Oxygen Heterocycles. Part IV. 2-Benzoylbenzofurans and Related Compounds with Biological Interest.*

By M. Bisagni, Ng. Ph. Buu-Hoï, and R. Royer.

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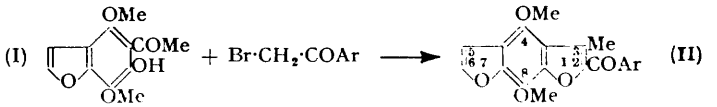
The chemistry of 2-aroylbenzofurans and their derivatives has been investigated, and some of the compounds showed œstrogenic activity. The Rap–Stoermer benzofuran cyclisation was successfully extended to *o*-hydroxy-ketones, including khellinone (5-acetyl-6-hydroxy-4 : 7-dimethoxybenzofuran), and several 2-aroyl-4 : 7-dimethoxy-3-methylbenzo[1 : 2-*b*, 4 : 5-*b*]difurans were prepared.

Recently, natural and synthetic œstrogenic substances have been found in oxygen-heterocyclic compounds such as some *iso*flavones, *iso*flavens (Bradbury and White, *J.*, 1951, **3447**; 1953, 871), and coumarins (Gley and Mentzer, *Compt. rend. Soc. Biol.*, 1945, **139**, 1055). The similarity between these and benzofuran derivatives suggested the investigation of 2-aroylbenzofurans and related compounds. 2-Benzoylbenzofuran was prepared by Rap (*Gazzetta*, 1895, **25**, II, 285) by the reaction of ω-bromoacetophenone with the sodio-derivative of salicylaldehyde, and this procedure was now successfully extended to substituted derivatives of each. Further, it was found that in the Rap reaction *o*-hydroxyaldehydes could be replaced by *o*-hydroxy-ketones; *o*-hydroxypropiophenone thus gave 2-benzoyl-3-ethyl- and 2-*p*-anisoyl-3-ethyl-benzofuran with ω-bromo- and ω-bromo-4-methoxy-acetophenone respectively. Khellinone (I) (Späth and Gruber, *Ber.*, 1938, **71**, 106; Schönberg and Sina, *J. Amer. Chem. Soc.*, 1950, **72**, 1611, 3396) readily gave



2-benzoyl-4 : 8-dimethoxy-3-methylbenzo[1 : 2-*b*, 5 : 4-*b*]difuran (II; R = Ph) with ω-bromoacetophenone, and similar derivatives were obtained with aryl-ω-bromo-ketones. On the other hand, *o*-hydroxy-ketones could not be used in the similar Stoermer synthesis of 2-acetylbenzofurans from chloroacetone (Stoermer, *Annalen*, 1900, **312**, 333; Stoermer and Schaeffer, *Ber.*, 1903, **36**, 2864), thus indicating that the methylene group in phenacyl ethers RO·CH_2·COAr is more reactive than in acetonyl ethers RO·CH_2·COMe.

2-*p*-Hydroxybenzoyl- and 3-ethyl-2-*p*-hydroxybenzoyl-benzofuran and 2-benzoyl-6-hydroxybenzofuran were readily obtained by demethylation of the corresponding methyl ethers with pyridine hydrochloride. Similar ketones with the aroyl group in position 3 (cf. preceding paper) included 3-benzoyl-2-ethyl-, 2-ethyl-3-*p*-toluoyl-, and 2-ethyl-3-phenylacetyl-benzofuran. Wolff–Kishner reduction of 2-benzoylbenzofuran readily afforded the 2-benzyl compound, which likewise underwent acylation, to give 3-acetyl-2-benzylbenzofuran.

The œstrogenic activities of the various benzofuran derivatives, determined in spayed mice by the Allen–Doisy test (subcutaneous injection), are in the Table. These results

* Part III, preceding paper.

stress the importance of a *p*-hydroxy-group in the 2-aroyl substituent, a requirement for œstrogenic activity similar to that observed in the *iso*flavone (Bradbury and White, *loc. cit.*) and the coumarin group.

During this research, a convenient technique for the preparation of 2 : 4-dihydroxybenzaldehyde from resorcinol, dimethylformamide, and phosphorus oxychloride was devised.

Œstrogenic activity of benzofurans

2-*p*-Hydroxybenzoyl	active at 1 mg.
3-Ethyl-2-*p*-hydroxybenzoyl	active between 1 and 10 mg.
2-Benzoyl-6-hydroxy	inactive at 1 mg.
3-Benzoyl-2-ethyl	inactive at 1 mg.
2-*p*-Anisoyl-3-ethyl	inactive at 10 mg.
2-*o*-Hydroxycinnamoyl	inactive at 1 mg.

Experimental

2-Benzylbenzofuran.—2-Benzoylbenzofuran, b. p. 214—216°/15 mm., m. p. 90° (from ethanol), was prepared in 58% yield according to Rap. A solution of this ketone (120 g.) and 85% hydrazine hydrate (110 g.) in diethylene glycol (300 c.c.) was refluxed for 10 min. and, on cooling, treated with potassium hydroxide (100 g.). The mixture was then heated for a further 3 hr. with removal of water, and after cooling it was acidified with dilute hydrochloric acid; the product was taken up in benzene and purified by distillation *in vacuo*. 2-Benzylbenzofuran was a pale yellow oil (77 g., 68% yield), b. p. 184—185°/16 mm., n_D^{20} 1·6056 (Found: C, 86·5; H, 5·9. Calc. for $C_{15}H_{12}O$: C, 86·5; H, 5·7%).

