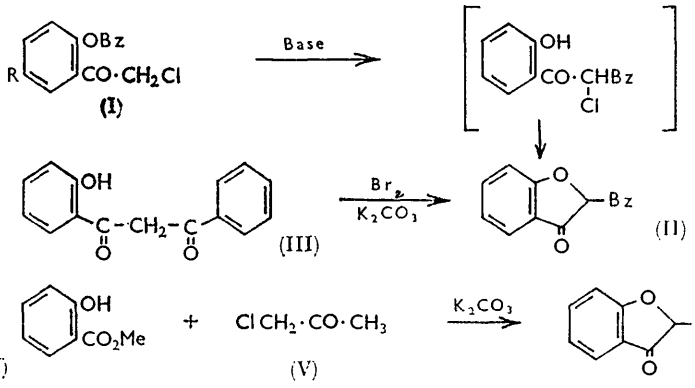
The direct synthesis of 2-benzoylcoumaranones has previously been achieved in only a few instances. von Auwers [1] prepared 2-benzoyl-5-methylcoumaranone by treatment of 2-benzoyloxy-ω-chloroacetophenone (I; R = Me) with base. Philbin, O'Sullivan, and Wheeler [2] prepared, among others, 2-benzoylcoumaranone (II). Geissman and Armen [3] obtained the latter compound by bromination of 2-hydroxydibenzoylmethane (III) in the presence of base. Geissman and Armen [3] also obtained 2-acetylcoumaranone (VI) by condensation of methyl salicylate (IV) with chloroacetone (V) in the presence of potassium carbonate.

Other preparations of 2-benzoylcoumaranones include the action of alkali on 2-benzylidenecoumaranone dibromides,[4] on 3,3-dibromoflavanones [5] and on 3-bromoflavones; [5] and the action of sodium peroxide on 2-benzylidenecoumaranones.[6]

It has now been found that condensation of ω-chloro-2,4,6-trimethoxyacetophenone

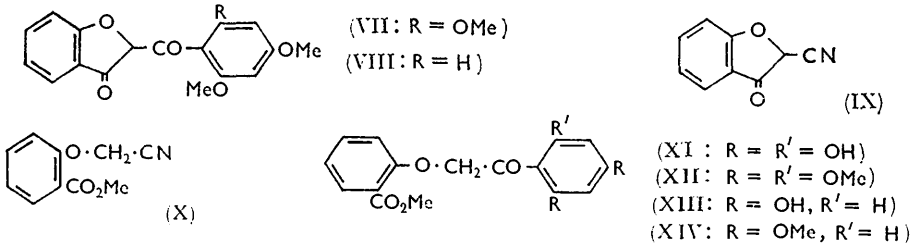
[1] K. von Auwers, *Ber.*, 1910, **43**, 2192.
[2] E. M. Philbin, W. I. A. O'Sullivan, and T. S. Wheeler, *J.*, 1954, 4174.
[3] T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.*, 1955, **77**, 1623.
[4] K. von Auwers and P. Pohl, *Annalen*, 1914, **405**, 243; K. von Auwers, *Ber.*, 1916, **49**, 409.
[5] S. D. Limaye, H. K. Pendse, R. M. Chandorkar, and G. V. Bhide, *Rasayanam*, 1956, **2**, 97; H. K. Pendse and S. D. Limaye, *ibid.*, p. 107; H. K. Pendse and K. S. Moghe, *ibid.*, p. 114; H. K. Pendse and N. D. Patwardhan, *ibid.*, p. 117; H. K. Pendse, *ibid.*, p. 121.
[6] W. E. Fitzmaurice, W. I. A. O'Sullivan, E. M. Philbin, T. S. Wheeler, and T. A. Geissman, *Chem. and Ind.*, 1955, 652.

with the sodium salt of methyl salicylate in xylene yields 2-(2,4,6-trimethoxybenzoyl)-coumaranone (VII). 2-Benzoylcoumaranone (II) and 2-(2,4-dimethoxybenzoyl)coumaranone (VIII) were similarly prepared. Attempts to prepare the benzoylcoumaranone



via 2-cyanocoumaranone (IX) by means of the Hoesch reaction were unsuccessful. When the cyclic nitrile (IX) was replaced by the open-chain compound (X), the Hoesch reaction proceeded smoothly and the esters (XI)—(XIV) were formed. Hydrolysis of the esters gave the corresponding acids.

