Oxidative Coupling. Part X.[1] Cyclisations of 2-Aminobenzophenones

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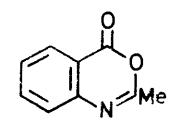
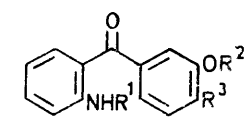
The oxidation of 2-amino-3′-hydroxy- or -methoxy-benzophenones gives hydroxy- or methoxy-9-acridones, coupling being observed *ortho* or *para* to the oxygen substituent.

WE have previously [1] described the role played by the 3′-amino-group in directing and activating 2-hydroxybenzophenones towards oxidative cyclisation with the formation of aminoxanthones. If the positions of the hydroxy- and amino-groups are reversed it becomes possible to synthesise 9-acridones by oxidative coupling. That the amino-group can participate in the formation of a diphenylamine-type linkage through intermolecular coupling is exemplified by the formation of phenoxazin-3-ones from 2-aminophenols [2-4] and of phenazines from anthranilic acids.[5,6] Intramolecular coupling results in the conversion, under oxidative conditions, of 2-aminophenyl phenyl ethers to phenoxazines,[7] 2-aminobiphenyls to carbazoles,[8,9] 2-anilinoanilines to phenazines,[10,11] and 2-aminobenzophenone to 9-acridone.[12] Phenylethylamines have been converted into indoles [13] and into *Erythrina* [14,15] and *Amaryllidaceae* type alkaloids.[16,17]

To ascertain whether the amino-group can be involved specifically in an intramolecular oxidative ring closure, directed by a hydroxy-group, to yield 9-acridones, the synthesis of 2-amino-3′-hydroxybenzophenones was investigated. Ullman and Denzler [18] had described some syntheses of 2-aminobenzophenones, but with substituents in the 3′-position the overall yields were low. The condensation of 2-nitrobenzoyl chloride with phenyl ethers [19] has limited application, and the condensation of 3-bromanisole with aroylcadmium chlorides yielded, surprisingly, the corresponding 4′-methoxybenzophenone; [20] this reaction was also unsuccessful in our hands. However, condensations of



(I)



(II)

2-methyl-3,1-benzoxazin-4-one (1) with the appropriate Grignard reagents, as described by Lothrop and Goodwin,[21] gave the *N*-acetyl-3′-methoxybenzophenones (II;

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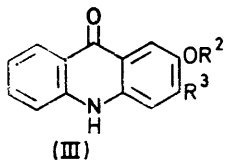
R^1 = Ac, R^2 = H or Me, R^3 = H, OH, or OMe) in acceptable yields. Hydrolysis yielded the methoxy-amine or hydroxy-amine according to the conditions.

The oxidation of 2-amino-3′-hydroxybenzophenone (II; $R^1 = R^2 = R^3$ = H) proved difficult; many of the oxidising agents known to be successful for phenol oxidation did not induce cyclisation, starting material being recovered in most cases. Potassium persulphate [9] or manganese(III) acetate [22] caused oxidative cyclisation of this benzophenone to a mixture of 2-hydroxy- and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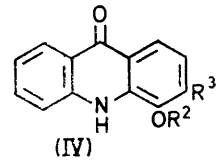
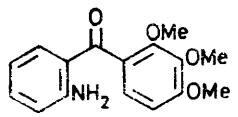

(IV)

4-hydroxy-9-acridone (III and IV; $R^1 = R^2 = R^3$ = H) in 1—8% yields; the Table summarises the products from the five benzophenones studied. In most cases cyclisation occurred as directed by a hydroxy- or methoxy-group to its *ortho*- or *para*-position.

These oxidative cyclisations may be relevant to the biogenesis of the acridone alkaloids.[23] These naturally occurring compounds are 9-acridones with 2-oxygen substituents [24] in many cases. Treatment of 2′-amino-2,3,4-trimethoxybenzophenone (V) with potassium persulphate gave 3,4-dimethoxy-9-acridone (VI), obtained by an intramolecular displacement of a methoxy-group rather than an oxidative cyclisation to yield a product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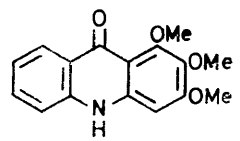
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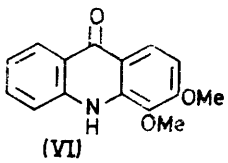
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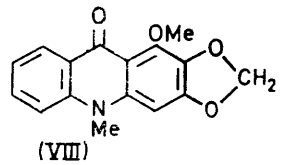
(VIII)

(VII) with an evoxanthine (VIII) type oxygenation pattern. Similar activation producing this type of cyclisation has been observed with erdin and geodin to yield a xanthone.[25] The similarity of oxygenation patterns and the occurrence of C-5 alkylated derivatives of xanthones [26] and 9-acridones [24] in natural products suggests similar biogenetic processes involving benzophenones as precursors, and the oxidative coupling reactions reported here present some evidence in favour of this type of biogenetic pathway.

