126. *Oxygen Heterocycles. Part VII.* Spasmolytic Ketones in the Benzofuran Series, and Related Compounds.*

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In view of the therapeutic activity of khellin, several 2- and 3-aroylbenzofurans bearing phenolic groups have been synthesised, and some of them found to display marked spasmolytic activity. In connection with this research, a number of new 3-aroylindoles have been prepared.

Khellin, 5 : 8-dimethoxy-2-methylfurano(4′ : 5′-6 : 7)chromone, has found wide therapeutic application because of its spasmolytic properties.[1] An attempt to find physiologically active molecules of simpler chemical structure resulted recently in several chromone derivatives endowed with spasmolytic action.[2] It was interesting to investigate whether simplification, by suppression of the γ-pyrone ring, to benzofuran derivatives would lead to active compounds. Biological studies under the direction of Professor Dallemagne (Liège) have shown that 2-*p*-hydroxybenzoylbenzofuran exerts a relaxant effect on the histamine and acetylcholine spasm and on the motility of guinea-pig intestine more pronounced than that of khellin itself.[3] As clinical use of this compound is impeded by its œstrogenic activity,[4] the preparation has been investigated of other benzofuran ketones destined for biological examination.

Friedel–Crafts condensation of *p*-anisoyl chloride with 2-ethylbenzofuran in the presence of stannic chloride readily gave 3-*p*-anisoyl-2-ethylbenzofuran (I; R = Me, R′ = H), which was converted into 2-ethyl-3-*p*-hydroxybenzoylbenzofuran (I; R = R′ = H) by demethylation with pyridine hydrochloride. Bromination of this hydroxy-compound resulted in

* Part VI, Routier, Buu-Hoï, and Royer, *J.*, 1956, 4276.

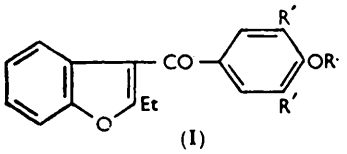
[1] See Burger, "Medicinal Chemistry," Interscience Publ., Inc., New York, 1951, Vol. I, p. 238.

[2] Schmutz, Lauener, Hirt, and Sanz, *Helv. Chim. Acta*, 1951, **34**, 767; also personal communication from Professor C. Mentzer.

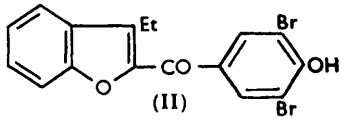
[3] Unpublished results; 3-methylchromone did not show appreciable activity in these tests.

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

disubstitution with formation of 3-(3 : 5-dibromo-4-hydroxybenzoyl)-2-ethylbenzofuran (I; R = H, R′ = Br); the stability of the compound towards alkalis indicated the nuclear site of substitution occupied by the halogen atoms, and reaction of methyl iodide with the sodio-derivative afforded 3-(3 : 5-dibromo-4-methoxybenzoyl)-2-ethylbenzofuran (I; R = Me, R′ = Br). Further proof of the stability and inertness of the benzofuran ring in these ketones was the bromination of 3-ethyl-2-*p*-hydroxybenzoylbenzofuran [4] to the dibromo-derivative (II).



(I)



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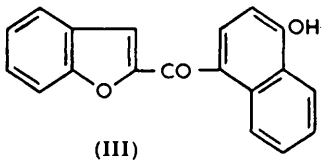

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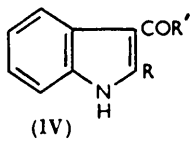

(IV)

2-Aroylbenzofurans were prepared by Rap–Stoermer condensation [5] of aromatic ω-bromo-ketones with salicylaldehyde; thus, the ω-bromo-derivatives of 3-chloro- and 3-fluoro-4-methoxyacetophenone afforded 2-(3-chloro-4-methoxybenzoyl)- and 2-(3-fluoro-4-methoxybenzoyl)-benzofuran, which were demethylated in the usual way to the corresponding hydroxy-ketones. In preliminary tests *in vitro*, these various hydroxy-compounds all showed spasmolytic properties, the bromo-derivatives being the least active. For comparative studies, 2-(2-hydroxy-5-methylbenzoyl)- and 2-*p*-bromobenzoyl-benzofuran, both of which lack the characteristic *p*-hydroxyl group, were prepared by the same method. An alternative route to 2-aroylbenzofurans consisted of Friedel–Crafts acylations with the chloride of coumarilic acid,[6] and this was used for the preparation of 2-(4-hydroxy-1-naphthoyl)benzofuran (III) *via* the methyl ether.

In the course of this work, a number of new 3-acylindoles (IV; R = H) and 3-acyl-2-methylindoles (IV; R = Me), listed in the Table, were prepared by the Oddo reaction [7] of various acid chlorides on the magnesium derivatives of indole and 2-methylindole. Detailed results of biological studies will be reported elsewhere.

