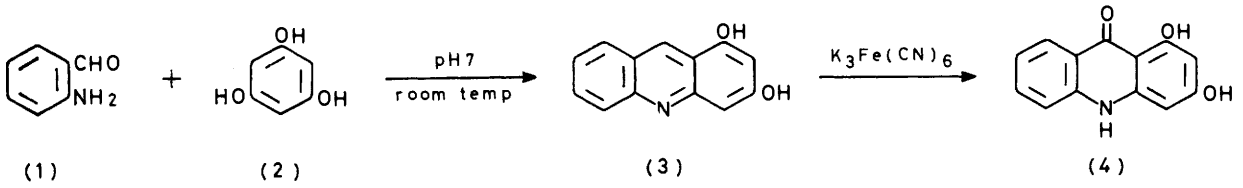
Biomimetic Synthesis of Acridone Alkaloids [1,2]

By **Joyce H. Adams, Padma Gupta, M. Shafiq Khan,** and **John R. Lewis,*** Chemistry Department, University of Aberdeen, Scotland AB9 2UE

Cyclisations of 2'-amino-, 2'-acetylamino-, or 2'-methylamino-2-methoxybenzophenones occur in the presence of sodium hydride in dimethyl sulphoxide to give acridone alkaloids. This cyclisation has relevance to the biosynthesis of these alkaloids. An alternative cyclisation can occur, giving 4-arylquinolines or 4-arylquinolones.

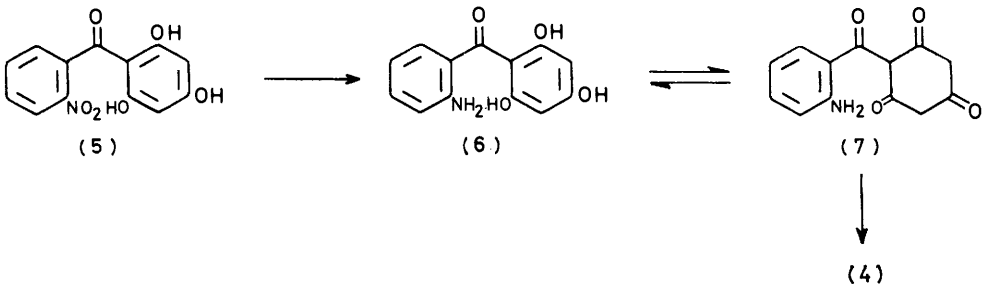
THE acridone alkaloids comprise *ca.* 35 members produced only by the Rutaceae family of higher plants. Their mode of biosynthesis was postulated by Sir Robert Robinson,[3] who suggested that anthranilic acid condensed with acetic acid to give the tricyclic acridone system. This postulate may have been prompted by the early observation [4] that 2-aminobenzaldehyde (1) condensed easily with phloroglucinol (2) to give 1,3-dihydroxyacridine (3). Compound (3) can be converted through oxidation [5] into 1,3-dihydroxy-9-acridone (4) (Scheme 1).



(1) (2) (3) (4)

SCHEME 1

In modern terms this sequence could involve the reaction of an activated anthranilic acid (as its coenzyme) with a triketide to produce an aminobenzophenone which on cyclisation produces a dihydroxy-9-acridone. In support of this hypothesis, both anthranilic and *N*-methylanthranilic acid have been shown experimentally to be precursors of the acridone alkaloids in *Acronychia baueri* [6] and in *Glycosmis arborea*,[7] and the cyclisation step has been achieved quantitatively by one or more of the hydroxy-functions in (5) prevented cyclisation concomitant with reduction. Cyclisation of 2-methoxyamino- or 2-methoxyacetamido-benzophenones can be achieved at room temperature through the use of sodium hydride in dimethyl sulphoxide whereby 2'-acetamido-2-methoxybenzophenone and related compounds yield 9-acridones.[9] Application of this type of cyclisation has now enabled the synthesis of a number of acridone alkaloids.



(5) (6) (7)

Thamnosma montana [10,11] contains both acridone (8; $R^1 = R^2 = R^3 = H$) and its 10-methyl derivative (8; $R^1 = R^2 = H$, $R^3 = Me$); the synthesis of acridone from 2'-amino-2-methoxybenzophenone proceeds in 47% yield.[9] For *N*-methyl-9-acridone (8; $R^1 = R^2 = H$,

[1] Presented at the Chemical Society Perkin Division Meeting in Stirling, December 17th, 1974.

