27. *Oxygen Heterocycles. Part X.*[1] *The Acylation of Benzofuran.*

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Benzofuran readily undergoes acylation in the 2-position by aliphatic acid anhydrides in the presence of phosphoric acid, the solvent being the acid corresponding to the anhydride. 2-Alkylbenzofurans have been prepared by reduction of the ketones, and benzofurylquinolines by Pfitzinger reactions.

2-Alkyl-3-hydroxyaroylbenzofurans are potent spasmolytic agents, and 2-ethyl-3-(4-hydroxy-3,5-di-iodobenzoyl)benzofuran has found therapeutic use in coronary disease.[2] Various 2-acylbenzofurans (I) have therefore acquired practical interest as convenient intermediates for the preparation of 2-alkylbenzofurans; and some of them, *e.g.*, 2-*o*-hydroxybenzoylbenzofuran, are of themselves potent spasmolytics. The only method so far described for the synthesis of 2-acylbenzofurans is the Stoermer–Schaeffer condensation of aliphatic α-bromo-ketones with salicylaldehyde,[3] but the yields are low;

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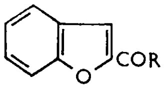
[1] Part IX, Buu-Hoï and Lavit, *J.*, 1959, 38.

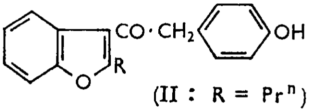
[2] Bisagni, Buu-Hoï, and Royer, *J.*, 1955, 3693; Charlier, "Coronary Vasodilatators," Pergamon Press, London, 1961.

[3] Stoermer, *Annalen*, 1901, **312**, 237; Stoermer and Schaeffer, *Ber.*, 1903, **36**, 2864.

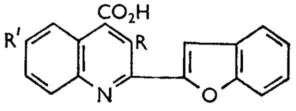
further, the purity of the final products depends on that of the bromo-ketones used and these, apart from the halogenoacetones, are difficult to purify.



(I)



(II : R = Pr^n)
(III : R = Bu^n)



(IV)

Benzofuran itself is known to be extremely sensitive to the ordinary Friedel–Crafts catalysts and is completely resinified by aluminium chloride even at very low temperatures.[4] We have now found, however, that it can readily be converted into 2-acetylbenzofuran by means of acetic anhydride in acetic acid, with 85% phosphoric acid as catalyst; this procedure was inspired by that recommended by Mindzhoian for the acetylation of furan.[5] When it was extended to higher acid anhydrides, it was necessary to replace acetic acid by the acids corresponding to the anhydrides used, as otherwise some 2-acetylbenzofuran was formed along with the desired 2-acylbenzofurans; this side-reaction, which increases with the molecular weight of the acylating agent, can be ascribed to the formation of unsymmetrical anhydrides CH_3·CO·O·CO·R from acetic acid and the symmetrical anhydrides by exchange reactions. The direct acylation of benzofuran represents a step forward in the practical use of this substance, which is present in large quantities in crude coal tar and for which no practical use had so far been found except in the manufacture of indene–coumarone polymers. Phosphoric acid-catalysed acylations (in the 3-position) were also possible with 2-alkylbenzofurans.

The 2-acylbenzofurans thus prepared were readily reduced to the corresponding 2-alkylbenzofurans by hydrazine hydrate and potassium hydroxide in diethylene glycol.[6] These were considerably more stable than benzofuran itself, and underwent normal aluminium chloride-catalysed Friedel–Crafts acylation with both aliphatic and aromatic acid chlorides, to give 3-acyl-2-alkylbenzofurans; 2-propyl- (II) and 2-butyl-3-*p*-hydroxyphenylacetylbenzofuran (III) were prepared from the corresponding methyl ethers by demethylation with pyridine hydrochloride, for biological evaluation of their spasmolytic activity. 3-Acyl-2-alkylbenzofurans with an aliphatic acyl group were readily converted by Wolff–Kishner–Huang-Minlon reduction into 2,3-dialkylbenzofurans.

Other compounds of pharmacological interest (as possible analgæsics and antipyretics) are benzofuranylcinchoninic acids (IV), which were prepared from 2-acylbenzofurans with various isatins by the Pfitzinger reaction; they are listed in the Table, along with the 2-benzofurylquinolines which were obtained by thermal decarboxylation. The cinchoninic acids thus prepared showed mild analgæsic and choleretic activity; an attempt to condense 3-acetyl-2-butylbenzofuran with isatin in the usual conditions was unsuccessful, probably because of steric hindrance.[7]

EXPERIMENTAL

Preparation of 2-Acetylbenzofuran.—A stirred mixture of freshly redistilled coumarone (60 g.), acetic anhydride (51 g.), acetic acid (50 g.), and phosphoric acid (12 g.; *d* 1·71) was refluxed at 130° for 4 hr. and left overnight at room temperature. After basification with ice-cold 5% aqueous sodium hydroxide, the product was taken up in chloroform, the chloroform solution was washed with water and dried (Na_2SO_4), the solvent was distilled, and the residue fractionated *in vacuo*. This gave 2-acetylbenzofuran (42—45 g.), m. p. and mixed m. p. 75—76° (from hexane) (lit.,[3] 75°).

