Oxidative Coupling. Part IX.[1] Cyclisation involving 3-Aminobenzophenones †

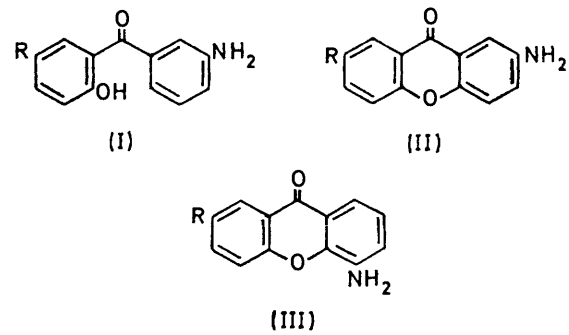
By I. H. Bowen and J. R. Lewis,* Chemistry Department, University of Aberdeen, Scotland

The oxidation of 3'-amino-2-hydroxybenzophenones leads to 2- or 4-aminoxanthones by oxidative coupling directed into positions *para* or *ortho* to the amino-group.

THE oxidative cyclisation of 2',3-dihydroxylated benzophenones to give xanthones has been established as a biosynthetic process,[2,3] this intramolecular coupling reaction involving two hydroxy-groups. In continuing our investigations into the synthesis of natural products through intramolecular oxidative coupling, we have examined the role of the amino-group in the oxidation of aminohydroxybenzophenones. That the amino-group can participate in and direct oxidative coupling intermolecularly has been shown by the synthesis of phenoxazin-3-ones from 2-aminophenols [4-6], and of hydrazines, azo-compounds, and biphenyls from aniline and its derivatives; [7-9] intramolecular coupling has been achieved in the conversion of diphenyl ethers into phenoxazines.[10]

By analogy with the oxidation of hydroxylated benzophenones, the presence of a 2-hydroxy-group and a 3'-amino-group in a benzophenone ought to enable oxidative cyclisation to give aminoxanthones, ring closure being directed *ortho* or *para* to the amino-group. 3'-Amino-2-hydroxybenzophenone and its 5-methyl derivative have been synthesised to study their oxidative behaviour.

3'-Amino-2-hydroxybenzophenone (I; R = H) was made by condensation of 3-nitrobenzoyl chloride with anisole and reduction of the resulting 2-hydroxy-3'-nitrobenzophenone [11] (isolated from the product mixture) with ammoniacal iron(II) sulphate. In a similar manner, methyl *p*-tolyl ether yielded a mixture of 2-methoxy-5-methyl-3'-nitrobenzophenone and the 2-hydroxy-analogue,[12] the latter giving the aminobenzophenone (I; R = Me) upon reduction.



The effect of pH upon the oxidation of these 2-amino-3'-hydroxybenzophenones was studied, since the various 2,3'-dihydroxybenzophenones investigated previously [2] gave pH-dependent results. The amphoteric nature of the aminobenzophenones enabled homogeneous reaction conditions to be used over the pH range 0—14. In neutral and alkaline solutions, potassium ferricyanide was used as oxidising agent; in acid solution potassium dichromate was employed. At pH 13, the benzophenone (I; R = Me) was converted into 2-amino-7-methylxanthone (II; R = Me) in 28% yield; the Table shows the relationship between yield and pH. Under these oxidations, the isomeric 5-amino-2-methylxanthone (III; R = Me) was also isolated; thus oxidative cyclisation

† Preliminary communication, *Chem. Comm.*, 1970, 1625.

[1] Part VIII, J. W. A. Findlay, P. Gupta, and J. R. Lewis, *J. Chem. Soc.* (*C*), 1969, 2761.

[2] J. E. Atkinson and J. R. Lewis, *J. Chem. Soc.* (*C*), 1969, 281.

[3] P. Gupta and J. R. Lewis, *J. Chem. Soc.* (*C*), 1971, 629.

[4] A. Butenandt, E. Siekert, and W. Shafer, *Annalen*, 1960, **632**, 143.

[5] H. Brockmann and F. Seela, *Tetrahedron Letters*, 1965, 4803.

[6] H. Brockmann and F. Seela, *Tetrahedron Letters*, 1968, 161.

[7] D. G. H. Daniels, F. T. Naylor, and B. C. Saunders, *J. Chem. Soc.*, 1951, 3433.

[8] O. Meth-Cohn and H. Suschitzky, *Chem. and Ind.*, 1969, 443.

[9] A. G. Hudson, A. E. Fedler, and J. C. Tatlow, *Tetrahedron*, 1970, **26**, 3790.