[2] Preliminary communication, M. S. Khan, J. R. Lewis, and R. A. Watt, *Chem. and Ind.*, 1975, 744.

[3] Sir Robert Robinson, 'Structural Relations of Natural Products,' Clarenden Press, Oxford, 1955.

[4] J. Eliasberg and P. Friedlander, *Ber.*, 1892, **25**, 1752.

[5] G. K. Hughes and E. Ritchie, *Austral. J. Sci. Res., Ser. A*, 1951, **4**, 423.

[6] R. H. Prager and H. M. Threadgold, *Austral. J. Chem.*, 1969, **22**, 2627.

[7] D. Gröger and S. Johne, *Z. Naturforsch.*, 1968, **23b**, 1032.

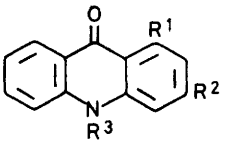
[8] I. H. Bowen, P. Gupta, and J. R. Lewis, *Chem. Comm.*, 1970, 1625.

[9] J. H. Adams, P. Gupta, M. S. Khan, J. R. Lewis, and R. A. Watt, *J.C.S. Perkin I*, 1976, 2089.

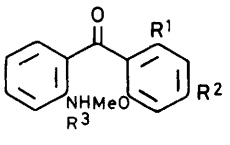
[10] D. L. Dreyer, *Tetrahedron*, 1966, **22**, 2923.

[11] P. T. O. Chang, G. A. Cordell, G. H. Aynilian, H. H. S. Fong, and N. R. Farnsworth, *Lloydia*, 1976, **38**, 134.

R^3 = Me) the benzophenone (9; $R^1 = R^2 = H$, R^3 = Me) (prepared by methylation of 2′-acetamido-2-methoxybenzophenone [9] followed by hydrolysis) upon



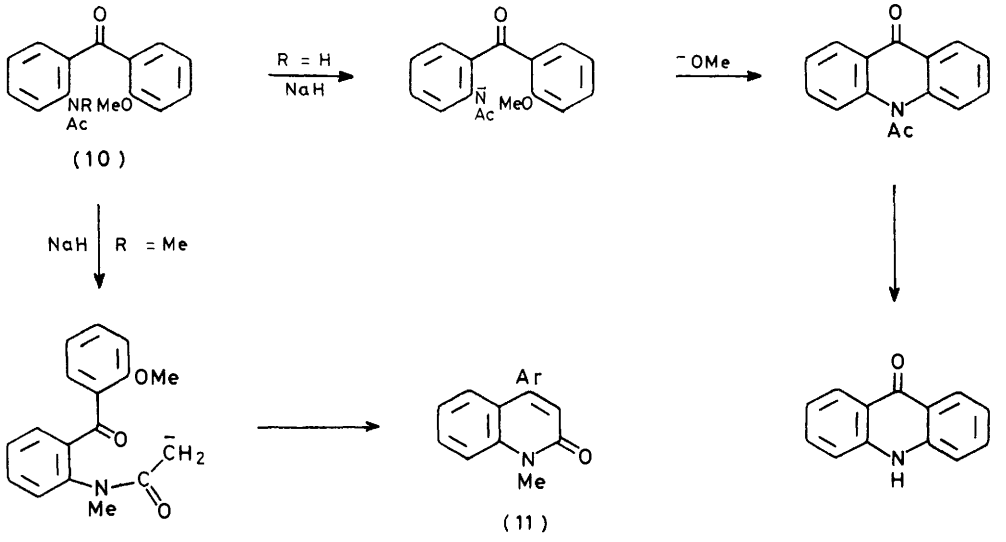
(8)



(9)

treatment with sodium hydride in dimethyl sulphoxide at 20 °C gave a quantitative yield of the alkaloid. 2′-Acetamido-2-methoxybenzophenone (9; $R^1 = R^2 =$ H, R^3 = Ac) gave 9-acridone (8; $R^1 = R^2 = R^3 = H$) upon treatment with sodium hydride in dimethyl sulphoxide presumably *via* the 10-acetyl derivative (8; $R^1 = R^2 = H$, R^3 = Ac) (10-acetylacridone is rapidly converted by sodium hydride in dimethyl sulphoxide into acridone). 2′-(*N*-Methylacetamido)-2-methoxybenzophenone (10; R = Me) with sodium hydride in dimethyl sulphoxide gave the 4-aryl-1-methylquinoline (11; Ar = 2-MeO·C_6H_4) in high yield. The non-availability of a hydrogen atom on nitrogen precludes formation of the acridone, thus allowing cyclisation to proceed *via* an intramolecular aldol-type reaction (Scheme 2). The alternative mode of cyclisation can also take place with 2′-acetamidobenzophenones, provided that the 2-methoxy-group is absent [*e.g.* (12)] to give 4-arylquinolines (13). A similar base-catalysed cyclisation of 2-acetamidobenzophenone with sodium hydroxide in dilute ethanol was reported [12] to give 2-hydroxy-4-phenylquinoline.[12]