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

[5] Mindzhoian, "Syntheses of Heterocyclic Compounds," Chapman & Hall, Ltd., London 1959, Vol. II, p. 12.

[6] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[7] Buu-Hoï and Cagniant, *Ber.*, 1943, **76**, 1269; *Bull. Soc. chim. France*, 1946, **13**, 123.

2-*Propionylbenzofuran*.—This *ketone* (40—42 g.), similarly prepared from coumarone (60 g.), propionic anhydride (68 g.), propionic acid (50 g.), and phosphoric acid (10 g.), formed colourless leaflets, m. p. 56°, from hexane (Found: C, 75·8; H, 5·7. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·8%). A mixture of this ketone (50 g.), 98% hydrazine hydrate (80 c.c.), and diethylene glycol (150 c.c.) was heated for 5 min. at 100°, potassium hydroxide (50 g.) added, and the mixture then refluxed for 2 hr. After cooling, water was added, and the product was taken up in benzene, washed with dilute hydrochloric acid, then with water, recovered, and fractionated *in vacuo*. 2-*Propylbenzofuran* (34 g.) was obtained as a colourless oil, b. p. 120°/12 mm., n_D^{19} 1·5431 (Found: C, 82·5; H, 7·6. Calc. for $C_{11}H_{12}O$: C, 82·5; H, 7·5%).

2-*Butyrylbenzofuran*.—Prepared from coumarone (60 g.), butyric anhydride (79 g.), butyric acid (50 g.), and phosphoric acid (15 g.), this *ketone* (I; R = Pr) formed colourless needles (32 g.), m. p. 71°, b. p. 170—171°/11 mm., from hexane (Found: C, 76·6; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). Replacement of butyric acid by acetic acid in this preparation yielded small amounts of 2-acetylbenzofuran along with 2-butyrylbenzofuran. Reduction of the latter ketone (39 g.) with hydrazine hydrate (52 c.c.) and potassium hydroxide (35 g.) in diethylene glycol (100 c.c.) afforded 2-*butylbenzofuran* (23 g.), b. p. 126°/11 mm., n_D^{21} 1·5358 (Found: C, 82·6; H, 8·1. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). A mixture of this benzofuran (11 g.), acetic anhydride (7 g.), and acetic acid (7 g.) was gently refluxed for 2 hr. at 130—135° with phosphoric acid (2 g.); the product was worked up in the usual way, to give 3-*acetyl*-2-*butylbenzofuran* (9 g.), b. p. 175—176°/13 mm., n_D^{20} 1·5511 (Found: C, 78·2; H, 7·7. $C_{14}H_{16}O_2$, requires C, 77·8; H, 7·5%. This ketone was also prepared by using aluminium chloride in the normal Friedel–Crafts procedure, but in somewhat lower yields. Wolff–Kishner reduction afforded a 70% yield of 2-*butyl*-3-*ethylbenzofuran*, b. p. 138°/13 mm., n_D^{22} 1·5342 (Found: C, 83·0; H, 9·1. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%).

Heptanoylation of Benzofuran.—This was effected with benzofuran (11 g.), heptanoic anhydride (b. p. 258°; 22 g.), heptanoic acid (b. p. 222°; 15 g.), and phosphoric acid (3 g.), to give 2-*heptanoylbenzofuran* (I; R = C_6H_{13}) (8 g.), b. p. 192°/12 mm., n_D^{22} 1·5451 (Found: C, 78·1; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%). Replacement of heptanoic acid by acetic acid as solvent produced a ~1 : 3 mixture of 2-acetyl- and 2-heptanoyl-benzofuran. Wolff–Kishner reduction of the latter ketone gave 2-*heptylbenzofuran* (80%), b. p. 158—160°/13 mm., n_D^{23} 1·5171 (Found: C, 83·2; H, 9·5. $C_{15}H_{20}O$ requires C, 83·4; H, 9·3%).