[10] K. S. Balachandran and I. Bhatnagar, *Chem. and Ind.*, 1969, 953.

[11] D. L. F. De Tar and D. I. Relyea, *J. Amer. Chem. Soc.*, 1954, **76**, 1680.

[12] G. S. Saharia and B. R. Sharma, *J. Indian Chem. Soc.*, 1956, **33**, 788.

was directed preferentially to the *para*-position but also to the *ortho*-position by the amino-group.

Yields of xanthone (II; R = Me) at various pH values

Oxidant, $K_2Cr_2O_7$			Oxidant, $K_3Fe(CN)_6$		
pH	Xanthone (% yield)	Recovered benzophenone (%)	pH	Xanthone (% yield)	Recovered benzophenone (%)
0	3	7	8	4	60
1	3	40	9	5	50
2	7	64	10	15	57
3	3	42	11	20	48
4	2	32	12	12	64
5	1	32	13	28	68
6	1	38	14	20	67
7	1	30			

Although the yields of xanthones produced in these oxidations of amino-activated benzophenones are lower than those obtained from the hydroxy-activated benzophenones, the ability of the amino-group to behave as an activating and a directing group in oxidative coupling has been established. The yields of *ortho*-cyclised products were low (*ca.* 5%) in every case, and optimum conversion into the 2-aminoxanthone occurred at pH 2 and pH 13.

The appropriate aminoxanthones were synthesised from the corresponding nitroxanthones by reduction; the nitroxanthones were produced by condensation of the appropriate phenol with either a methyl chlorobenzoate or a methyl *p*-tolylsulphonyloxybenzoate, under Ullmann conditions, followed by hydrolysis of the diphenyl ether ester produced and dehydrative cyclisation.

EXPERIMENTAL

2-Hydroxy-3'-nitrobenzophenone.—3-Nitrobenzoic acid (17 g) was converted into the acid chloride with phosphorus pentachloride in carbon disulphide (50 ml); to this mixture were added anisole (12 g) in carbon disulphide (100 ml) and anhydrous aluminium chloride (30 g), and the mixture was refluxed for 2 h. Evaporation and treatment of the residue with ice–hydrochloric acid gave an oil which yielded a phenolic fraction (4·08 g) crystallising from methanol–ether to give 2-hydroxy-3'-nitrobenzophenone,[11] m.p. 93·5—94·5°, $\nu_{max.}$ (KBr) 1632 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 221 (log ε 4·25), 339 (4·27), 263 (4·20), and 340 nm (3·58). In this reaction the main product, corresponding to *para*-substitution on anisole (*i.e.* 4-methoxy-3'-nitrobenzophenone) was not demethylated and was conveniently separated from the required 2-hydroxy-compound.

3'-Amino-2-hydroxybenzophenone (I; R = H).—The foregoing nitro-compound (250 mg) was suspended in aqueous iron(II) sulphate solution (3 mg in 5 ml) containing hydrochloric acid (0·2N; 0·1 ml). Ammonia (*d* 0·880; 0·51 ml) was added and the mixture was shaken at 90° until the green colour had disappeared. Addition of ammonia was repeated (×3), accompanied by shaking, and the solution was finally made alkaline, cooled, filtered through Celite, and extracted with ethyl acetate. The aqueous alkaline solution was acidified and extracted with ethyl acetate, and the aqueous acidic solution was neutralised with sodium hydrogen carbonate solution. Re-extraction with ethyl acetate and evaporation of the extract yielded the *amino-benzophenone* (189 mg), which formed yellow prisms, m.p. 119—120° (from methanol), $\nu_{max.}$ (KBr) 3470 and 3375 (NH_2), and 1625 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 219·5 (log ε 4·21), 244 (4·28), and 337 nm (3·77) (Found: C, 73·3; H, 5·4. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2%).

2-Hydroxy-5-methyl-3'-nitrobenzophenone (I; R = Me).—Friedel–Crafts condensation of 4-methylanisole and 3-nitrobenzoyl chloride as already described gave, from the neutral extracts, 2-methoxy-5-methyl-3'-nitrobenzophenone (12·4 g), m.p. 102° (from methanol–chloroform);[12] from the alkaline extract after neutralisation was obtained 2-hydroxy-5-methyl-3'-nitrobenzophenone,[12] m.p. 102° (from methanol–chloroform), $\nu_{max.}$ (KBr) 1630 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 227 (log ε 4·03), 265 (3·91), and 354 nm (3·60). Reduction of the nitrobenzophenone (9 g) with iron(II) sulphate–ammonia, as before, gave *3'-amino-2-hydroxy-5-methylbenzophenone* (I; R = Me) (6·7 g), m.p. 115—120°, $\nu_{max.}$ (KBr) 3450, 3365 (NH_2), and 1632—1615 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 222·5 (log ε 4·37), 243 (4·33), and 349 nm (3·78) (Found: C, 73·7; H, 5·9. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·7%).