The conversion of the methoxylated esters (XII) and (XIV) into the corresponding coumaranones, (VII) and (VIII), respectively, was readily achieved using base.



Experimental

Melting points were determined using a Kofler hot-stage apparatus. Ultraviolet spectra were measured using a Perkin-Elmer 137 Spectrometer, for ethanol solutions. Infrared spectra were recorded in Nujol using a Unicam S.P. 200 Spectrometer.

Methyl 2-cyanomethoxybenzoate (X).—Methyl salicylate (55 g.) was treated with chloroacetonitrile (30 g.) in ethyl methyl ketone (100 ml.) in the presence of potassium carbonate (42 g.) and potassium iodide (1 g.) according to the method of Djerassi and Scholz.[7] The product was distilled and the *cyano-ester* (25 g., 36%) was collected at 179—181°/17 mm. It crystallised from benzene–petroleum (b. p. 60—80°) as white needles, m. p. 54—56°, $\lambda_{max.}$ 208, 230, and 287 mμ (ε 14,000, 7050, and 2100), $\nu_{max.}$ 1710 cm.$^{-1}$ (CO) (Found: C, 63·0; H, 4·9; N, 7·4. $C_{10}H_9NO_3$ requires C, 62·8; H, 4·75; N, 7·3%).

2-Cyanocoumaran-3-one (IX).—Methyl 2-cyanomethoxybenzoate (1 g.) was stirred and refluxed in benzene (30 ml.) with sodium methoxide (from 0·12 g. sodium) for 1½ hr. Water was added to the cooled solution, and after acidification the aqueous portion was extracted with ether. Evaporation of the ether yielded *2-cyanocoumaranone* (0·65 g., 78%), m. p. 145—147° (EtOH), $\lambda_{max.}$ 209, 239, 232, and 295 (infl.) mμ (ε 10,700, 11,500, 12,600, and 9400), $\nu_{max.}$ 2350 (CN) and 3250 cm.$^{-1}$ (OH) (Found: C, 67·4; H, 3·4; N, 8·9. $C_9H_5NO_2$ requires C, 67·9; H, 3·2; N, 8·8%). The compound is soluble in alkali and dissolves slowly in aqueous hydrogen carbonate.

[7] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 1688.

2,4,6-*Trihydroxy*-ω-(2-*methoxycarbonylphenoxy*)*acetophenone* (XI).—Dry hydrogen chloride was passed for 1½ hr. into a solution of phloroglucinol (2·5 g.) and methyl 2-cyanomethoxybenzoate (3·8 g.) in dry ether (50 ml.). The ether was decanted from a white solid which on crystallisation from methanol afforded *methyl* 2-[2-*imino*-2-(2,4,6-*trihydroxyphenyl*)*ethoxy*]*benzoate hydrochloride*, m. p. 180° (Found: C, 53·7; H, 5·8; Cl, 8·8; N, 3·41. $C_{16}H_{15}NO_6$,HCl,C_2H_5OH requires C, 54·0; H, 5·5; Cl, 8·9; N, 3·5%).

The imine hydrochloride (1 g.) was dissolved in ethanol (100 ml.) and hydrolysed by refluxing with water (100 ml.). Distillation of the ethanol resulted in precipitation of 2,4,6-*trihydroxy*-ω-(2-*methoxycarbonylphenoxy*)*acetophenone*, white needles (0·84 g.), m. p. 224—226° (decomp.) (EtOH), $\lambda_{max.}$ 213 and 230 mμ (ε 23,500 and 20,600), $\nu_{max.}$ 1680 (CO) and 3020 cm.$^{-1}$ (OH) (Found: C, 60·0; H, 4·3; OMe, 8·8. $C_{16}H_{14}O_7$ requires C, 60·4; H, 4·4; OMe, 9·8%).