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EXPERIMENTAL

2-Amino-3′-methoxybenzophenone (II; $R^1 = R^3$ = H, R^2 = Me).—2-Methyl-3,1-benzoxazin-4-one [21] (10 g) in dry benzene (50 ml) was added to a solution of 3-methoxyphenylmagnesium bromide [from 3-bromanisole (11·6 g) in tetrahydrofuran (60 ml)], and the mixture was stirred for 2 h. Addition of dilute sulphuric acid followed by washing the organic layer with water, drying, and evaporation gave *2-acetamido-3′-methoxybenzophenone* (II; R^1 = Ac, R^3 = H, R^2 = Me) (6·1 g) as a pale yellow oil, b.p. 190—193° at 1·3 mmHg, $\nu_{max.}$ (KBr) 3300 (NH), 1700, and 1635 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 214 (log ε 4·53), 227 (4·63), 263 (4·27), and 322 nm (3·93) (Found: C, 71·6; H, 5·7. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6%). The amide (2 g) was refluxed in ethanol (20 ml) containing conc. hydrochloric acid (10 ml) for 2 h and the product worked up to give the amine (1·3 g) as a yellow oil; distillation (165—168° at 0·01 mmHg) gave *2-amino-3′-methoxybenzophenone* (II; $R^1 = R^3$ = H, R^2 = Me), m.p. 46—48°, $\nu_{max.}$ (KBr) 3455, 3345 (NH_2), and 1635 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 210sh (log ε 4·39), 229 (4·42), 263sh (3·99), 300 (3·36), and 381 nm (3·79) (Found: C, 74·3; H, 5·9. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·8%), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·6.

2-Amino-3′-hydroxybenzophenone (II; $R^1 = R^2$ = H).—The foregoing amide (6 g) was heated under reflux with hydrogen bromide (50 ml) (60%) for 3 h. The mixture was poured on ice; work-up gave an oil which was chromatographed on silica gel. Elution with benzene–ethyl acetate (95 : 5) gave *2-amino-3′-hydroxybenzophenone* (II; $R^1 = R^2 = R^3$ = H) (3·5 g), m.p. 104°, $\nu_{max.}$ (KBr) 3475 (NH_2), 3360 (NH_2 and OH), and 1620 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 217sh (log ε 4·22), 234 (4·40), 265sh (4·02), and 388 nm (3·88) (Found: C, 73·2; H, 5·2. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2%), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·5.

2-Amino-3′,4′-dimethoxybenzophenone (II; R^1 = H, R^2 = Me, R^3 = OMe).—This amine, prepared by the method of Ullmann and Denzler,[18] had b.p. 196 at 0·05 mmHg, m.p. (methanol–benzene) 76°, $\nu_{max.}$ (KBr) 3440, 3330 (NH_2), and 1620 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 208·5 (log ε 4·39), 234 (4·48), 273sh (3·93), 306 (3·82), and 377 nm (3·88), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·48 (and in ethyl acetate 0·9). In an improved preparation condensation of 2-methyl-3,1-benzoxazin-4-one with 3,4-dimethoxyphenylmagnesium bromide gave the crude acetamide (II; R^1 = Ac, R^2 = Me, R^3 = OMe), which was hydrolysed to the amine.

2-Methoxy- and 2-Hydroxy-9-acridone.—Condensation of *o*-chlorobenzoic acid and *p*-anisidine followed by dehydrative cyclisation [27] gave 2-methoxy-9-acridone, m.p. 270—280° (lit.,[27] 282—284°), $\lambda_{max.}$ (EtOH) 214·5 (log ε 4·25), 250·5 (4·67), 271 (4·64), 304 (3·56), 393 (3·92), and 413 nm (3·95), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·19, and, from the alkaline washings upon acidification, 2-hydroxy-9-acridone, m.p. 275—278° (lit.,[28] 281—282°), $\lambda_{max.}$ (EtOH) 214 (log ε 4·30), 252 (4·61), 270 (3·59), 296 (3·49), 402 (3·86), and 418 nm (3·86), R_F [silica gel; in ethyl acetate–benzene (1 : 3)] 0·06.

