159. *Cyclodehydration Processes. Part I. Benzofuran Derivatives formed by Cyclisation of ω-Aryloxyacetophenones.*

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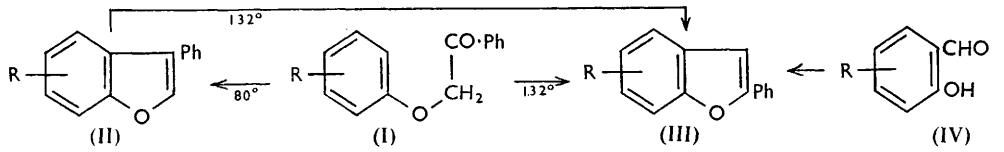
ω-Phenoxyacetophenone and the three isomeric ω-tolyloxyacetophenones are cyclised by polyphosphoric acid at 132° to 2-phenyl- and 7-, 6-, and 5-methyl-2-phenyl-benzofuran respectively; the expected 3-phenylbenzofuran derivatives are not thus obtained. Cyclisation at $>80°$ converts ω-phenoxyacetophenone into 3-phenylbenzofuran, which is isomerised to 2-phenylbenzofuran by polyphosphoric acid at 132°.

Since cyclodehydration of several phenacyl phenyl sulphides afforded 2- and not 3-substituted thionaphthens,[1] we have investigated the cyclodehydration of several ω-aryloxyacetophenones[2] (I). The literature records many instances[3] in which 3-methylbenzofurans have been prepared by cyclisation of β-ketoalkoxybenzenes, but for the analogous arylbenzofurans the only record is that ω-phenoxyacetophenone is not cyclised by zinc chloride, phosphoric oxide, oxalic acid, sulphuric acid, or sodium.[4]

In the preparation of phenacyl phenyl sulphides by interaction of thiols and aracyl halides, pyridine was found[1] to be an effective condensing medium, but the corresponding reaction with phenols failed owing to the rapid formation of aracyl pyridinium halides. ω-Aryloxyacetophenones (I) are however conveniently made by this reaction in boiling acetone in the presence of potassium carbonate, which is a better method than use of

[1] Banfield, Davies, Gamble, and Middleton, *J.*, 1956, 4791.
[2] For a preliminary note see Davies and Middleton, *Chem. and Ind.*, 1957, 599.
[3] Bradsher, *Chem. Rev.*, 1946, **38**, 455.
[4] Stoermer and Atenstädt, *Ber.*, 1902, **35**, 3560.

aqueous sodium hydroxide. In both methods aracyl chlorides give lower yields than bromides.



(II) (I) (III) (IV)

Polyphosphoric acid has been found to be an effective cyclising agent for ω-phenoxyacetophenone (I; R = H) and the three ω-tolyloxyacetophenones (I; R = Me), but in each case, ring closure at 132° was accompanied by a rearrangement. The parent compound (I; R = H) gave a 71% yield of 2-phenylbenzofuran identical with a specimen synthesised [5] in a basic medium from salicylaldehyde and ethyl α-bromo-α-phenylacetate. ω-*o*-Tolyloxyacetophenone (I; R = *o*-Me) at 132° afforded only 7-methyl-2-phenylbenzofuran (III; R = 7-Me), identical with a specimen synthesised from 2-hydroxy-3-methylbenzaldehyde (IV; R = 3-Me), and ω-*p*-tolyloxyacetophenone (I; R = *p*-Me) gave 5-methyl-2-phenylbenzofuran (III; R = 5-Me) identical with the product obtained from 2-hydroxy-5-methylbenzaldehyde (IV; R = 5-Me). ω-*m*-Tolyloxyacetophenone (I; R = *m*-Me) gave only 6-methyl-2-phenylbenzofuran (III; R = 6-Me), obtained also from 2-hydroxy-4-methylbenzaldehyde (IV; R = 4-Me).