3-Acetyl-2-benzylbenzofuran.—To an ice-cooled solution of 2-benzylbenzofuran (30 g.) and acetyl chloride (13 g.) in dry carbon disulphide (150 c.c.), stannic chloride (40 g.) was added in small portions, and the mixture kept at room temperature for 1 hr. After decomposition with hydrochloric acid, the organic layer was washed with water and dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The *ketone* (13 g.) was a yellow, viscous oil, b. p. 228—230°/18 mm., n_D^{19} 1·6181, giving an orange-red halochromy with sulphuric acid (Found: C, 81·9; H, 5·8. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%). The *oxime* formed colourless leaflets, m. p. 134°, from ligroin (Found: C, 76·9; H, 5·7. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·6%).

3-Benzoyl-2-ethylbenzofuran.—This *ketone* (3·5 g.), prepared as above from 2-ethylcoumarone (10 g.), benzoyl chloride (11 g.), and stannic chloride (18 g.; 18 hr. at room temperature), was a yellow oil, b. p. 210°/15 mm., giving a red halochromy in sulphuric acid (Found: C, 81·6; H, 5·8%). The *oxime* formed colourless needles, m. p. 118°, from ligroin (Found: C, 77·2; H, 5·4%).

3-p-Anisoyl-2-ethylbenzofuran.—Prepared from 2-ethylbenzofuran (6·5 g.), *p*-anisoyl chloride (8 g.), and stannic chloride (12 g.), this *ketone* was a viscous yellow oil (4·5 g.), b. p. 225—226°/15 mm., n_D^{23} 1·6249 (Found: C, 81·9; H, 6·4. $C_{18}H_{16}O_3$ requires C, 81·8; H, 6·1%). The *oxime* formed colourless needles, m. p. 161°, from ligroin (Found: C, 77·6; H, 6·0. $C_{18}H_{17}O_3N$ requires C, 77·4; H, 6·0%).

2-Ethyl-3-phenylacetylbenzofuran.—Prepared from 2-ethylbenzofuran (10 g.), phenylacetyl chloride (12 g.), and stannic chloride (16 g.), this *ketone* (11 g.) was a yellow oil, b. p. 232—233°/16 mm., n_D^{20} 1·6138 (Found: C, 82·0; H, 6·2%); the *oxime* formed leaflets, m. p. 117°, from ligroin (Found: C, 77·7; H, 6·3%).

2-Benzoyl-3-ethylbenzofuran.—To a solution of *o*-hydroxypropiophenone (30 g.) and potassium hydroxide (13 g.) in ethanol (150 c.c.), ω-bromoacetophenone (40 g.) was added, and the mixture refluxed for 2½ hr. The oil precipitated on addition of water was taken up in benzene and purified by distillation *in vacuo*. The *ketone* (14 g., 28%) was a pale yellow oil, b. p. 215—218°/15 mm., n_D^{25} 1·6270 (Found: C, 81·3; H, 5·5%). Wolff–Kishner reduction of this ketone (5 g.) with hydrazine hydrate (3 g.) and potassium hydroxide (2 g.) in diethylene glycol (25 c.c.) afforded *2-benzyl-3-ethylbenzofuran* (2·5 g.), a pale yellow oil, b. p. 202—204°/16 mm., n_D^{25} 1·5940 (Found: C, 86·1; H, 6·6. $C_{17}H_{16}O$ requires C, 86·4; H, 6·7%).

2-p-Anisoylbenzofuran.—To a solution of salicylaldehyde (20·5 g.) and potassium hydroxide (10·5 g.) in ethanol (150 c.c.), ω-bromo-4-methoxyacetophenone (38 g.) was added, and the mixture refluxed for 3 hr. The precipitated potassium bromide was filtered off, and the *ketone* which separated from the filtrate on cooling was recrystallised from ethanol, giving colourless leaflets (15 g.), m. p. 97° (Found: C, 76·1; H, 5·0. $C_{16}H_{12}O_3$ requires C, 76·1; H, 4·7%). A mixture of this ketone (10 g.) and redistilled pyridine hydrochloride (20 g.) was refluxed for

40 min., and the precipitate formed on addition of water was recrystallised several times from benzene, giving 2-*p*-hydroxybenxoylbenzofuran, cream-coloured needles (8 g.), m. p. 192—193°, soluble in aqueous alkalis with a yellow colour. Zwayer and Kostanecki (*Ber.*, 1908, **41**, 1332) gave m. p. 179—180°.