2-Aminoxanthone.—2-Nitroxanthone[13] (38 mg) was reduced with iron(II) sulphate–ammonia, as already described, to give 2-aminoxanthone[14] (30 mg), m.p. 199° (subl.), $\nu_{max.}$ (KBr) 3408, 3312 (NH_2), and 1640—1615 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 214 (log ε 3·99), 252 (4·58), 304 (3·51), and 390 nm (3·58), R_F (silica gel) in chloroform 0·11; in ethyl acetate 0·75.

4-Aminoxanthone.—4-Nitroxanthone[13] was similarly reduced to give 4-aminoxanthone,[14] m.p. 196—200°, $\nu_{max.}$ (KBr) 3480, 3355 (NH_2), and 1658 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 239·5 (log ε 4·36), 259 (4·39), 298·5 (3·66), and 370 nm (3·44), R_F (silica gel) in chloroform 0·36; in ethyl acetate 0·81.

Methyl 5-Nitro-2-p-tolyloxybenzoate.—Methyl 2-chloro-5-nitrobenzoate[15] (4 g) was refluxed in pyridine (30 ml) containing *p*-cresol (8·5 g) for 2 h; the mixture was added to dil. hydrochloric acid and extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution and water, dried, and evaporated to leave the *p-tolyl ether* (1·5 g), m.p. 139—141° (from benzene–ethanol), $\nu_{max.}$ (KBr) 1733 (C=O), $\lambda_{max.}$ (EtOH) 226 (log ε 4·20) and 301 nm (4·07) (Found: C, 62·9; H, 4·8; N, 5·0. $C_{15}H_{13}NO_5$ requires C, 62·7; H, 4·5; N, 4·9%).

2-Methyl-7-nitroxanthone.—The foregoing ether (500 mg) was hydrolysed by heating with sodium hydroxide solution (2N; 50 ml) for 30 min. The solution was then acidified and extracted with ethyl acetate. Evaporation of the extract addition of conc. sulphuric acid (10 ml), and heating on a steam-bath for 1 h yielded a solution which deposited a solid on dilution with water. This solid was extracted into ethyl acetate; the solution was washed with sodium hydrogen carbonate solution and worked up in the usual way to give 2-methyl-7-nitroxanthone[16] (210 mg), m.p. 219—221°, $\nu_{max.}$ (KBr) 1658 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 224 (log ε 4·29), 251 (4·38), 287 (4·21), and 310 nm (3·93).

2-Amino-7-methylxanthone (II; R = Me).—2-Methyl-7-nitroxanthone (130 mg) was reduced as before with iron(II)

[13] A. Akagi and T. Iwashige, *J. Pharm. Soc. Japan*, 1954, **74**, 610.

[14] A. A. Goldberg and H. A. Walker, *J. Chem. Soc.*, 1953, 1348.

[15] H. Rupe, *Ber.*, 1897, **30**, 1097.

[16] J. Meisenheimer, R. Hanssen, and A. Wächterowitz, *J. prakt. Chem.*, 1928, **119**, 315.

sulphate–ammonia to give *2-amino-7-methylxanthone* (86 mg), m.p. 163—165° (subl. 145°), $\nu_{max.}$ (KBr) 3410, 3335 (NH_2), and 1620 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 221 (log ε 4·08), 257 (4·37), 310 (3·57), and 392·5 nm (3·61) (Found: C, 74·7; H, 4·8; N, 6·3. $C_{14}H_{11}NO_2$ requires C, 74·7; H, 4·9; N, 6·2%), R_F (silica gel) in chloroform 0·14; in ethyl acetate 0·75.