Experimental

3-p-*Anisoyl-2-ethylbenzofuran* (I; R = Me, R′ = H).—To an ice-cooled solution of 2-ethylbenzofuran [8] (20 g.) and *p*-anisoyl chloride (23·5 g.) in dry carbon disulphide (150 c.c.), stannic chloride (40 g.) was added dropwise with stirring, and the mixture left for 3 hr. at room temperature, then poured into water. The organic layer was washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4), the solvent removed, and the residue (22 g.) crystallised from light petroleum, giving colourless prisms, m. p. 81° (Found : C, 77·3; H, 5·6. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·8%). The orientation in this *compound* was deduced from the fact that 2 : 3-dialkylbenzofurans fail to undergo stannic chloride-catalysed acylation; [8] the anisoyl group must therefore have entered position 3 of the furan nucleus.

2-*Ethyl*-3-p-*hydroxybenzoylbenzofuran* (I; R = R′ = H).—A mixture of the foregoing ketone (20 g.) and redistilled pyridine hydrochloride (50 g.) was gently refluxed for 30 min.,

[5] Rap, *Gazzetta*, 1895, **25**, II, 285; Stoermer, *Annalen*, 1900, **312**, 333; Stoermer and Schaeffer, *Ber.*, 1903, **36**, 2864.

[6] Zwayer and von Kostanecki, *Ber.*, 1908, **41**, 1338.

[7] Oddo, *Gazzetta*, 1910, **40**, II, 353; Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 131; Buu-Hoï, Hoán, and Xuong, *J.*, 1951, 3499.

[8] Cf. Bisagni, Buu-Hoï, and Royer, *J.*, 1955, 3688.

and, on cooling, dilute hydrochloric acid was added. The precipitated *hydroxy-ketone* which solidified overnight was dried and recrystallised from aqueous ethanol, then from *cyclo*hexane, giving colourless prisms, m. p. 126—127° (12 g.), soluble in aqueous alkalis to yellow solutions

3-Aroylindoles.

Indole	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-*p*-Anisoyl- [a]	208°	$C_{16}H_{13}O_2N$	76·5	5·3	76·5	5·2
3-*o*-Chlorobenzoyl-	188	$C_{15}H_{10}ONCl$	70·1	3·9	70·4	3·9
3-*p*-Ethylbenzoyl-	199	$C_{17}H_{15}ON$	81·8	6·0	81·9	6·1
3-1′-Naphthoyl- [b]	236	$C_{19}H_{13}ON$	83·8	4·6	84·1	4·8
3-2′-Naphthoyl-	257	$C_{19}H_{13}ON$	83·9	4·6	84·1	4·8
3-1′-Naphthylacetyl-	229	$C_{20}H_{15}ON$	84·1	5·0	84·2	5·3
3-2′-Furoyl-2-methyl-	165	$C_{14}H_{11}O_2N$	74·9	4·6	74·7	4·9
3-2′-Thenoyl-2-methyl-	167	$C_{14}H_{11}ONS$	69·6	4·5	69·7	4·6
2-Methyl-3-phenylacetyl-	200	$C_{17}H_{15}ON$	81·6	5·9	81·9	6·1
2-Methyl-3-1′-naphthylacetyl-	208	$C_{21}H_{17}ON$	84·1	5·5	84·3	5·7

[a] Demethylation with pyridine hydrochloride afforded a dark substance, soluble in aqueous alkalis.
[b] This compound and the two following ones were recrystallised from benzene.

(Found: C, 76·3; H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). Into a solution of this compound (4 g.) in acetic acid (15 c.c.) and water (10 c.c.), bromine (4·8 g.) in acetic acid was stirred in small portions, and the mixture left for 4 hr. at room temperature; after dilution with water, the product was taken up in benzene, washed with aqueous sodium hydrogen sulphite, and dried (Na_2SO_4), the solvent removed, and the residue recrystallised from *cyclo*hexane, giving 3-(3 : 5-*dibromo*-4-*hydroxybenzoyl*)-2-*ethylbenzofuran* (I; R = H, R′ = Br), yellowish prisms (4 g.), m. p. 147—148° (Found: C, 47·9; H, 2·9; Br, 37·3. $C_{17}H_{12}O_3Br_2$ requires C, 48·1; H, 2·8; Br, 37·7%). A solution of this compound (1·2 g.) and potassium hydroxide (0·2 g.) in ethanol (50 c.c.) was refluxed for 15 min. with methyl iodide (1 g.), and most of the solvent was distilled off. The precipitate formed on dilution with water crystallised from benzene, giving 3-(3 : 5-*dibromo*-4-*methoxybenzoyl*)-2-*ethylbenzofuran* (I; R = Me, R′ = Br), colourless prisms (1 g.), m. p. 217—218° (Found: C, 49·1; H, 3·0; Br, 36·3. $C_{18}H_{14}O_3Br_2$ requires C, 49·3; H, 3·2; Br, 36·5%).

2-(3 : 5-*Dibromo*-4-*hydroxybenzoyl*)-3-*ethylbenzofuran* (II).—A solution of 3-ethyl-2-*p*-hydroxybenzoylbenzofuran (1 g.) in aqueous acetic acid was treated with bromine (1·2 g.) in the usual way; the halogenated *ketone* formed yellowish prisms (1·2 g.), m. p. 147°, from *cyclo*hexane (Found: C, 48·0; H, 2·8; Br, 37·3%).