2-p-*Anisoyl*-3-*ethylbenzofuran*.—This *ketone*, prepared from *o*-hydroxypropiophenone (45 g.), potassium hydroxide (17 g.), and ω-bromo-4-methoxyacetophenone (65 g.) in ethanol (4 hours' refluxing), was a yellow oil (23 g.), b. p. 245—247°/17 mm., n_D^{21} 1·6447, which crystallised (Found : C, 76·9; H, 5·8. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%). Demethylation of this ketone (12 g.) with pyridine hydrochloride (20 g.) as above, yielded 3-*ethyl*-2-p-*hydroxybenzoylbenzofuran* (10 g.), yellowish needles, m. p. 167—168° (from benzene) (Found : C, 76·3; H, 5·1. $C_{17}H_{14}O_3$ requires C, 76·6; H, 5·2%).

2 : 4-*Dihydroxybenzaldehyde*.—The following procedure was convenient : to a mixture of resorcinol (220 g.) and dimethylformamide (146 g.), phosphorus oxychloride (153 g.) was added in small portions with stirring, and the mixture kept for 2 hr. at room temperature; the thick magma was treated with a hot 50% aqueous solution of sodium acetate (1500 c.c.) to complete dissolution and, on cooling, the product was taken up in ether; the ethereal layer was washed with water, dried (Na_2SO_4), and evaporated. The residue gave on distillation *in vacuo* 2 : 4-dihydroxybenzaldehyde (125 g.), m. p. 135° (from water).

2-*Benzoyl*-6-*methoxybenzofuran*.—A solution of 2-hydroxy-4-methoxybenzaldehyde (13·5 g.) and potassium hydroxide (5·5 g.) in ethanol was refluxed with ω-bromoacetophenone (18 g.) for 3 hr. After cooling, water was added, and the *ketone* was collected and crystallised from methanol, giving colourless leaflets (11 g.), m. p. 105° (Found : C, 76·3; H, 4·9 $C_{16}H_{12}O_3$ requires C, 76·1; H, 4·7%) (red halochromy in sulphuric acid). 2-*Benzoyl*-6-*hydroxybenzofuran*, prepared by refluxing this ketone (4 g.) and pyridine hydrochloride (8 g.) for 40 min., formed cream-coloured needles, m. p. 215° (from aqueous ethanol) (Found : C, 75·3; H, 4·5. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2%), giving yellow solutions in aqueous alkalis.

5-*Acetyl*-4 : 6 : 7-*trimethoxybenzofuran*.—Khellinone (44 g.) was prepared by refluxing a solution of khellin (50 g.) in 10% aqueous potassium hydroxide (500 c.c.) for 2 hr. After cooling, the insoluble impurities were filtered off, the filtrate acidified with dilute hydrochloric acid, and the yellow precipitate collected and crystallised from aqueous methanol (m. p. 100—101°). A solution of khellinone (16 g.) in 10% aqueous potassium hydroxide (50 g.) was heated with methyl sulphate (11 g.) at 100° for 30 min. After alternate addition of potassium hydroxide and methyl sulphate (5 g.), the mixture was basified, and the precipitated oil taken up in benzene and purified by fractionation *in vacuo*. 5-*Acetyl*-4 : 6 : 7-*trimethoxybenzofuran* (12·5 g.) was a pale yellow oil, b. p. 138—140°/0·1 mm., $n_D^{22·5}$ 1·5542, with an aromatic odour (Found : C, 62·1; H, 5·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%).

2-*Benzoyl*-4 : 8-*dimethoxy*-3-*methylbenzo*(1 : 2-b, 5 : 4-b)*difuran* (II; Ar = Ph).—To a solution of khellinone (6 g.) and potassium hydroxide (2 g.) in ethanol (25 c.c), ω-bromoacetophenone (6 g.) was added, and the mixture refluxed for 18 hr. The precipitate of sodium bromide was filtered off, and the filtrate concentrated; the *benzodifuran* precipitated on cooling gave bright yellow leaflets (4 g.), m. p. 127°, from ligroin or aqueous ethanol (Found : C, 71·1; H, 4·7. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·7%) The bathochromic effect produced by the introduction of a second furan ring is probably due to the resonance between the two furan rings *via* the benzene nucleus (cf. II).

2-p-*Methylbenzoyl*-4 : 7-*dimethoxy*-3-*methylbenzo*(1 : 2-b. 5 : 4-b)*difuran* (II; Ar = *p*-C_6H_4Me), similarly prepared from ω-bromo-4-methoxyacetophenone (6 g.), khellinone (6 g.), and potassium hydroxide (2 g.), formed yellow needles (4·2 g.), m. p. 124°, from ethanol (Found : C, 71·9; H, 5·2. $C_{21}H_{18}O_5$ requires C, 72·0; H, 5·1%). The 2-p-*ethylbenzoyl analogue* (II; Ar = *p*-C_6H_4Et) formed bright yellow needles, m. p. 118°, from ligroin (Found : C, 72·2; H, 5·6. $C_{22}H_{20}O_5$ requires C, 72·5; H, 5·5%). The 2-p-*Anisoyl analogue* (II; Ar = *p*-C_6H_4OMe) formed yellow needles, m. p. 135°, from ligroin (Found : C, 69·0; H, 5·0. $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%).

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Department of Organic Chemistry,
The Radium Institute, University of Paris. [*Received, June 9th*, 1955.]