558. *The Preparation of Some 2-Amino- and 2-Phthalimido-benzophenones.*

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Many substituted 2-phthalimidobenzophenones have been prepared by a Friedel–Crafts condensation of *o*-phthalimidobenzoic acid with substituted benzenes, and yields of approximately 70% were obtained in all cases where strongly electron-repelling groups were present; in absence of these groups yields were low.

When this method is inapplicable, the 2-phthalimidobenzophenones were obtained readily by fusion of the 2-aminobenzophenones with phthalic anhydride. The best general preparative method for 2-aminobenzophenones was that developed by Lothrup and Goodwin.

In earlier communications [1,2] it was reported that, whereas 2,4-dimethoxy- and 4-methoxy-2′-phthalimidobenzophenones condensed with hydrazine to form substituted 1,2,4-triazacyclohepta-2,5,7-trienes, other 2-phthalimidobenzophenones underwent the normal Ing and Manske decomposition.[3] To investigate the effect of substituents on the reaction between hydrazine and 2-phthalimidobenzophenones, a number of 2-phthalimidobenzophenones were prepared.

The most obvious route seemed to be reaction of 2-aminobenzophenones with phthalic

[1] Engels, Lamchen, and Wicken, *Proc. Chem. Soc.*, 1958, 191.
[2] Engels, Lamchen, and Wicken, *J.*, 1959, 2694.
[3] Ing and Manske, *J.*, 1926, 2348.

anhydride, and we found that at 180—200° this gave good yields; the method is, however, limited by the availability of the 2-aminobenzophenones. The most exploited route [4] to 2-aminobenzophenones involves Friedel–Crafts condensation of a substituted toluene-*p*-sulphonylanthraniloyl chloride with benzene or a substituted benzene, followed by acid-hydrolysis: its disadvantage, when highly activating substituents are present, is the ease of sulphonation during hydrolysis. We have found that the phthaloyl group can be used to protect the amino-group, the 2-phthalimidobenzophenones being obtained directly and, if desired, these could usually be decomposed to give the corresponding 2-aminobenzophenones. In this manner we have prepared 4-methoxy-,[2] 2,4-dimethoxy-,[2] 4-methylthio-, and 2,4-dimethyl-2′-phthalimidobenzophenone. With aluminium chloride in tetrachloroethane, yields of 62—76% of purified material were obtained, except in the case of 2,4-dimethyl-2′-phthalimidobenzophenone where only a 22% yield was obtained. 2-Phthalimidobenzophenone itself was obtained in only 8% yield, indicating that the best results with this method are obtained when the benzene ring is activated by substituents. It is of interest that when a deactivating group is present, as in phthalanil, the condensation with 2-phthalimidobenzoyl chloride was completely unsuccessful; however, under the more vigorous conditions of boiling in nitrobenzene, phthalanil and 2-phthalimidobenzoyl chloride with zinc chloride in only catalytic quantities gave a yield of 17% of 2,4′-diphthalimidobenzophenone.

That this method is also applicable to the preparation of 3- and 4-phthalimidobenzophenones was shown by our preparation of 2,4-dimethoxy-3′- and -4′-phthalimidobenzophenone in the same high yields.[2] In a similar way 2-3′-nitrophthalimidobenzyol chloride with dimethylresorcinol gave 2,4-dimethoxy-2′-(3-nitrophthalimido)benzophenone.

In the preparation of 4-methoxy-2-phthalimidobenzophenone this method could not be used since during the condensation of phthalic anhydride with 4-methoxyanthranilic acid decarboxylation produced 3-phthalimidoanisole. Other cases where a Friedel–Crafts condensation could not give the benzophenone with substituents in the desired positions, *e.g.*, 2-methoxy-2′-phthalimidobenzophenone, were also encountered. Here the 2-aminobenzophenones had to be prepared first. For such cases we have found Lothrup and Goodwin's method [5] the most useful, namely, addition of phenylmagnesium bromide to acetanthranil at 0°, giving 2-acetamidobenzophenone which could be hydrolysed in good yield to 2-aminobenzophenone. We prepared similarly 2-amino-4-methoxy-, -2′-methoxy-, and -2′,4-dimethoxy-benzophenone and have converted them into the phthalimidobenzophenones by fusion with phthalic anhydride at 180—200°. In this method the substituent groups retain their positions and exert no orientating effect on the reaction as is found in a Friedel–Crafts reaction; the effect of substituent groups on the formation of the Grignard reagent is, however, a limitation, nitro-groups for instance completely preventing it.

