504. *Oxygen Heterocycles. Part VIII.* Aroylbenzofurans, Aroyldibenzofurans, and Aroylcoumarins of Potential Biological Interest.*

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New 2- and 3-aroylbenzofurans, and 2-aroyldibenzofurans, most of them halogen-containing, have been synthesised, and the Knoevenagel condensation of *o*-hydroxy-aldehydes with aroylacetic esters to give 3-aroylcoumarins has been investigated.

Some aroylbenzofurans have spasmolytic properties. As they often have also undesirable œstrogenic activity,[1] new 2- and 3-aroylbenzofurans bearing substituents (Cl, Br, alkyl, etc.) known to be unfavourable to œstrogenic activity in the hexœstrol series,[2] have now been synthesised for biological evaluation.

5-Chloro-2-aroylbenzofurans were prepared by Rap–Stoermer condensation[3] of 5-chlorosalicylaldehyde with ω-bromoacetophenones. Phenolic derivatives (I; R = H,

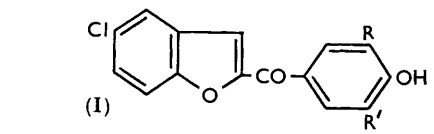
* Part VII, *J.*, 1957, 625.

[1] Bisagni, Buu-Hoï, and Royer, *J.*, 1955, 3693.

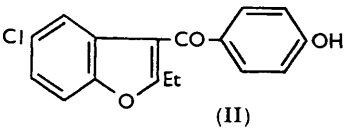
[2] Cf. Buu-Hoï, Lavit, and Xuong, *J.*, 1953, 2612; Buu-Hoï, Corre-Hurst, and Xuong, *Bull. Soc. Chim. biol.*, 1955, **37**, 871.

[3] Rap, *Gazzetta*, 1895, **25**, II, 285; Stoermer, *Annalen*, 1900, **312**, 333.

R′ = H, Cl, or Me) were obtained by demethylation with pyridine hydrochloride of the methoxy-ketones similarly prepared from 4-ω-bromoacetylanisoles. Similar condensations and demethylation were performed with 5-bromosalicylaldehyde. Treatment with bromine in acetic acid gave, from 5-chloro-2-*p*-hydroxybenzoylbenzofuran, the dibromo-derivative (I; R = R′ = Br), and from 5-bromo-2-(3-chloro-4-hydroxybenzoyl)benzofuran, a monobromo-derivative.



(I)



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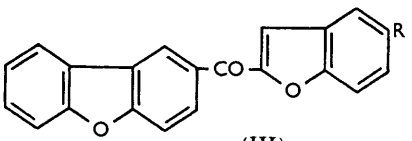

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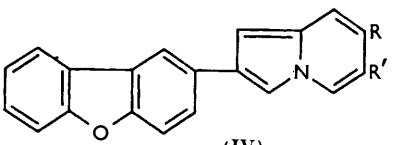

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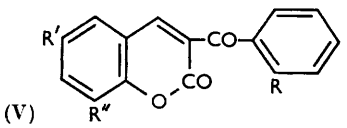

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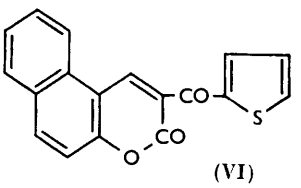

(VI)

5-Chloro-3-aroylbenzofurans were synthesised by Friedel–Crafts acylation of 2-substituted 5-chlorobenzofurans; thus, anisoyl chloride, 5-chloro-2-ethylbenzofuran, and stannic chloride afforded an excellent yield of 3-*p*-anisoyl-5-chloro-2-ethylbenzofuran, which was demethylated to the phenolic ketone (II). Ketones containing both the benzofuran and the dibenzofuran nucleus were synthesised from 2-acetyldibenzofuran,[4] which with bromine in acetic acid yielded 2-bromoacetyldibenzofuran; Rap–Stoermer condensation of the latter with 5-chloro- and 5-bromo-salicylaldehyde afforded 2-(5-chloro-2-benzofuroyl)dibenzofuran (III; R = Cl) and its bromo-analogue (III; R = Br). Other reactions of 2-bromoacetyldibenzofuran included condensation with 2-picoline to an *N*-picolinium salt, which underwent a Tschitschibabin cyclisation [5] in aqueous alkali to 2-2′-dibenzofurylpyrrocoline (IV; R = R′ = H); the 6- and the 7-methyl homologue of the latter were similarly obtained from 2 : 5- and 2 : 4-lutidine.