1-Hydroxy-10-methyl-9-acridone (8; R^1 = OH, R^2 = H, R^3 = Me) occurs in *Ruta graveolens* [13] and *Boenninghausenica albiflora*,[14] and has been isolated from the callus cultures obtained from the meristematic cells of *Ruta graveolens*; [15] its synthesis was achieved through cyclisation of 2′-methylamino-2,6-dimethoxybenzophenone (9; R^1 = OMe, R^2 = H, R^3 = Me) followed by demethylation. This benzophenone was prepared by condensation of the lithio-derivative of 1,3-dimethoxybenzene [16] with 2-methyl-3,1-benzoxazin-4-one [to yield the benzophenone (9; R^1 = OMe, R^2 = H, R^3 = Ac)] followed by methylation and hydrolysis. Cyclisation of 2,4,6-trimethoxy-2′-methylaminobenzophenone (9; $R^1 = R^2$ = OMe, R^3 = Me) also occurred rapidly and quantitatively to give the alkaloid (8; $R^1 = R^2$ = OMe, R^3 = Me), previously isolated from *Acronychia baueri* [17] and from *Vepris amphody*.[18] Its demethylated counterpart, 1-hydroxy-3-methoxy-10-methyl-9-acridone (8; R^1 = OH, R^2 = OMe, R^3 = Me) has recently been



(10)

(11)

SCHEME 2

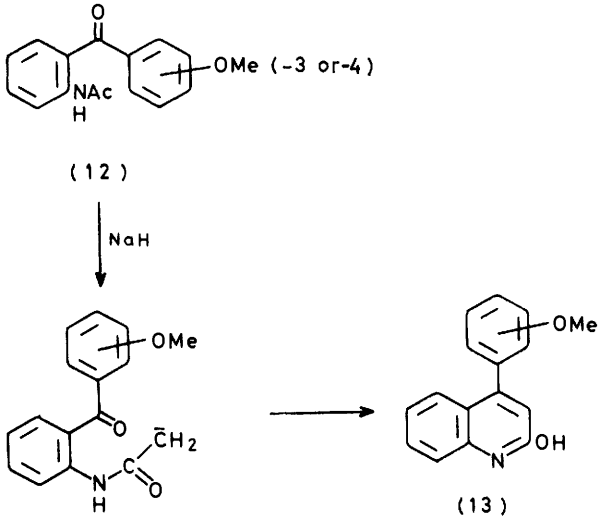
isolated from *Ruta graveolens*; [19] its presence in tissue cultures of *R. graveolens* has been reported earlier.[16]

From the relative ease of cyclisation of 2′-methylamino-2-methoxybenzophenones it can be inferred that the biosynthesis of acridone alkaloids proceeds through condensation of anthranilic or *N*-methylanthranilic acid with a triketide to give the appropriate 2-aminobenzophenone, which subsequently cyclises by an intramolecular nucleophilic process. A similar intramolecular nucleophilic displacement but involving oxygen has

[12] E. Camps, *Arch. Pharmazie*, 1904, **237**, 683.
[13] J. Reisch, K. Szendrei, I. Novak, E. Minker, and Zs. Rózsa, *Experientia*, 1971, **27**, 1005.
[14] Zs. Rózsa, K. Szendrei, I. Novak, J. Reisch, and E. Minker, *Pharmazie*, 1975, **30**, 753.
[15] W. Scharlemann, *Z. Naturforschung*, 1972, **27**, 806.
[16] R. Levine and J. R. Sommers, *J. Org. Chem.*, 1974, **39**, 3559.
[17] J. A. Lamberton and J. R. Price, *Austral. J. Chem.*, 1953, **6**, 66.
[18] Ch. Kan-Fan, B. C. Das, P. Boiteau, and P. Potier, *Phytochemistry*, 1970, **9**, 1283.
[19] J. Reisch, Zs. Rózsa, K. Szandrei, I. Novak, and E. Minker, *Phytochemistry*, 1977, **16**, 151.