2-p-*Bromobenzoylbenzofuran*.—A solution of salicylaldehyde (8 g.) and potassium hydroxide (3 g.) in ethanol (150 c.c.) was refluxed for 4 hr. with ω : 4-dibromoacetophenone (15 g.), the ethanol was distilled off, and the residue treated with water. The *ketone* (12 g.) crystallised as colourless needles, m. p. 151°, from *cyclo*hexane (Found: C, 59·8; H, 3·1. $C_{15}H_9O_2Br$ requires C, 59·8; H, 3·0%).

2-(3-*Fluoro*-4-*methoxybenzoyl*)*benzofuran*.—Similarly prepared from salicylaldehyde (12 g.), potassium hydroxide (5·6 g.), and ω-bromo-3-fluoro-4-methoxyacetophenone [9] (24 g.), this *ketone* formed colourless leaflets (15 g.), m. p. 114° (Found: C, 71·9; H, 4·0. $C_{16}H_{11}O_3F$ requires C, 71·7; H, 4·1%). A mixture of this compound (13 g.) and pyridine hydrochloride (25 g.) was refluxed for 45 min.; dilute hydrochloric acid was added after cooling, and the precipitate crystallised twice from benzene, giving 2-(3-*fluoro*-4-*hydroxybenzoyl*)*benzofuran* (8 g.), as yellowish prisms, m. p. 153—154° (Found: C, 70·2; H, 3·8. $C_{15}H_9O_3F$ requires C, 70·3; H, 3·5%).

2-(3-*Chloro*-4-*methoxybenzyoyl*)*benzofuran*.—Prepared in 48% yield from ω-bromo-3-chloro-4-methoxyacetophenone (30 g.), salicylaldehyde (16 g.), and potassium hydroxide (7 g.) in ethanol (200 c.c.), this *ketone*, b. p. 280—285°/15 mm. (slight dec.), formed colourless needles, m. p. 110°, from ligroin (Found: C, 66·7; H, 3·9. $C_{16}H_{11}O_3Cl$ requires C, 67·0; H, 3·8%). 2-(3-*Chloro*-4-*hydroxybenzoyl*)*benzofuran* (8 g.), prepared from this ketone (12 g.) and pyridine hydrochloride (20 g.), crystallised as pale yellow needles, m. p. 196°, from benzene (Found: C, 65·8; H, 3·4; Cl, 12·7. $C_{15}H_9O_3Cl$ requires C, 66·0; H, 3·3; Cl, 13·0%).

2-(2-*Methoxy*-5-*methylbenzoyl*)*benzofuran*.—Prepared from ω-bromo-2-methoxy-5-methylacetophenone (25 g.; prepared by bromination of 2-methoxy-5-methylacetophenone in acetic

[9] Buu-Hoï, Xuong, and Lavit, *J. Org. Chem.*, 1953, **18**, 910.

acid), salicylaldehyde (12 g.), and potassium hydroxide (6 g.) in ethanol, this *ketone* (12 g.) formed a pale yellow, viscous oil, b. p. 209—211°/3 mm. (Found: C, 76·5; H, 5·2. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). 2-(*2-Hydroxy-5-methylbenzoyl*)*benzofuran* (9 g.), obtained on demethylation of the foregoing compound (11·5 g.), formed yellowish leaflets, m. p. 70—71°, from methanol (Found: C, 75·9; H, 5·1. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%).

2-(*4-Methoxy-1-naphthoyl*)*benzofuran*.—This compound was prepared in two ways: (*a*) the Rap–Stoermer method, from salicylaldehyde (15 g.), 1-bromoacetyl-4-methoxynaphthalene (30 g.), and potassium hydroxide (6 g.), gave the *ketone* (35%), b. p. 250—255°/1 mm., colourless needles, m. p. 139° (from methanol) (Found: C, 79·1; H, 4·6. $C_{20}H_{14}O_3$ requires C, 79·4; H, 4·6%); (*b*) by Friedel–Crafts condensation (70% yield) of coumariloyl chloride (18 g.), methyl α-naphthyl ether (16 g.), and aluminium chloride (15 g.) in nitrobenzene at room temperature.

2-(*4-Hydroxy-1-naphthoyl*)*benzofuran* (III), prepared from the foregoing ketone (9 g.) and purified *via* its sodium salt, formed yellowish prisms (7 g.), m. p. 206°, from benzene (Found: C, 79·2; H, 3·8. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·2%).

Oddo Synthesis of 3-Acylindoles.—To a Grignard reagent prepared from ethyl bromide (13 g.) and magnesium (3 g.) in anhydrous ether, indole (5 g., or the equivalent amount of 2-methylindole) was added, and the mixture refluxed for 2 hr. on the water-bath; the solution was cooled in ice, and the appropriate acid chloride (1 mol., dissolved in ether) was added in small portions with stirring, and the mixture refluxed for a further hour. After cooling, cold 10% aqueous ammonium chloride was added, and the solid formed on evaporation of the ether was washed with water, dried, and crystallised from methanol. Yields were 60—70%.

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