4-Methoxy- and 4-Hydroxy-9-acridone.—Under similar

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conditions *o*-anisidine and *o*-chlorobenzoic acid yielded 4-methoxy-9-acridone, m.p. 290—295° (lit.,[29] 293°), $\lambda_{max.}$ (EtOH) 219 (log ε 4·21), 255·5 (3·59), 299·5 (3·59), 312·5 (3·64), 381 (3·91), and 398 nm (3·88), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·34, and 4-hydroxy-9-acridone, m.p. 300—306° (lit.,[28] 290—300°), $\lambda_{max.}$ (EtOH) 219 (log ε 4·18), 255 (4·71), 299 (3·57), 312·5 (3·61), 382 (3·85), and 398 nm (3·83), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·33.

2,3-*Dimethoxy*-9-*acridone*.—A sample prepared by the method of Ionescu [30] had m.p. 303—305° (lit.,[30] 298°), $\lambda_{max.}$ (MeOH) 213 (log ε 4·27), 237 (4·40), 262 (4·60), 270sh (4·64), 277 (4·76), 324 (3·86), 365sh (3·76), 392 (3·99), and 400 nm (4·00), R_F (silica gel; ethyl acetate) 0·52.

3,4-*Dimethoxy*-9-*acridone*.—A sample supplied by Professor Ionescu had m.p. 225—228° (lit.,[30] 225°),[30] $\lambda_{max.}$ (MeOH) 212sh (log ε 4·25), 220 (4·32), 259 (4·78), 284 (4·24), 328 (3·72), 380 (3·72), and 400 nm (3·95), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·39.

Oxidation of 2-Aminobenzophenones.—(a) *Potassium persulphate*. The amine (or its derivative) (100 mg) dissolved in dioxan (5 ml) was added to water (100 ml), then potassium persulphate (100 mg) in water (30 ml) was slowly added with stirring to the hot solution (90°) during 1 h under nitrogen. The solution was heated on a steam-bath for a further 1 h, cooled, and extracted with ethyl acetate. The product was separated by t.l.c. to give the components as indicated in the Table. All compounds were identified by t.l.c., u.v., and m.p. comparisons. In the acidic solution oxidations, the water was replaced by 0·5M-sulphuric acid (100 ml).

(b) *Manganese triacetate*.—The amine (100 mg) was dissolved in glacial acetic acid (50 ml), moist manganese triacetate (3 g) was added, and the mixture was heated on a steam bath for 3 h. The acetic acid was removed under reduced pressure and the residue extracted with ethyl acetate (3 × 30 ml). The extract was washed with sodium hydrogen carbonate solution and water, dried, and evaporated to leave a brown residue (91 mg). T.l.c. showed several spots; those corresponding to the appropriate acridones were removed from preparative plates and the extracts were identified by comparison (m.p. and u.v. spectra) with authentic compounds. Yields are quoted in the Table. The oxidation product from 2-amino-3′-methoxybenzophenone (100 mg) was chromatographed (preparative t.l.c.) on silica gel [benzene–ethyl acetate (3 : 1)]. Bands at R_F 0·19, 0·34, and 0·6 corresponded to 2-methoxy- and 4-methoxy-9-acridone and starting material. 2-Methoxy-9-acridone (4·0 mg) had m.p. and mixed m.p. 270—280°, 4-methoxy-9-acridone (3·5 mg) had m.p. and mixed m.p. 288—293°; starting material (62 mg) had m.p. and mixed m.p. 43—47°. The u.v. spectra of the products were identical with those of authentic samples.

Similar procedures were used for the product separations and identifications from the other oxidations.