Several coumarin derivatives have been reported to possess sedative properties,[6] and a number of 3-aroylcoumarins (V) were therefore prepared, by Knoevenagel condensation of ethyl benzoylacetate and ethyl *o*-chlorobenzoylacetate with various *o*-hydroxy-aldehydes in the presence of piperidine. The non-hydroxylated 3-benzoyl- (V; R = H) and 3-*o*-chlorobenzoyl-coumarin (V; R = Cl) were thus prepared. 3-2′-Thenoyl-5 : 6-benzocoumarin (VI) was similarly obtained from 2-hydroxy-1-naphthaldehyde and ethyl 2-thenoylacetate. 3-Acetyl-[7] and 3-benzoyl-7-hydroxycoumarin,[8] were conveniently synthesised by reaction of 2 : 4-dihydroxybenzaldehyde with ethyl acetoacetate and benzoylacetate.

[4] Buu-Hoï and Royer, *Rec. Trav. chim.*, 1948, **67**, 183.
[5] Tschitschibabin, *Ber.*, 1927, **60**, 1607; Buu-Hoï, Jacquignon, Xuong, and Lavit, *J. Org. Chem.*, 1954, **19**, 1370.
[6] von Werder, *Merck's Jahresber.*, 1936, **50**, 88.
[7] Weiss and Merksammer, *Monatsh.*, 1928, **50**, 120.
[8] Ghosal, *J. Indian Chem. Soc.*, 1926, **3**, 108.

New 3-aroylcoumarins.

Coumarin	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-Benzoyl-6-bromo-	177°	$C_{16}H_9O_3Br$	58·1	2·6	58·4	2·7
3-Benzoyl-6-chloro-	163	$C_{16}H_9O_3Cl$	67·2	3·3	67·5	3·2
3-Benzoyl-6 : 8-dichloro-	188	$C_{16}H_8O_3Cl_2$	60·5	2·5	60·2	2·5
3-Benzoyl-8-methoxy-	147	$C_{17}H_{12}O_4$	72·9	4·3	72·8	4·2
3-Benzoyl-6-bromo-8-methoxy-	204	$C_{17}H_{11}O_4Br$	56·6	3·1	56·8	3·1
3-Benzoyl-6-benzyl-	154	$C_{23}H_{16}O_3$	80·9	4·7	81·2	4·7
3-Benzoyl-6-benzyl-8-bromo-	161	$C_{23}H_{15}O_3Br$	66·2	3·7	65·9	3·6
3-*o*-Chlorobenzoyl-6-chloro-	151	$C_{16}H_8O_3Cl_2$	60·5	2·8	60·2	2·5
6 : 8-Dibromo-3-*o*-chlorobenzoyl-	196	$C_{16}H_7O_3Br_2Cl$	43·7	1·4	43·4	1·6
3-*o*-Chlorobenzoyl-6 : 8-di-iodo-	210	$C_{16}H_7O_3I_2Cl$	36·0	1·4	35·8	1·3
3-*o*-Chlorobenzoyl-7-hydroxy- [a]	268	$C_{16}H_9O_4Cl$	63·6	2·9	63·9	3·0

[a] Soluble in aqueous alkalis, to give yellow solutions.

Experimental

2-p-*Bromobenzoyl-5-chlorobenzofuran.*—To a solution of redistilled 5-chlorosalicylaldehyde (10 g.) and potassium hydroxide (3·6 g.) in ethanol (150 c.c.), ω : 4-dibromoacetophenone (18 g.) was added, and the mixture refluxed for 3 hr.; after evaporation of the solvent, water was added, and the *product* collected, and recrystallised twice from ethanol–benzene, giving colourless leaflets (15 g.), m. p. 202° (Found : C, 53·7; H, 2·4. $C_{15}H_8O_2BrCl$ requires C, 53·7; H, 2·4%).

5-Chloro-2-(2 : 4-dimethylbenzoyl)benzofuran.—Similarly prepared from ω-bromo-2 : 4-dimethylacetophenone (10 g.), 5-chlorosalicylaldehyde (6·8 g.), and potassium hydroxide (2·4 g.) in ethanol (120 c.c.), this *ketone* formed prisms (8 g.), m. p. 96°, from ethanol (Found : C, 71·7; H, 4·6. $C_{17}H_{13}O_2Cl$ requires C, 71·7; H, 4·6%).

5-Chloro-2-(p-hydroxybenzoyl)benzofuran (I; R = R′ = H).—The crude methyl ether (10 g.), prepared from 5-chlorosalicylaldehyde (15 g.), ω-bromo-4-acetylanisole (22 g.), and potassium hydroxide (5·3 g.) in ethanol (150 c.c.), was refluxed with redistilled pyridine hydrochloride (15 g.) for 30 min., and water was added after cooling. The precipitate obtained was washed with water, and redissolved in aqueous sodium hydroxide. Acidification with acetic acid afforded a precipitate which recrystallised from aqueous ethanol as prisms (6 g.), m. p. 238° (Found : C, 66·5; H, 3·3. $C_{15}H_9O_3Cl$ requires C, 66·1; H, 3·3%). To a solution of this *ketone* (1 g.) in acetic acid, bromine (1 g., in acetic acid) was added with stirring, and the product poured into water; the precipitate yielded, on recrystallisation from acetic acid, *5-chloro-2-(3 : 5-dibromo-4-hydroxybenzoyl)benzofuran*, prisms (1 g.), m. p. 201° (Found : C, 41·6; H, 1·5. $C_{15}H_7O_3Br_2Cl$ requires C, 41·8; H, 1·6%).