Methyl 3-Nitro-2-p-tolylsulphonyloxybenzoate.—Methyl 3-nitrosalicylate (10 g) in aqueous acetone (20%; 300 ml) containing sodium hydroxide (2N; 30 ml) was treated with toluene-*p*-sulphonyl chloride (10 g) and the mixture was kept at room temp. for 22 h. The acetone was evaporated off and excess of sodium hydroxide solution was added. The precipitate was collected and dissolved in benzene–ether (1 : 1), and the organic solution was washed with sodium hydrogen carbonate solution and water, dried, and evaporated to give an oil (7·3 g), which crystallised from methanol as prisms, m.p. 88—90°, of the *sulphonate*, $\nu_{max.}$ (KBr) 1734 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 229 nm (4·18) (Found: C, 51·4; H, 3·9; N, 3·8. $C_{15}H_{13}NO_7S$ requires C, 51·3; H, 3·7; N, 4·0%).

Methyl 3-Nitro-2-p-tolyloxybenzoate.—Methyl 3-nitro-2-*p*-tolylsulphonylbenzoate (3 g) and *p*-cresol (2 g) were refluxed in dry pyridine (30 ml) for 1 h. The mixture was diluted with dilute hydrochloric acid and extracted with ethyl acetate; work-up gave the *ether* which after t.l.c. yielded a yellow solid (920 mg), m.p. 56—58°, $\nu_{max.}$ (KBr) 1734 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 227 nm (4·22) (Found: C, 62·9; H, 4·8; N, 4·9. $C_{15}H_{13}NO_5$ requires C, 62·7; H, 4·5; N, 4·9%).

2-Nitro-5-methylxanthone.—The foregoing ether (700 mg) was hydrolysed and cyclised as described previously to give *2-nitro-5-methylxanthone* (220 mg), m.p. 164—166°, $\nu_{max.}$ (KBr) 1670 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 232 (log ε 4·51), 294 (3·71), and 349 nm (3·88) (Found: C, 65·6; H, 3·6; N, 5·6. $C_{14}H_9NO_4$ requires C, 65·9; H, 3·5; N, 5·5%).

5-Amino-2-methylxanthone (III; R = H).—2-Methyl-5-nitroxanthone (100 mg) was reduced with iron(II) sulphate–ammonia to give *5-amino-2-methylxanthone* (44 mg), m.p. 189—191°, $\nu_{max.}$ (KBr) 3460, 3335 (NH_2), and 1650 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 216 (log ε 4·11), 239 (4·48), 261 (4·55), 300 (3·65), and 372 nm (3·62) (Found: C, 74·8; H, 4·9; N, 6·1. $C_{14}H_{11}NO_2$ requires C, 74·7; H, 4·9; N, 6·2%).

Oxidation of 3′-Amino-2-hydroxy-5-methylbenzophenone (I; R = Me).—(a) *In alkaline solution.* The benzophenone (50 mg) was dissolved in oxygen-free sodium hydroxide solution (0·1N; 50 ml) containing potassium ferricyanide (100 mg) and stirred under nitrogen. After 3 h the solution was made strongly alkaline and extracted with ethyl acetate (2 × 35 ml). The organic layer was washed with water, dried, and evaporated to give a residue, which separated on t.l.c. (silica gel; chloroform) into two bands. The major component was 2-amino-7-methylxanthone (II; R = Me) and the other band yielded a small quantity of 5-amino-2-methylxanthone (III; R = Me). Both compounds were identified by R_F comparisons (t.l.c.) with authentic xanthones. The major component had m.p. 162—165°, $\lambda_{max.}$ (EtOH) 221 (log ε 4·08), 257 (4·55), 310 (3·56), and 382·5 nm (3·62).

In a similar manner, 3′-amino-2-hydroxybenzophenone (I; R = H) gave 2-aminoxanthone (II; R = H) and 4-aminoxanthone (III; R = H), identified by mixed m.p. and R_F comparisons. The former, m.p. and mixed m.p. 199°, had $\lambda_{max.}$ (EtOH) 214 (log ε 3·99), 252 (4·58), 304 (3·51), and 390 nm (3·58).

Solutions of various pH values were obtained by use of B.D.H. buffers; results of oxidations of such solutions are quoted in the Table. Yields were obtained by chromatographic separation of the products (p.l.c.) and weighing the xanthone and benzophenone thus isolated.

(b) *In acid solution.* The benzophenone (I; R = Me) (50 mg) was dissolved or suspended in the appropriate solution (50 ml) containing potassium dichromate (120 mg), and the mixture was stirred under nitrogen for 3 h; the solution was neutralised with sodium hydrogen carbonate and extracted with ethyl acetate to give a complex mixture of products. T.l.c. revealed the presence of 2-amino-7-methylxanthone (II; R = Me) and starting material. Variation of pH gave the results quoted in the Table.

We thank the S.R.C. for a studentship (to I. H. B.).

[1/1583 *Received*, 1*st September*, 1971]