Other known 2-aminobenzophenones, *e.g.*, 2-amino-2′-methyl-, -4′-methyl-, -4′-bromo-, and -4′-hydroxy-benzophenone, were similarly converted in good yield into the phthalimidobenzophenones by fusion with phthalic anhydride. 2-Aminoacetophenone gave 2-phthalimidoacetophenone.

The reaction of these substituted 2-phthalimidobenzophenones with hydrazine forms the basis of another paper.

Experimental

2-3′-Nitrophthalimidobenzoic Acid.—Equivalent quantities of anthranilic acid (10 g.) and 3-nitrophthalic anhydride (14·2 g.) were fused at 180—200° for 30 min. The crystalline product was recrystallised three times from glacial acetic acid to produce *2-3′-nitrophthalimidobenzoic acid* (16 g., 70%) as needles, m. p. 222—224° (Found: C, 57·6; H, 2·8; N, 9·1. $C_{15}H_8O_6N_2$ requires C, 57·8; H, 2·6; N, 9·0%).

2-Phthalimidobenzophenone.—*o*-Phthalimidobenzoic acid (20 g.) and phosphorus pentachloride (16 g.) were refluxed in dry, sulphur-free benzene (100 ml.) for 2 hr. After cooling,

[4] Cf. Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646
[5] Lothrup and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363.

powdered, anhydrous aluminium chloride (27 g.) was added in 30 min. An exothermic reaction produced a brownish-black complex. The mixture was left at room temperature for 1 hr., then refluxed for 1 hr. The complex was decomposed with ice and hydrochloric acid, and the excess of benzene removed by steam-distillation. The residual solid was filtered off and washed with dilute hydrochloric acid and then water. The solid was taken up in ether, and washed with dilute sodium hydroxide solution, then with water. The ether was dried and evaporated, to leave white crystals which were recrystallised from ethanol to yield 2-phthalimidobenzophenone (2 g., 8%) as needles, m. p. 198—199° (Engels, Lamchen, and Wicken [2] reported 199°).

2,4-*Dimethyl-2'-phthalimidobenzophenone.*—*o*-Phthalimidobenzoic acid (25 g.) was stirred with phosphorus pentachloride (20 g.) in dry redistilled *m*-xylene (100 ml.) for 1 hr. at 50—60°. To the cooled solution powdered anhydrous aluminium chloride (30 g.) was added in 30 min. The mixture was stirred at 80—90° for a further 4 hr., then worked up as above. The brown oil obtained on evaporation crystallised only when kept in the minimum amount of ether overnight at 0°; crystals were formed which then recrystallised from dilute ethanol to give 2,4-*dimethyl-2'-phthalimidobenzophenone* as rods (7 g., 22%), m. p. 172—175° (Found: C, 78·0; H, 5·0; N, 3·9. $C_{23}H_{17}O_3N$ requires C, 77·7; H, 4·8; N, 3·9%).

4-*Methylthio-2'-phthalimidobenzophenone.*—*o*-Phthalimidobenzoic acid (26·7 g.) was stirred vigorously with phosphorus pentachloride (21 g.) in dry *sym*-tetrachloroethane (100 ml.) for 2 hr. To the cooled solution, thioanisole (13 g.) was added, and then aluminium chloride (27 g.) in 30 min. The mixture was stirred at 40—50° for a further hour, decomposed, and steam-distilled as above. The residue, dissolved in benzene, was washed with 10% sodium carbonate and then water. The dried benzene solution on evaporation gave a solid residue, which recrystallised (charcoal) from acetic acid gave 4-*methylthio-2'-phthalimidobenzophenone* as rods (27 g., 73%), m. p. 192—195° (Found: C, 71·3; H, 4·05; N, 3·6; S, 8·5. $C_{22}H_{15}O_3NS$ requires C, 70·7; H, 4·05; N, 3·75; S, 8·6%).