Normal Friedel–Crafts Reactions with 2-*Alkylbenzofurans*.—These could be performed either with aluminium chloride, or, better, with stannic chloride, in which case the following procedure was used: To a stirred solution of 2-propylbenzofuran (4 g.) and benzoyl chloride (3·5 g.) in carbon disulphide (30 c.c.), stannic chloride (7 g.) was added during 30 min. at 10—15°, and the mixture was kept overnight at room temperature. After decomposition with cold dilute hydrochloric acid, the organic layer was washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent distilled off, and the residue fractionated *in vacuo*; 3-*benzoyl*-2-*propylbenzofuran* was a pale yellow viscous oil (3 g.), b. p. 211°/12 mm., n_D^{22} 1·6022 (Found: C, 81·5; H, 5·9. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). Acylation of 2-propylbenzofuran (16 g.) with *p*-methoxyphenylacetyl chloride (19 g.) and stannic chloride (30 g.) in carbon disulphide (100 c.c.) similarly yielded 3-p-*methoxyphenylacetyl*-2-*propylbenzofuran* (18 g.), b. p. 248—249°/11 mm. (Found: C, 77·6; H, 6·8. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%); demethylation was effected by refluxing a mixture of this ketone (5 g.) and pyridine hydrochloride (15 g.) for 15 min., the product being taken up in chloroform after addition of dilute hydrochloric acid, the chloroform solution dried ($CaCl_2$), the solvent distilled off, and the residue recrystallised from hexane, to give 3-p-*hydroxyphenylacetyl*-2-*propylbenzofuran* (II) (1·5 g.), prisms, m. p. 83° (Found: C, 77·4; H, 6·2. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·2%). 2-*Butyl*-3-p-*methoxyphenylacetylbenzofuran*, prepared from 2-butylbenzofuran (8·5 g.) as for the propyl homologue, had b. p. 252—253°/10 mm. (10 g.) (Found: C, 78·0; H, 7·1. $C_{21}H_{22}O_3$ requires C, 78·2; H, 6·9%); demethylation gave 2-*butyl*-3-p-*hydroxyphenylacetylbenzofuran* (III). b. p. 271—272°/11 mm. (Found: C, 77·6; H, 6·6. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%).

Pfitzinger Reactions.—A solution of the ketone (1 mol.) and the appropriate isatin (1 mol.) in a minimum of ethanol containing potassium hydroxide (3 mol.; dissolved in a minimum of water) was refluxed for 18 hr.; the solvent was distilled off *in vacuo*, the residue was taken up in water, and the neutral impurities were removed by ether-extraction. The *cinchoninic acid* (see Table) obtained on acidification with acetic acid was crystallised from ethanol, giving yellowish or colourless needles. Yields were highest with 2-acetylbenzofuran (85—90%), Cinchoninic acid and corresponding quinolines.

		Found (%)				Required (%)		
Substance	M. p.	C	H	N	Formula	C	H	N
2-*Benzofuran-2′-ylcinchonic acids*								
6-methyl	320°	75·0	4·5	—	$C_{19}H_{13}NO_3$	75·2	4·3	—
3-methyl	262	,,	,,	—	,,	,,	,,	—
3,6-dimethyl	244	75·4	5·0	—	$C_{20}H_{15}NO_3$	75·7	4·8	—
6-bromo-3-methyl	140	59·9	3·4	—	$C_{19}H_{12}BrNO_3$	59·7	3·1	—
3-ethyl	269	75·4	5·0	—	$C_{20}H_{15}NO_3$	75·7	4·8	—
2-*Benzofuran-2′-ylquinolines*								
6-methyl	151	83·1	5·2	—	$C_{18}H_{13}NO$	83·4	5·1	—
picrate	232	—	—	11·3	$C_{24}H_{16}N_4O_8$	—	—	11·5
3-methyl	133	83·1	5·4	—	$C_{18}H_{13}NO$	83·4	5·1	—
picrate	227	—	—	11·2	$C_{24}H_{16}N_4O_8$	—	—	11·5
3,6-dimethyl	101	83·4	5·5	—	$C_{19}H_{15}NO$	83·5	5·5	—
picrate	239	—	—	11·0	$C_{25}H_{18}N_4O_8$	—	—	11·2
6-bromo-3-methyl	140	63·8	3·8	—	$C_{18}H_{12}BrNO$	63·9	3·6	—
picrate	213	—	—	9·6	$C_{24}H_{15}BrN_4O_8$	—	—	9·9
3-ethyl	99	83·4	5·8	—	$C_{19}H_{15}NO$	83·5	5·5	—

and lowest with 2-butyrylbenzofuran (65—70%). The cinchoninic acids (IV), heated above their m. p.s, gave the corresponding *quinolines* (see Table), which crystallised from ethanol as colourless leaflets, giving bright yellow picrates.

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