The above ester (100 mg.) was refluxed in ethanol–10% hydrochloric acid until a clear solution was obtained. The ethanol was distilled off, and 2,4,6-*trihydroxy*-ω-(2-*carboxyphenoxy*)-*acetophenone* crystallised out. It was recrystallised from ethanol as white needles (89 mg.), m. p. 230° (decomp.), $\lambda_{max.}$ 208, 229, and 294 mμ (ε 18,000, 10,500, and 13,400), $\nu_{max.}$ 1690 cm.$^{-1}$ (CO) (Found: C, 57·7; H, 4·4. $C_{15}H_{12}O_7$ requires C, 59·2; H, 4·0%). The acid dissolves slowly in sodium hydrogen carbonate to give a yellow solution.

2,4,6-*Trimethoxy*-ω-(2-*methoxycarbonylphenoxy*)*acetophenone* (XII).—The reaction was carried out on phloroglucinol trimethyl ether, as described above. The *ester* (95%) was crystallised from ethanol as white plates, m. p. 104—106°, $\lambda_{max.}$ 215, 323 (infl.), and 287 mμ (ε 17,900, 16,900, and 9000), $\nu_{max.}$ 1710 cm.$^{-1}$ (CO) (Found: C, 62·9, H, 5·6; OMe, 32·8. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·7; 4OMe, 34·4%). The compound is insoluble in sodium hydrogen carbonate and in sodium hydroxide.

Hydrolysis of the ester gave 2,4,6-*trimethoxy*-ω-(2-*carboxyphenoxy*)*acetophenone* as white plates, m. p. 185—187° (EtOH–$CHCl_3$), $\lambda_{max.}$ 223 and 282 mμ (ε 15,900 and 6800), $\nu_{max.}$ 1700 cm.$^{-1}$ (CO) (Found: C, 62·8; H, 5·3; OMe, 26·4. $C_{18}H_{18}O_6$ requires C, 62·4; H, 5·2; 3OMe, 26·9%). The acid dissolves slowly in aqueous hydrogen carbonate.

2,4-*Dihydroxy*-ω-(2-*methoxycarbonylphenoxy*)*acetophenone* (XIII).—The reaction was carried out on resorcinol, as above, but with the addition of anhydrous zinc chloride as catalyst. The resulting *ester* was obtained as fine white plates, double m. p. 94—98° and 138° (C_6H_6), $\lambda_{max.}$ 219, 233 (infl.), and 286 mμ (ε 16,200, 14,500, and 12,600), $\nu_{max.}$ 1690 (CO) and 3400 cm.$^{-1}$ (OH) (Found: C, 63·7; H, 4·6; OMe, 10·0. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·7; OMe, 10·2%).

The corresponding *acid* formed colourless needles, m. p. 244—246° (decomp.) (MeOH–$CHCl_3$), $\lambda_{max.}$ 225 and 289 mμ (ε 16,500 and 11,800), $\nu_{max.}$ 1690 cm.$^{-1}$ (CO) (Found: C, 62·3; H, 4·3. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%).

2,4-*Dimethoxy*-ω-(2-*carboxyphenoxy*)*acetophenone*.—The reaction was carried out on resorcinol dimethyl ether (1·38 g.) as previously described, using zinc chloride. After being set aside overnight, the contents of the flask had separated into two layers. The lower layer was separated and washed with ether. It was dissolved in ethanol (50 ml.), water (50 ml.) was added; and the solution was refluxed for 30 min. Solvent was slowly distilled off, when the *dimethoxy-acid* precipitated. It was collected and recrystallised from ethanol as short white rods (12%), m. p. 185—187°, $\lambda_{max.}$ 212, 231, 274, and 305 mμ (ε 14,500, 11,200, 8400, and 7070), $\nu_{max.}$ 1705 (CO) and 3025 cm.$^{-1}$ (OH) (Found: C, 64·8; H, 5·25; OMe, 20·0. $C_{17}H_{16}O_6$ requires C, 64·55; H, 5·3; 2OMe, 19·6%).