It is possible that the 3-phenyl isomers are the first cyclisation products, since ω-phenoxyacetophenone in polyphosphoric at room temperature or at 80° affords 3-phenylbenzofuran (II; R = H) identical with a specimen synthesised [6] from 2 : 3-dihydro-3-oxobenzofuran and phenylmagnesium bromide. Moreover, 3-phenylbenzofuran (II; R = H) is isomerised to the 2-phenyl isomer by polyphosphoric acid at 132°. At 110° a mixture of the 2- and 3-phenyl isomers is formed, which recalls the simultaneous appearance [7] of both the isomers when the lactone of *o*-hydroxydiphenylacetic acid was heated with phosphorus tribromide at 200—220°.

The anomalous cyclisation of ω-aryloxyacetophenones is thus in line with that of aracyl phenyl sulphides. For a nitrogen analogue, *N*-phenacylaniline, it has been shown [8] that cyclisation in the presence of an acid catalyst yields 2-phenylindole and that zinc chloride at 170 ° quantitatively converts 3- into 2-phenylindole in 15 minutes.[9] But the 3-phenylindole is not necessarily an intermediate in the formation of the 2-phenyl isomer.[8a]

2-Phenylbenzofurans usually have higher melting points than the corresponding 3-phenyl compounds, as in the thionaphthen series.[1] 2-Phenyl-benzofuran and -naphthalene give a satisfactory trinitrofluorenone derivative but 3-phenylbenzofuran and 1-phenylnaphthalene do not; this has been used to separate mixtures of the 2- and 3-phenylbenzofuran (see p. 824). Aryl-benzofurans and -naphthalenes are also similar in their inability to form stable picrates.

Experimental

Preparation of ω-Aryloxyacetophenones.—Two methods are exemplified in the preparation of ω-phenoxyacetophenone.

Method 1. Phenol (9·4 g., 0·1 mol.), phenacyl bromide (19·9 g., 0·1 mol.), and anhydrous potassium carbonate (13·8 g.) were refluxed in acetone (50 ml.) with continuous stirring for 4 hr., then poured into water (500 ml.) and chilled, and the resultant solid crystallised from ethanol, to give ω-phenoxyacetophenone, m. p. 71—72° (15·0 g., 71%). Further recrystallisation from ethanol gave m. p. 72·5—73° [Mohlau [10] reports m. p. 72°, Guss,[11] m. p. 71—72°, and Yates,[12] m. p. 73—73·5° (corr.)]. The 2 : 4-dinitrophenylhydrazone formed orange plates

[5] Kawai, Nakamura, and Sugiyama, *Ber.*, 1939, **72**, 1146.
[6] Stoermer and Barthelmes, *Ber.*, 1915, **48**, 68.
[7] Stoermer, *Ber.*, 1903, **36**, 3990.
[8] Mann and his co-workers, *J.*, (*a*) 1943, 58; (*b*) 1948, 847, 858, and references cited therein.
[9] Fischer and Schmidt, *Ber.*, 1888, **21**, 1811.
[10] Mohlau, *Ber.*, 1882, **15**, 2498.
[11] Guss, *J. Amer. Chem. Soc.*, 1949, **71**, 3462.
[12] Yates, *ibid.*, 1952, **74**, 5380.

(from ethanol–benzene), m. p. 182·5—183·5° [Guss [11] reports m. p. 183—184° (uncorr.)]. When the bromide was replaced by the chloride (15·5 g., 0·1 mol.), a 30% yield was obtained.

Method 2. Adding 10% aqueous sodium hydroxide (50 ml.) to phenol (0·1 mol.) and phenacyl bromide (0·1 mol.) in water (30 ml.) at 100° with stirring during 30 min., and stirring and heating for a further 30 min. gave the product, m. p. 70—72° (12·4 g., 58%). Use of the chloride gave a 25% yield.