2,3,4-*Trimethoxy*-2′-*nitrobenzophenone*. — 1,2,3-Trimethoxybenzene (7 g) dissolved in dry ether (100 ml) was added to *N*-chloro-2-nitrobenzanilide [from 2-nitrobenzanilide (7 g) and phosphorus pentachloride (7 g) in dry petroleum (100 ml; b.p. 60—80°)] at 0—10°. A solution of anhydrous aluminium chloride (6·5 g) in dry ether (50 ml) was slowly added and the mixture was stirred at 0—10° for 1 h and at room temperature for 4 h. The solvent was removed under reduced pressure and ice was added, followed by 50% hydrochloric acid (50 ml). The mixture was then heated on a steam-bath for 3 h. On cooling a solid formed, which was filtered off and recrystallised from methanol to give 2,3,4-*trimethoxy*-2′-*nitrobenzophenone* (5·2 g), m.p. 84°, $\lambda_{max.}$ (EtOH) 216 (log ε 4·47), 229sh (4·35), and 281 nm (4·31), $\nu_{max.}$ (KBr) 1658 cm^{-1} (C=O) (Found: C, 60·4; H, 5·0. $C_{16}H_{15}NO_6$ requires C, 60·7; H, 4·8%).

Benzophenone	Oxidant	Temp. (°C)	Product 9-acridone (%)
2-NH_2-3′-OMe	$K_2S_2O_8$(H$^+$)	90	2-OMe(4) + 4-OMe (3·5)
2-NH_2-3′-OMe	$K_2S_2O_8$(H$^+$)	90	2-OH(4) + 4-OH (4)
2-NH_2-3′-OMe	$K_2S_2O_8$(neut.)	90	2-OH (1)
2-NH_2-3′-OH	$K_2S_2O_8$(neut.)	70	2-OH (2)
2-AcNH-3′-OMe	$K_2S_2O_8$(neut.)	90	2-OMe (1)
2-NH_2-3′,4′-$(OMe)_2$	$K_2S_2O_8$(H$^+$)	70	2,4-$(OMe)_2$(7) + 3,4-$(OMe)_2$ (1)
2-NH_2-3′-OH	$Mn(OAc)_3,2H_2O$	90	2-OH(8) + 4-OH(6)
2-NH_2-3′-OMe	$Mn(OAc)_3,2H_2O$	90	2-OMe(8) + 4-OMe(5)
2-NH_2-3′,4′-$(OMe)_2$	$Mn(OAc)_3,2H_2O$	90	2,3-$(OMe)_2$(6) + 3,4-$(OMe)_2$ (3)

2′-*Amino*-2,3,4-*trimethoxybenzophenone*.—The nitrobenzophenone (600 mg) in ethanol (90 ml) containing water (6 ml), ammonium chloride (600 mg), and zinc moss (2 g) was refluxed for 3 h. The mixture was filtered and the filtrate evaporated to dryness; the residue was extracted with ethyl acetate. The extract was washed with water, dried, filtered, and evaporated to dryness to give a solid which crystallised from methanol to give the *amine* (430 mg), m.p. 126°, $\lambda_{max.}$ (EtOH) 213 (log ε 4·36), 232 (4·34), 264 (3·83), and 384 nm (3·77), $\nu_{max.}$ (KBr) 3490, 3330 (NH_2), and 1625 cm^{-1} (C=O) (Found: C, 66·9; H, 6·0. $C_{16}H_{18}NO_4$ requires C, 67·0; H, 6·0%).

The *acetyl* derivative, prepared by treatment with acetic anhydride–pyridine, had m.p. 108°, $\lambda_{max.}$ (EtOH) 213 (log ε 4·48), 236 (4·33), 265sh (4·01), 271 (4·02), and 327 nm (3·82), $\nu_{max.}$ (KBr) 3230 (NH), 1705 (Ac), and 1643 cm^{-1} (C=O) (Found: C, 65·5; H, 5·6. $C_{18}H_{19}NO_5$ requires C, 65·6; H, 5·8%), R_F [silica gel; benzene–ethyl acetate (3 : 1)] 0·38.

Oxidation of 2′-*Amino*-2,3,4-*trimethoxybenzophenone*.—The amine (300 mg) in acetic acid (30 ml) was heated on a steam-bath with manganese triacetate (2 g) for 4 h and the solvent was then removed under reduced pressure. Extraction of the residue with ethyl acetate and evaporation of the extract yielded an oil, which separated into three main components on preparative layer chromatography [silica gel; benzene–ethyl acetate (3 : 1)] to give starting material (200 mg), R_F 0·53, identified by m.p. and mixed m.p. (126—128°) and u.v. spectrum, its acetyl derivative (52 mg), identified by m.p. and mixed m.p. (106—108°) and u.v. spectrum, R_F 0·38, and 3,4-dimethoxy-9-acridone, m.p. and mixed m.p. 220—227°, u.v. spectrum identical with that of an authentic sample, R_F 0·39.

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