been invoked to account for the biogenesis of some fungal xanthones.[20]

Recently the isolation of the benzophenone (9; R^1 = R^2 = OMe, R^3 = Me) from *Teclea grandifolia*,[21] *Diphasia*



klaineana, and *Teclea verdoorniana* [22] has been reported; the presence of 1,3-dimethoxy-10-methyl-9-acridone (8; R^1 = R^2 = OMe, R^3 = Me) in the last-named plant [23] further supports the postulated relationship between 2-aminobenzophenones and 9-acridones.

EXPERIMENTAL

I.r. spectra were measured for KBr discs and n.m.r. spectra for solutions in $CDCl_3$ unless stated otherwise. Mass spectra were measured with an A.E.I. MS30 spectrometer.

10-Acetyl-9-acridone (8; R^1 = R^2 = H, R^3 = Ac).—Acridone (1 g) was dissolved in tetrahydrofuran (THF) (50 ml), NaH (60%; 185 mg) was added, and the mixture was stirred at room temperature for 1 h. Acetyl chloride (2 ml) was added and stirring continued for 2 h. Three further successive additions of NaH followed by acetyl chloride were made over 36 h. The mixture was poured into iced water and filtered to give a solid (782 mg), which crystallised from acetone giving *N-acetylacridone*, m.p. 77—80°, $\lambda_{max.}$ (MeOH) 215 (log ε 3.02), 251 (3.38), 260sh (3.21), 360 (2.63), and 376 nm (2.59), $\nu_{max.}$ 1 765, 1 725, 1 640, and 1 630 cm^{-1}, τ 1.70 (2 H, dd, *J* 2 and 8 Hz, H-1 and -8), 2.15—2.65 (6 H, complex, ArH), and 7.67 (3 H, s, COMe) (Found: C, 75.9; H, 5.0. $C_{15}H_{11}NO_2$ requires C, 75.9; H, 4.7), *m/e* 237 (3%), 196 (3), 195 (100), 157 (3), and 149 (3).

Hydrolysis of 10-Acetyl-9-acridone.—*N*-Acetylacridone (40 mg) was dissolved in Me_2SO (0.5 ml) and NaH (60%; 8 mg) was added. After 1 min a trace of starting material was still present; after 2 min only acridone was observed. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate to give, after the usual work up, 9-acridone (20 mg), m.p. and mixed m.p. 300—305° (from ethyl acetate). A repeat reaction showed almost complete conversion into acridone over 1 min.

2-Methoxy-2-N-methylacetamidobenzophenone (10; R = Me).—2′-Acetamido-2-methoxybenzophenone [8] (0.5 g) dissolved in Me_2SO (30 ml) was cooled to 14 °C, and methyl iodide (5 ml) was added, followed by NaH (60%; 112 mg, 1.5 mol. equiv.). The mixture was kept at 14 °C for 14 h then poured into water and extracted with ethyl acetate. The product was isolated in the usual way to give a yellow oil (0.579 g), which on trituration with ether and crystallisation from ether gave the *N-methyl derivative* as needles, m.p. 122—123°, $\lambda_{max.}$ (MeOH) 223 (log ε 3.27), 256sh (3.03), and 310 nm (2.52), $\nu_{max.}$ 1 660 cm^{-1}, τ 2.40—3.2 (8 H, complex, ArH), 6.34 (3 H, s, OMe), 7.00 (3 H, s, NMe), and 8.18 (3 H, s, COMe) (Found: C, 71.8; H, 6.0. $C_{17}H_{17}NO_3$ requires C, 72.0; H, 6.0), *m/e* 283 (3%), 241 (25), 240 (45), 226 (16), 224 (32), 217 (10), 210 (14), and 148 (100).