5-Chloro-2-(4-methoxy-3-methylbenzoyl)benzofuran.—This *ketone* (3·8 g.), prepared from ω-bromo-4-methoxy-3-methylacetophenone (6 g.), 5-chlorosalicylaldehyde (4·6 g.), and potassium hydroxide (2 g.), formed prisms, m. p. 128°, from ethanol (Found : C, 68·3; H, 4·5. $C_{17}H_{13}O_3Cl$ requires C, 67·9; H, 4·3%). Demethylation with pyridine hydrochloride (4 g.) yielded *5-chloro-2-(4-hydroxy-3-methylbenzoyl)benzofuran* (I; R = H, R′ = Me), crystallising as needles, m. p. 205°, from aqueous ethanol (Found : C, 67·2; H, 4·1. $C_{16}H_{11}O_3Cl$ requires C, 67·0; H, 3·8%).

5-Chloro-2-(3-chloro-4-hydroxybenzoyl)benzofuran (I; R = H, R′ = Cl).—The crude methyl ether (7 g.), prepared from ω-bromo-3-chloro-4-methoxyacetophenone (11 g.), 5-chlorosalicylaldehyde (11·3 g.), and potassium hydroxide (4 g.), was demethylated by pyridine hydrochloride (10 g.), giving the *hydroxy-ketone* (3 g.), prisms, m. p. 240° (from ethanol–benzene) (Found : C, 58·9; H, 2·7. $C_{15}H_8O_3Cl_2$ requires C, 58·6; H, 2·6%). Bromination of this compound (2·5 g.) with bromine (1 g.) in acetic acid yielded a monosubstitution product.

5-Bromo-2-(3-chloro-4-methoxybenzoyl)benzofuran.—Prepared from 5-bromosalicylaldehyde (11·5 g.; purified by distillation *in vacuo*), ω-bromo-3-chloro-4-methoxyacetophenone (15 g.), and potassium hydroxide (3·2 g.) in ethanol in the usual way, this *ether* formed prisms, m. p. 203°, from ethanol (Found : C, 52·3; H, 2·8. $C_{16}H_{10}O_3BrCl$ requires C, 52·5; H, 2·7%). Demethylation yielded *5-bromo-2-(3-chloro-4-hydroxybenzoyl)benzofuran*, prisms, m. p. 221° (from aqueous ethanol) (Found : C, 50·9; H, 2·4. $C_{15}H_8O_3BrCl$ requires C, 51·2; H, 2·3%); this (2 g.) with bromine (1·2 g.) in acetic acid gave *5-bromo-(5-bromo-3-chloro-4-hydroxybenzoyl)benzofuran* (2·1 g.),

crystallising as prisms, m. p. 178°, from aqueous ethanol (Found : C, 41·8; H, 1·6. $C_{15}H_7O_3Br_2Cl$ requires C, 41·8; H, 1·6%).

3-p-*Anisoyl*-5-*chloro*-2-*ethylbenzofuran*.—To a water-cooled solution of 5-chloro-2-ethylbenzofuran [9] (12 g.) and *p*-anisoyl chloride (13 g.) in dry carbon disulphide (200 c.c.), stannic chloride (19 g.) was added dropwise with stirring, and the mixture left for 6 hr. at room temperature. After the usual treatment, a *ketone* (12 g.) was obtained which crystallised as leaflets, m. p. 165° from ethanol (Found : C, 68·4; H, 4·6. $C_{18}H_{15}O_3Cl$ requires C, 68·7; H, 4·8%). Demethylation yielded 5-*chloro*-2-*ethyl*-3-p-*hydroxybenzoylbenzofuran* (II), prisms, m. p. 189° (from benzene) (Found : C, 68·0; H, 4·5. $C_{17}H_{13}O_3Cl$ requires C, 67·9; H, 4·3%).

2-*Bromoacetyldibenzofuran*.—2-Acetyldibenzofuran was prepared by Friedel–Crafts acetylation of dibenzofuran according to Buu-Hoï and Royer; [4] bromination of this ketone (11 g.) with bromine (6·9 g.) in acetic acid yielded the *bromo-derivative* (11 g.), which formed needles, m. p. 95°, from methanol (Found : C, 58·0; H, 3·0; Br, 27·5. $C_{14}H_9O_2Br$ requires C, 58·1; H, 3·1; Br, 27·6%).