2,4-*Dimethoxy*-ω-(2-*methoxycarbonylphenoxy*)*acetophenone* (XIV).—2,4-Dihydroxy-ω-(2-methoxycarbonylphenoxy)acetophenone (167 mg.) and potassium carbonate (153 mg.) were refluxed for 3 hr. in acetone (25 ml.) containing methyl iodide (5 ml.). The solvent was distilled off and the residue taken up in ether–water. The ether layer was washed with 5% sodium hydroxide, dried (Na_2SO_4), and evaporated to yield the *dimethoxyester* (98·3 mg.) as a gum, which crystallised as white prisms, m. p. 86—87° (EtOH), $\lambda_{max.}$ 213, 231, 272, and 305 mμ (ε 21,400, 18,800, 13,900, and 12,700), $\nu_{max.}$ 1725 cm.$^{-1}$ (CO) (Found: C, 65·3; H, 5·5; OMe, 28·2. $C_{18}H_{18}O_6$ requires C, 65·6; H, 5·5; 3OMe, 28·2%). Hydrolysis of the ester with ethanol–dilute hydrochloric acid yielded the acid, m. p. 185—187°, obtained above.

2-*Benzoylcoumaran*-3-*one* (II).—Sodium (745 mg.) was dissolved in ethanol (50 ml.). Ethyl salicylate (5·38 g.) was added and the ethanol removed *in vacuo*. Xylene (50 ml.) was added to the residue, followed by phenacyl chloride (5 g.). The whole was refluxed with stirring for 1½ hr. The solution was cooled and extracted with 10% sodium hydroxide, which, after acidification, yielded the 2-benzoylcoumaran-3-one (4·2 g.). It crystallised as yellow needles, m. p. 82—83°

(EtOH), $\lambda_{max.}$ 214, 242, and 343 mμ (ε 12,700, 10,700, and 16,050), $\nu_{max.}$ 1710 cm.$^{-1}$ (CO) (Found: C, 76·0; H, 4·5; Calc. for $C_{15}H_{10}O_3$: C, 75·5; H, 4·2%).

2-(2,4-*Dimethoxybenzoyl*)*coumaran*-3-*one* (VIII).—(*a*) This *compound*, prepared from ω-chloro-2,4-dimethoxyacetophenone [8] as described for 2-benzoylcoumaranone, formed yellow needles, m. p. 110—113° (EtOH), $\lambda_{max.}$ 211, 236, and 348 mμ (ε 20,850, 15,500, and 20,300) $\nu_{max.}$ 1600 cm.$^{-1}$ (CO) (Found: C, 68·3; H, 4·95; OMe, 20·55. $C_{17}H_{14}O_5$ requires C, 68·45; H, 4·7; 2OMe, 20·8%).

(*b*) 2,4-Dimethoxy-ω-(2-methoxycarbonylphenoxy)acetophenone (50 mg.) was refluxed for 1 hr. in benzene (5 ml.) containing sodium methoxide (0·1 g.). Water was added and the mixture shaken. The aqueous layer was separated and acidified to yield the required dimethoxybenzoylcoumaranone (34 mg.), yellow needles, m. p. and mixed m. p. 110—113° (EtOH).

2-(2,4,6-*Trimethoxybenzoyl*)*coumaran*-3-*one* (VII).—(*a*) This *compound*, prepared as described above from ω-chloro-2,4,6-trimethoxyacetophenone,[9] formed pale yellow needles, m. p. 172—174° (EtOH), $\lambda_{max.}$ 212, 230 (infl.), and 320 mμ (ε 23,200, 10,400, and 12,800) (Found: C, 64·9; H, 4·9; OMe, 26·7. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9; 3OMe, 28·4%).

(*b*) 2,4,6-Trimethoxy-ω-(2-methoxycarbonylphenoxy)acetophenone (1·2 g.) was refluxed for 2½ hr. in benzene containing sodium methoxide (0·2 g.). The mixture was worked up as described above. The product was obtained as pale yellow needles, m. p. 172—174°. Its properties were identical with trimethoxybenzoylcoumaranone (VII) described above.

We thank the D.S.I.R. for the award of a Research Studentship (to D. L. H.).

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Manchester 13. [*Received, October 20th*, 1964.]

[8] A. Sonn, *Ber.*, 1918, **51**, 1829.
[9] K. Freudenberg, H. Fikentsher, and M. Harder, *Annalen*, 1925, **441**, 157.