Cyclisation of the Benzophenone (10; R = Me).—The benzophenone (10; R = Me) (100 mg) was dissolved in Me_2SO (14 ml) and NaH (60%; 85 mg) was added. The mixture was stirred for 88 h at room temperature and worked up to give the product (91 mg). Crystallisation from ether gave *4-(2-methoxyphenyl)-2-quinolone*, m.p. 173—174°, $\lambda_{max.}$ (MeOH) 212sh (log ε 3.91), 233 (4.19), 245sh (3.87), 279 (3.73), 318sh (3.56), 333 (3.61), and 345sh nm (3.48), $\nu_{max.}$ 3 425 (NH) and 1 630 cm^{-1} (CO), τ 2.3—7.2 (8 H, complex, ArH), 7.32 (1 H, s, C=CH), 6.25 (3 H, s, NMe or OMe), and 6.29 (3 H, s, NMe or OMe) (Found: C, 77.0; H, 5.6. $C_{17}H_{15}NO_2$ requires C, 77.1; H, 5.6%), *m/e* 265 (100%), 250 (4), 248 (6), 236 (7), 234 (2), 223 (25), 222 (11), 207 (4), and 165 (4). Treatment of the benzophenone with aqueous methanolic sodium hydroxide under reflux for 3 h also gave this quinolone.

2-Methoxy-2′-methylaminobenzophenone (9; R^1 = R^2 = H, R^3 = Me).—The benzophenone (10; R = Me) (500 mg) was dissolved in ethanol (20 ml) containing 20% hydrochloric acid (80 ml) and the mixture was refluxed for 8 h. More hydrochloric acid (conc.; 100 ml) was added and the reflux was continued for an additional 8 h. The mixture was cooled, neutralised with sodium hydroxide solution, and extracted with ether. Work-up gave a yellow oil (472 mg), which crystallised from ether giving the *methylaminobenzophenone* (9; R^1 = R^2 = H, R^3 = Me) as a yellow solid, m.p. 94°, $\lambda_{max.}$ (MeOH) 222 (log ε 3.21), 265 (2.16), and 395 nm (2.12), $\nu_{max.}$ 3 330 (NH) and 1 625 cm^{-1} (CO), τ 1.10br (1 H, s, NH), 2.5—3.4 (8 H, complex, ArH), 6.28 (3 H, s, OMe), and 7.2 (3 H, d, *J* 6 Hz, NMe) (Found: C, 74.7; H, 6.2. $C_{15}H_{15}NO_2$ requires C, 74.6; H, 6.2%), *m/e* 241 (100%), 240 (14), 226 (14), 224 (18), 210 (13), and 195 (13).

Cyclisation of 2-Methoxy-2′-methylaminobenzophenone (9; R^1 = R^2 = H, R^3 = Me).—The amine (100 mg) was dissolved in Me_2SO (10 ml), NaH (60%; 100 mg) was added, and the mixture was left at room temperature for 1 h (t.l.c. indicated complete disappearance of starting material). The mixture was poured into water and extracted with ethyl acetate; work-up gave a yellow solid (80 mg) which crystallised from ethanol as 10-methyl-9-acridone (64 mg), m.p. and mixed m.p. 204—205 and 199—203°, respectively, identical (spectral properties) with authentic *N*-methylacridone.[11]

2′-Acetamido-2,6-dimethoxybenzophenone (9; R^2 = H, R^1 = OMe, R^3 = Ac).—1,3-Dimethoxybenzene (8.5 g) was

[20] J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074.
[21] A. C. Casey and A. Malhotra, *Tetrahedron Letters*, 1975, 401.
[22] P. G. Waterman, *Phytochemistry*, 1975, **14**, 2092.
[23] P. G. Waterman, personal communication.

dissolved in anhydrous ether (380 ml) and n-butyl-lithium (4.0 g, 1 mol. equiv.) in ether (50 ml) was added. The mixture was stirred and refluxed for 20 h, 2-methyl-3,1-benzoxazin-4-one [9] (10 g) in anhydrous ether (50 ml) was added, and the mixture was refluxed for a further 3 h. Dilute hydrochloric acid was added to the cooled mixture and the product isolated in the usual way as a solid which crystallised from ether as the *acetamide* (2.8 g), m.p. 123°, $\lambda_{max.}$ (MeOH) 228 (log ε 4.38), 238 (4.38), 263 (4.13), 269 (4.14), and 330 nm (3.76), $\nu_{max.}$ 1 648 (ArCO) and 1 695 cm^{-1} (NHAc), τ −1.80br (1 H, s, NH), 1.24 (1 H, d, *J* 8 Hz, 3'-H), 2.3—3.2 (4 H, complex, ArH), 3.38 (2 H, d, 3- and 5-H), 6.28 (6 H, s, OMe), and 7.72 (3 H, s, NHAc) (Found: C, 68.1; H, 5.6. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7%), *m/e* 299 (100%), 257 (11), 240 (8), 239 (6), 226 (56), 211 (7), 165 (32), 138 (32), 134 (45), 120 (16), and 119 (28).