2-(5-*Chloro*-2-*benzofuroyl*)*dibenzofuran* (III; R = Cl).—A solution of 5-chlorosalicylaldehyde (4·1 g.) and potassium hydroxide (1·5 g.) in ethanol was refluxed for 3 hr. with the foregoing ω-bromo-ketone (8 g.); after evaporation of ethanol and addition of water, the precipitated *product* which formed crystallised as needles (7 g.), m. p. 203°, from ethanol–benzene (Found : C, 72·4; H, 3·1; Cl, 9·9. $C_{21}H_{11}O_3Cl$ requires C, 72·7; H, 3·2; Cl, 10·2%).

2-(5-*Bromo*-2-*benzofuroyl*)*dibenzofuran* (III; R = Br).—Similarly prepared from 5-bromosalicylaldehyde, this *ketone* formed prisms, m. p. 196°, from ethanol–benzene (Found : C, 64·5; H, 3·0. $C_{21}H_{11}O_3Br$ requires C, 64·5; H, 2·8%).

2-2′-*Dibenzofurylpyrrocoline* (IV; R = R′ = H).—A solution of 2-ω-bromoacetyldibenzofuran (2·9 g.) and 2-picoline (2 g.) in ethanol (20 c.c.) was heated at 60° for 1 hr., and ether was added after cooling. The α-picolinium salt, precipitated as prisms, decomp. *ca.* 210°, was dissolved in water (150 c.c.), and the solution boiled for a few minutes with sodium hydrogen carbonate (3 g.); the precipitate which was formed was collected, washed with water, dried, and crystallised from ethanol–benzene, giving sublimable leaflets, m. p. 194—195° (Found : C, 84·8; H, 4·8; N, 4·8. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 4·9%). 2-2′-*Dibenzofuryl*-6-*methylpyrrocoline* (IV; R = H, R′ = Me), similarly prepared with 2 : 5-lutidine, formed sublimable leaflets, m. p. 187° (decomp.), from ethanol–benzene (Found : C, 85·2; H, 5·1; N, 4·7. $C_{21}H_{15}ON$ requires C, 84·9; H, 5·1; N, 4·7%). 2-2′-*Dibenzofuryl*-7-*methylpyrrocoline* (IV; R = Me, R′ = H), prepared from 2 : 4-lutidine, formed leaflets, m. p. 203° (decomp.) (Found : C, 85·3; H, 4·9; N, 4·7%).

3-*Benzoyl*-7-*hydroxycoumarin*.—To a mixture of equimolecular amounts of 2 : 4-hydroxybenzaldehyde and ethyl benzoylacetate, a few drops of piperidine (dissolved in ethanol) were added; the solid formed overnight was recrystallised from ethanol, giving colourless needles (85%), m. p. 242° (lit.,[8] m. p. 241°). 3-Acetyl-7-hydroxycoumarin, similarly prepared by use of ethyl acetoacetate, formed needles, m. p. 237°, from ethanol (lit.,[7] m. p. 236°).

Preparation of 3-*Aroylcoumarins* (V).—The aldehydes used were : 5-chloro-, 5-bromo-, 5-benzyl-, 3-benzyl-5-bromo-, 3-methoxy-, 5-bromo-3-methoxy-, 3 : 5-dichloro-, and 3 : 5-dibromo-salicylaldehyde. 5-Bromo-3-methoxysalicylaldehyde, prepared from *o*-vanillin according to Davies,[10] was characterised by its *thiosemicarbazone*, which crystallised as yellowish prisms, m. p. 263—264°, from ethanol–benzene (Found : N, 15·0. $C_9H_{10}O_2N_3SBr$ requires N, 15·4%). The Knoevenagel condensations with ethyl benzoylacetate and ethyl *o*-chlorobenzoylacetate were performed as above, and recrystallisation was from benzene or ethanol–benzene. The *coumarins* thus prepared were sublimable, colourless compounds which readily crystallised.

3-2′-*Thenoyl*-5 : 6-*benzocoumarin* (VI).—Prepared from 2-hydroxy-1-naphthaldehyde (1·7 g.), ethyl 2-thenoylacetate (2 g.), and piperidine (3 drops), this *coumarin* formed yellowish needles (2·8 g.), m. p. 245°, from ethanol (Found : C, 70·5; H, 3·5. $C_{18}H_{10}O_3S$ requires C, 70·6; H, 3·3%).

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[9] Bisagni, Buu-Hoï, and Royer, *J.*, 1955, 3688.
[10] Davies, *J.*, 1923, **123**, 1579.