2,4-*Dimethoxy-2'-(3-nitrophthalimido)benzophenone.*—Prepared as above from 2-3'-nitrophthalimidobenzoic acid (25 g.), phosphorus pentachloride (18 g.), *sym*-tetrachloroethane (100 ml.) (stirred for 2 hr. at 70°), dimethylresorcinol (15 g.), and aluminium chloride (25 g.), the purple complex was worked up in the same way as above. Distillation of the benzene gave a pale oil which solidified and on recrystallisation from glacial acetic acid yielded 2,4-*dimethoxy-2'-(3-nitrophthalimido)benzophenone* (6 g., 17%) as rectangular prisms, m. p. 248—250° (Found: C, 64·3; H, 3·65; N, 6·5. $C_{23}H_{16}O_7N_2$ requires C, 63·9; H, 3·7; N, 6·5%).

2,4'-*Diphthalimidobenzophenone.*—*o*-Phthalimidobenzoic acid (10 g.) was stirred with phosphorus pentachloride (8 g.) in anhydrous nitrobenzene (50 ml.) at 80° for 2 hr. Phthalanil (8·4 g.) and crushed anhydrous zinc chloride (1 g.) were added and the mixture refluxed for 6 hr. After cooling, the solution was made slightly alkaline with dilute aqueous sodium hydroxide, and the excess of nitrobenzene removed by steam-distillation. The black tarry residue was treated with charcoal in glacial acetic acid and from the filtered solution a light brown amorphous solid (5 g.) was slowly precipitated. Repeated recrystallisation from acetic acid yielded 2,4'-*diphtalimidobenzophenone* (3 g., 17%) as long white needles, m. p. 309—312° (Found: C, 73·3; H, 3·7; N, 5·8. $C_{29}H_{16}O_5N_2$ requires C, 73·7; H, 3·4; N, 5·9%).

m-*Phthalimidoanisole.*—4-Methoxyanthranilic acid (0·5 g.) and phthalic anhydride (0·45 g.) were refluxed in acetic acid (20 ml.) for 2 hr. The hot solution was poured into water (250 ml.), and the pale brown precipitate was recrystallised from dilute ethanol, to give m-*phthalimidoanisole* (0·53 g., 60%) as white needles, m. p. 123—124° (Found: C, 71·3; H, 4·4. $C_{15}H_{11}O_3N$ requires C, 71·2; H, 4·35%).

2-*Amino-4-methoxybenzophenone.*—Phenylmagnesium bromide, prepared from bromobenzene (14·1 g.) and magnesium (2·17 g.) in dry ether (200 ml.), was slowly added with stirring under strictly anhydrous conditions to an ice-cold suspension of 4-methoxyacetanthranil (17·5 g.) in dry benzene (200 ml.) during 30 min. The thick yellow suspension was stirred at room temperature for a further 30 min., the mixture then becoming too sticky for stirring. Hydrolysis of the complex with dilute hydrochloric acid was slow; it was allowed to proceed overnight, and completed by steam-distillation which also removed the solvents. The oily residue was ether-extracted and washed with dilute sodium hydroxide and water, then dried and evaporated to leave a thick oil. Without further purification this oil, presumably 2-acetamido-4-methoxybenzophenone, was hydrolysed by refluxing it with concentrated hydrochloric acid (20 ml.) and 96% ethanol (100 ml.) for 1 hr. This solution was then treated with charcoal, filtered, made alkaline with ammonia, diluted with water (200 ml.), and chilled in ice; a pale

yellow solid separated. Recrystallisation from dilute ethanol yielded *2-amino-4-methoxybenzophenone* (6·5 g., 32%) as pale yellow needles, m. p. 109—111° (Found: C, 73·9; H, 5·8; N, 6·0. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8; N, 6·2%).

The acidic aqueous solution, after ether-extraction, was made alkaline with ammonia and re-extracted with ether to yield another 0·5 g. of the compound.

2-Amino-2′-methoxybenzophenone.—A Grignard reagent was prepared from *o*-iodoanisole (29 g.) and excess of activated magnesium powder [6] (4 g.) in anhydrous ether (100 ml.). Unchanged magnesium was removed by filtration through glass wool. The ethereal solution was added slowly (30 min.) under anhydrous conditions to a stirred solution of acetanthranil (20 g.) in dry benzene (150 ml.) at 0°. A pale orange precipitate was formed almost immediately. The suspension was stirred for a further hour at room temperature and at 30° for a further 30 min. The mixture was worked up as above, to give the crude 2-acetamido-2′-methoxybenzophenone, which was then hydrolysed as above. After dilution, the solution was made alkaline with ammonia and ether-extracted. Evaporation of the ether gave 2-amino-2′-methoxybenzophenone (9 g., 32%), yellow plates (from dilute ethanol), m. p. 109—111° (Inagaki [7] reported m. p. 110—111° for the compound made by a different method).