2,6-*Dimethoxy*-2'-N-*methylacetamidobenzophenone*.— The foregoing acetamide (1 g) dissolved in Me_2SO (30 ml) was treated with methyl iodide (10 ml) at 14 °C followed by NaH (224 mg). The mixture was stirred for 16 h then poured into water and extracted with ethyl acetate (4 × 50 ml). Work-up and crystallisation from ether gave the N-*methylacetamido-derivative* (703 mg), $\lambda_{max.}$ (MeOH) 219 (log ε 4.34), 227sh (4.18), 245sh (4.13), and 285sh nm (3.60), $\nu_{max.}$ 1 660 cm^{-1} (ArCO), τ 2.2—2.9 (5 H, complex, ArH), 3.44 (2 H, d, *J* 8 Hz, 3- and 5-H), 6.34 (6 H, s, OMe), 7.12 (3 H, s, NMe), and 2.24 (3 H, s, NHAc) (Found: C, 68.9; H, 6.2. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1%), *m/e* 313 (1%), 270 (2), 273 (2), 260 (2), 255 (2), 165 (2), 148 (100), and 133 (4).

2,6-*Dimethoxy*-2'-*methylaminobenzophenone* (9; R^1 = OMe, R^2 = H, R^3 = Me).—The foregoing *N*-methylacetamide (40 mg) was dissolved in methanol (15 ml) containing concentrated hydrochloric acid (50 ml) and the mixture was heated on a steam-bath for 12 h. It was then cooled, carefully neutralised ($NaHCO_3$), and extracted with ether (4 × 200 ml). The product was isolated as a yellow oil (0.3 g) which solidified on trituration with ether. Crystallisation from methanol gave the *methylaminobenzophenone* (232 mg), m.p. 214—215°, $\lambda_{max.}$ (MeOH) 207 (log ε 4.46), 222 (4.31), 235sh (4.06), 261sh (3.80), 266 (3.79), and 391 nm (3.75), $\nu_{max.}$ 3 318 (NH) and 1 615 cm^{-1} (CO), τ 1.04br (1 H, s, NH), 2.50—3.70 (7 H, complex, ArH), 6.30 (6 H, s, 2- and 6-OMe), and 7.02 (3 H, s, NMe) (Found: C, 70.9; H, 6.3. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3%), *m/e* 371 (100%), 254 (8), 240 (56), 225 (22), 165 (10), 139 (6), 134 (9), and 105 (25).

Cyclisation of the Benzophenone (9; R^1 = OMe, R^2 = H, R^3 = Me) *to* 1-*Methoxy*-10-*methyl*-9-*acridone* (8; R^1 = OMe, R^2 = H, R^3 = Me).—The benzophenone (100 mg) dissolved in Me_2SO (10 ml) was stirred at room temperature with NaH (60% dispersion washed with benzene before addition; 88 mg) for 6.5 h; all the benzophenone had then disappeared. Isolation gave 1-methoxy-10-methyl-9-acridone, m.p. 160—162° (lit.,[24] m.p. 164°) (from ethyl acetate), $\lambda_{max.}$ (MeOH) 205 (log ε 4.04), 218 (4.09), 258 (4.52), 299sh (3.65), 306 (3.62), and 398 nm (3.71), $\nu_{max.}$ 1 718 cm^{-1} (CO), τ 1.50 (1 H, dd, *J* 2 and 8 Hz, H-5), 2.2—3.5 (6 H, complex, ArH), 6.0 (3 H, s, OMe), and 6.22 (3 H, s, NMe), *m/e* 239 (100%), 238 (25), 222 (28), 210 (63), 209 (14), 193 (16), 181 (8), 167 (5), and 166 (10).