Similarly were prepared ω-o-*tolyloxyacetophenone* (method 1, 57%; 2, 36%), needles (from ethanol), m. p. 62·5—63° (Found: C, 79·45; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%) [2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol–benzene), m. p. 186·5—187·5° (Found: N, 13·4. $C_{21}H_{18}N_4O_5$ requires N, 13·8%)], ω-*m*-tolyloxyacetophenone (method 1, 51%; 2, 42%), needles (from ethanol), m. p. 74—74·5° (Found: C, 79·9; H, 6·3%) (Kunckell [13] reports m. p. 84°) [2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol–benzene), m. p. 183·5—184·5° (Found: N, 13·45%)], and ω-*p*-tolyloxyacetophenone (method 1, 54%; 2, 38%), needles (from ethanol), m. p. 64·5—65·5° (Found: C, 79·5; H, 6·4%) (Kunckell [13] reports m. p. 68°) [2 : 4-*dinitrophenylhydrazone*, needles (from ethanol–benzene), soften at 181—183° and change into prisms, m. p. 186—186·5° (Found: N, 13·7%)].

Phenol (9·4 g., 0·1 mol.) and phenacyl chloride (15·5 g., 0·1 mol.) were heated in pyridine (25 ml.) at 100°. After 40 min. crystals began to appear and after a further 20 min. the mixture had completely solidified. Filtration and recrystallisation (charcoal) from 95% ethanol gave needles (very soluble in cold water), m. p. 108—109°; Babcock *et al.*[14] report m. p. 109—110° for phenacylpyridinium chloride monohydrate. The same product was obtained in 2 hr. at room temperature. Use of phenacyl bromide gave phenacylpyridinium bromide, prisms (from ethanol), m. p. 198—199° (decomp.); Baker [15] reports m. p. 199—200° (decomp.).

Cyclisation of ω-Aryloxyacetophenones.—The polyphosphoric acid was prepared from phosphoric oxide (420 g.) and phosphoric acid (200 ml.; *d* 1·75).

The cyclisation procedure was as follows: Polyphosphoric acid (20 g.) was preheated at the desired temperature for 20 min. and then 2·0 g. of the compound were added all at once. After being heated with continuous stirring for the desired time, the reactants were cooled, treated with water (500 ml.), and steam-distilled.

(i) ω-*Phenoxyacetophenone*. At 132° (chlorobenzene bath) for 2 hr. this compound gave 2-phenylbenzofuran which recrystallised (charcoal) from ethanol in plates (71%), m. p. and mixed m. p. 121° (Found: C, 86·7; H, 5·3. Calc. for $C_{14}H_{10}O$: C, 86·6; H, 5·2%); von Kostanecki and Tambor,[16] and Stoermer and Reuter,[17] report m. p. 120—121°. It yielded a 2 : 4 : 7-*trinitrofluorenone derivative*, orange-red needles (from absolute ethanol–benzene), m. p. and mixed m. p. 169—170° (Found: N, 8·2. $C_{13}H_5N_3O_7$,$C_{14}H_{10}O$ requires N, 8·25%). Cyclisation at 179° for 2—4 hr. gave 56—45% yields.

Cyclisation at 80° for 3½ hr. gave 3-phenylbenzofuran (1·5 g., 82%), b. p. 110°/0·3 mm., m. p. 42—43°, mixed m. p. 41—42°. Lower yields were obtained by reaction at 80° for 1 hr. or at room temperature for 7 hr.

Reaction at 110° (2 hr.) gave a mixture of 2- and 3-phenylbenzofuran. A distilled specimen was treated in 1 : 1-benzene–absolute alcohol with an excess of 2 : 4 : 7-trinitrofluorenone in the same solvent. The precipitated complex (mixed m. p.) of 2-phenylbenzofuran was collected. The mother-liquor was passed through an alumina column, followed by benzene. Concentration of the colourless eluate gave 3-phenylbenzofuran, m. p. 42—43° and mixed m. p. 40—42°.