2-Amino-2′,4-dimethoxybenzophenone.—This was prepared as 2-amino-2′-methoxybenzophenone, by using same quantities but with 4-methoxyacetanthranil (14 g.). After hydrolysis with alcoholic hydrochloric acid, the alcoholic solution was treated with charcoal, made alkaline with ammonia, diluted with water (200 ml.), and chilled in ice. An oil separated and slowly solidified. Recrystallisation from dilute ethanol yielded 2-amino-2′,4-dimethoxybenzophenone (5 g., 24%) as pale yellow rods, m. p. 119—121° (Found: C, 70·1; H, 6·0; N, 5·3. $C_{15}H_{15}O_3N$ requires C, 70·1; H, 5·85; N, 5·4%).

4-Methoxy-2-phthalimidobenzophenone.—2-Amino-4-methoxybenzophenone (4 g.) was fused with phthalic anhydride (2·6 g.) at 180—200° for 30 min. The clear melt obtained set to a glass on cooling, and recrystallisation from ethanol yielded *4-methoxy-2-phthalimidobenzophenone* (4 g., 64%) as rods, m. p. 143—145° (Found: C, 73·9; H, 4·5; N, 3·8. $C_{22}H_{15}O_4N$ requires C, 73·9; H, 4·2; N, 3·9%).

Similarly were prepared:

2-Methoxy-2′-phthalimidobenzophenone [6 g., 76%; from 2-amino-2′-methoxybenzophenone (5 g.) and phthalic anhydride (3·2 g.)], colourless rods (from acetic acid), m. p. 205—207° (Found: C, 74·0; H, 4·3; N, 3·8. $C_{22}H_{15}O_4N$ requires C, 73·9; H, 4·2; N, 3·9%).

2′,4-Dimethoxy-2-phthalimidobenzophenone [1·5 g., 67%; from 2-amino-2′,4-dimethoxybenzophenone (1·5 g.) and phthalic anhydride (0·86 g.)], rods (from dilute acetic acid), m. p. 175—177° (Found: C, 71·3; H, 4·6; N, 3·5. $C_{23}H_{17}O_5N$ requires C, 71·3; H, 4·4; N, 3·6%).

2-Methyl-2′-phthalimidobenzophenone [68%; from 2-amino-2′-methylbenzophenone [5] (5 g.) and phthalic anhydride (3·5 g.)], needles (from acetic acid), m. p. 185—188° (Found: C, 77·2; H, 4·3; N, 4·0. $C_{22}H_{15}O_3N$ requires C, 77·4; H, 4·4; N, 4·1%).

4-Methyl-2′-phthalimidobenzophenone (80%; from 2-amino-4′-methylbenzophenone [8] (3·5 g.) and phthalic anhydride (2·5 g.), 30 min.]. The light coloured glass obtained on cooling was recrystallised needles (from ethanol), m. p. 167—169° (Found: C, 78·1; H, 4·5; N, 4·05. $C_{22}H_{15}O_3N$ requires C, 77·4; H, 4·4; N, 4·1%).

4-Bromo-2′-phthalimidobenzophenone [77%; from 2-amino-4′-bromobenzophenone [9] (6 g.) and phthalic anhydride (3·2 g.), for 20 min.], diamond-shaped prisms (from acetic acid), m. p. 212—215° (Found: C, 61·9; H, 3·0; N, 3·6; Br, 19·8. $C_{21}H_{12}O_3NBr$ requires C, 62·1; H, 3·0; N, 3·45; Br, 19·7%).

4-Hydroxy-2′-phthalimidobenzophenone [78%; from 2-amino-4′-hydroxybenzophenone [10] (6·5 g.) and phthalic anhydride (4·5 g.), for 20 min.], plates (from acetic acid), m. p. 233—235° (Found: C, 73·6; H, 3·9; N, 3·9. $C_{21}H_{13}O_4N$ requires C, 73·4; H, 3·8; N, 4·1%).

2-Phthalimidoacetophenone [44%; from 2-aminoacetophenone [11] (6 g.) and phthalic anhydride (6·6 g.), 30 min.], plates (from dilute ethanol), m. p. 132—134° (Found: C, 72·7; H, 4·0; N, 5·2. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·15; N, 5·3%).

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