1-*Hydroxy*-10-*methyl*-9-*acridone* (8; R^1 = OH, R^2 = H, R^3 = Me).—The foregoing methoxyacridone (60 mg) was refluxed in benzene (20 ml) with anhydrous $AlCl_3$ (60 mg) for 0.5 h. After careful addition of ice and dilute hydrochloric acid the organic layer was separated, washed with water, dried, and evaporated to give a solid (56 mg), which crystallised from ether (25 mg) to yield the alkaloid (8; R^1 = OH, R^2 = H, R^3 = Me), m.p. 190—192° (lit.,[15,24] 192—194°), $\lambda_{max.}$ (MeOH) 206 (log ε 3.34), 216 (3.29), 243 (3.44), 257sh (3.65), 262 (3.66), 302 (2.85), 313 (2.89), and 404 nm (2.83), $\nu_{max.}$ (KBr) 3 440 (OH) and 1 625 cm^{-1} (bonded CO), τ −4.36 (1 H, s, OH), 1.55 (1 H, dd, *J* 2 and 7 Hz, H-5), 2.10—3.50 (6 H, complex, ArH), and 6.18 (3 H, s, NMe).

2,4,6-*Trimethoxy*-2'-*methylaminobenzophenone* (9; R^1 = R^2 = OMe, R^3 = Me).—2'-Amino-2,4,6-trimethoxybenzophenone [9] (1 g) dissolved in acetone (50 ml) was treated with MeI (5 g), and anhydrous K_2CO_3 (8 g) at room temperature for 12 h. The mixture was then heated under reflux for 12 h, and filtered, and the solid was washed with fresh acetone. The extracts were filtered and evaporated to dryness to give a yellow solid (0.8 g) which consisted of two components. Chromatography on silica gel [elution with benzene–ethyl acetate (95 : 5)] gave 2,4,6-*trimethoxy*-2'-*methylaminobenzophenone* (9; R^1 = R^2 = OMe, R^3 = Me) (400 mg), m.p. 195°, $\lambda_{max.}$ (EtOH) 216 (log ε 3.51), 233 (3.53), 262sh (3.02), 270 (3.03), and 398 nm (3.03), $\nu_{max.}$ 3 320 (NH) and 1 630 cm^{-1} (CO), τ 1.05br (1 H, s, NH), 2.7 (1 H, dd, *J* 2 and 7 Hz, 3'-H), 3.3 (1 H, d, *J* 9 Hz, 6'-H), 3.5—3.6 (2 H, d, *J* 8 and 6 Hz, 4'- or 5'-H), 6.5 (3 H, s, 4-OMe), 6.32 (6 H, s, 2- and 6-OMe), and 7.04 (3 H, d, *J* 4 Hz, NMe) (Found: C, 67.9; H, 6.8%; M^+, 301.1312. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4%; *M*, 301.1313), *m/e* 301 (32%), 274 (6), 260 (89), 255 (10), 240 (3), 226 (6), 212 (3), 195 (14), 168 (100), 152 (6), 139 (25), 134 (10), 133 (22), 132 (9), 106 (11), 105 (100), and 104 (45). The second component, 2'-*dimethylamino*-2,4,6-*trimethoxybenzophenone*, was eluted with benzene–ethyl acetate (9 : 1) and crystallised from methanol (yield 460 mg); m.p. 130°, $\lambda_{max.}$ (EtOH) 215 (log ε 3.54), 241 (3.53), 275sh (2.93), and 392 nm (2.79), $\nu_{max.}$ 1 650 cm^{-1} (CO), τ 2.5—3.7 (4 H, complex, ArH), 3.86 (2 H, s, 3- and 4-H), 6.16 (3 H, s, OMe), 6.32 (6 H, s, 2- and 6-OMe), and 7.07 (3 H, s, NMe) (Found: C, 68.9; H, 6.8%; M^+, 315.1472. $C_{18}H_{21}NO_4$ requires C, 68.6; H, 6.7%; *M*, 317.1470), *m/e* 315 (71%), 300 (10), 299 (100), 183 (3), 195 (2), and 147 (5).