(ii) ω-*Tolyloxyacetophenones*. Only the cyclisations at 132° during 2 hr. are now reported. The products were:

6-Methyl-2-phenylbenzofuran (50%), needles (from ethanol); m. p. and mixed m. p. 140—140·5° (Found: C, 86·65; H, 6·0. Calc. for $C_{15}H_{12}O$: C, 86·5; H, 5·8%) (Stoermer [18] reports m. p. 135·5° [2 : 4 : 7-*trinitrofluorenone compound*, orange needles (from absolute ethanol–benzene), m. p. 153—154° (Found: N, 7·8. $C_{13}H_5N_3O_7$,$C_{15}H_{12}O$ requires N, 8·0%)].

5-Methyl-2-phenylbenzofuran (61%), needles (from ethanol), m. p. and mixed m. p. 130—130·5° (Found: C, 86·7; H, 5·8%) (Stoermer [18] reports m. p. 129°) [2 : 4 : 7-*trinitrofluorenone compound*, orange needles (from absolute ethanol–benzene), m. p. 145° (Found: N, 7·9%)].

[13] Kunckell, *Ber.*, 1897, **30**, 577.
[14] Babcock, Nakamura, and Fuson, *J. Amer. Chem. Soc.*, 1932, **54**, 4408.
[15] Baker, *J.*, 1932, 1155.
[16] von Kostanecki and Tambor, *Ber.*, 1909, **42**, 826.
[17] Stoermer and Reuter, *Ber.*, 1903, **36**, 3981.
[18] Stoermer, *Ber.*, 1911, **44**, 1853.

7-*Methyl*-2-*phenylbenzofuran* (55%), an oil which, purified through the 2 : 4 : 7-*trinitrofluorenone compound*, m. p. 191—192° (Found: N, 7·95%), afforded prisms (from ethanol), m. p. 32·5—33° (Found: C, 86·7; H, 6·0%). The mother-liquors from the trinitrofluorenone compound preparation were passed through an alumina column, followed by benzene: no product was present in the eluate [cf. (i) above.]

Independent Syntheses of 2-*Phenylbenzofurans.*—2-Phenylbenzofuran was prepared by the method of Kawai *et al.*[5] from ethyl α-bromo-α-phenylacetate and salicylaldehyde. Similarly were obtained 5- (21%), 6- (28%), and 7-methyl-2-phenylbenzofuran (48%).

3-*Phenylbenzofuran.*—(a) *Synthesis.* 2 : 3-Dihydro-3-oxobenzofuran (from *o*-hydroxy-ω-chloroacetophenone by the method of Fries and Pfaffendorf [19]) (8·2 g., 1 mol.) in dry benzene (100 ml.) was added during 20 min. to phenylmagnesium bromide [from bromobenzene (28·8 g., 3 mol.) and magnesium (4·4 g., 3 mol.)] in dry ether (100 ml.). After 2 hr. on a steam-bath, the mixture was decomposed with ice and hydrochloric acid, and the ether layer washed with 2N-sodium hydroxide until the washings were almost colourless. The dried ($CaCl_2$) ether solution was then concentrated, to give 3-phenylbenzofuran (3·7 g., 31%), b. p. 110°/0·3 mm., m. p. 42—43° (Found: C, 86·8; H, 5·4%), which did not give a picrate or 2 : 4 : 7-trinitrofluorenone compound. Stoermer and Barthelmes [6] obtained only a " small yield " of 3-phenylbenzofuran by this method. Stoermer and Kippe [20] report m. p. 42°.

(b) *Isomerisation.* 3-Phenylbenzofuran (1·0 g.) was heated with polyphosphoric acid (20 g.) at 132° for 2 hr. Steam-distillation then gave 2-phenylbenzofuran, m. p. and mixed m. p. 120—121° (0·8 g., 80%).

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[19] Fries and Pfaffendorf, *Ber.*, 1910, **43**, 214.
[20] Stoermer and Kippe, *ibid.*, 1903, **36**, 4006.