2'-*Acetamido*-4-*methoxybenzophenone* (9; R^1 = H, R^2 = Me, R^3 = Ac).—The Grignard reagent from 1-bromo-4-methoxybenzene (11.6 g) in THF (50 ml) was treated with 2-methyl-3,1-benzoxazin-4-one [9] (10 g) in dry benzene (125 ml) at 0 °C for 1 h and at 30 °C for an additional 1 h. The solution was carefully acidified with dilute sulphuric acid, washed (aq. $NaHCO_3$ and water), dried, and evaporated to leave an oil (14.87 g). This was heated to 100 °C under reduced pressure for 1 h to remove anisole, and the residue (a solid on cooling) was crystallised from ethanol to give the *acetamidobenzophenone* (7.5 g), m.p. 122—124°, $\lambda_{max.}$ (EtOH) 213sh (log ε 3.38), 233 (3.52), and 295 nm (3.37), $\nu_{max.}$ 3 210 (NH), 1 650 (COAr), and 1 675 cm^{-1} (COMe), τ −0.5br (1 H, s, NH), 1.47 (1 H, d, *J* 8 Hz, 3'-H), 2.1—3.2 (7 H, complex, ArH), 6.13 (3 H, s, OMe), and 7.83 (3 H, s, COMe) (Found: C, 71.6; H, 5.55. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6%), *m/e* 269 (20%), 227 (32), 226 (100), 212 (14), 210 (4), 135 (9), and 134 (5).

Cyclisation of 2'-*Acetamido*-4-*methoxybenzophenone* (9; R^1 = H, R^2 = OMe, R^3 = Ac) *to* 2-*Hydroxy*-4-(4-*methoxy*-

[24] G. K. Hughes, N. K. Matheson, A. T. Norman, and E. Ritchie, *Austral. J. Sci. Res., Ser. A*, 1952, **5**, 206.

phenyl)quinoline (13).—The benzophenone (500 mg) was dissolved in Me_2SO (20 ml) and NaH (60%; 97 mg) was added. After stirring at room temperature for 32 h, isolation of the product in the usual way gave a white solid (481 mg), which crystallised from methanol as *needles* (366 mg), m.p. 243—245°, $\lambda_{max.}$ (MeOH) 213 (log ε 3.41), 231 (3.56), 280 (2.96), and 333 nm (2.80), $\nu_{max.}$ 1 678 cm^{-1} (CO), τ −2.65br (1 H, s, OH), 2.3—3.1 (8 H, complex ArH), 3.32 (1 H, s, $-CH=$), and 6.13 (3 H, s, OMe) (Found: C, 76.6; H, 5.4. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2%), *m/e* 251 (100%), 250 (50), 237 (3), 236 (8), 223 (2), 220 (2), 210 (2), 208 (16), 180 (10), and 152 (7).

2′-*Acetamido*-3-*methoxybenzophenone*.—The Grignard reagent from 1-bromo-3-methoxybenzene (116 g) in THF (50 ml) was treated with 2-methyl-3,1-benzoxazin-4-one (10 g) in dry benzene (50 ml) as above. Work-up gave an oil (12.6 g) which was distilled at 165—168° and 0.01 mmHg to give the *benzophenone* (7.3 g), m.p. 89—90° (from ethyl acetate), $\lambda_{max.}$ (MeOH) 208 (log ε 4.25), 224 (4.37), 258 (3.93), and 310 nm (3.57), $\nu_{max.}$ 3 300 (NH), 1 635 (CO), and 1 698 cm^{-1} (CONH), τ −0.74br (1 H, s. NH), 1.42 (1 H. d. *J* 8 Hz, 3′-H), 6.19 (3 H, s, OMe), and 7.81 (3 H, s, COMe) (Found: C, 71.6; H, 5.8. $C_{16}H_{15}NO_3$ requires C, 71.9; H, 5.6%), *m/e* 269 (35%), 227 (75), 226 (100), 197 (7), 196 (56), 134 (18), and 120 (45).

Cyclisation of 2′-*Acetamido*-3-*methoxybenzophenone to* 2-*Hydroxy*-4-(3-*methoxyphenyl)quinoline* (13).—The benzophenone (500 mg) was dissolved in Me_2SO (20 ml) and NaH (60%; 97 mg) was added at room temperature. After 18 h more NaH (48 mg) was added and the mixture set aside for a further 3 h. Starting material had then completely disappeared. Work-up gave a yellow solid (520 mg) which crystallised from methanol to give the *quinoline* as a white solid (193 mg), m.p. 185—187°, $\lambda_{max.}$ (MeOH) 214sh (log ε 3.53), 229 (3.65), 281 (2.97), and 325 nm (2.86), $\nu_{max.}$ 1 655 cm^{-1} (CO), τ −2.90br (1 H, s, OH), 2.2—3.0 (8 H, complex, ArH), 3.25 (1 H, s, $-CH=$), and 6.15 (3 H, s, OMe) (Found: C, 76.4; H, 5.4. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2%), *m/e* 251 (100%), 250 (8), 220 (20), 180 (3), 149 (6), and 135 (5).

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