Synthesis of 5*H*-Furo[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-ones and 8*H*-Pyrano[3',2':5,6]benzofuro[3,2-*c*]pyridin-8-ones (Pyridopsoralens)

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5*H*-Furo[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-ones(pyrido[3,4-*c*]psoralens) (3) have been obtained by the von Pechmann reaction starting from 6-hydroxy-2,3-dihydrobenzofuran acetates plus 1-benzyl-3-ethoxycarbonylpiperidin-4-one and subsequent dehydrogenation. The synthesis of their 8*H*-pyrano[3',2':5,6]benzofuro[3,2-*c*]pyridin-8-one isomers (14) and (17) was achieved by two ways using: (i) ring closure of 4-formyl-3-hydroxy-2-methylbenzofuro[3,2-*c*]pyridine, and (ii) cyclisation of piperidinone *O*-(4,7-dimethylcoumarin-7-yl)oxime derivatives and aromatization.

Psoralens have been extensively studied as photosensitizing agents.[1-4] Their biological properties have been attributed to their ability to promote DNA interstrand cross-links under UVA irradiation which result from two cyclo-C-4-additions between 3,4 and 4',5' psoralen double bonds and the 5,6 double bond of two pyrimidine bases (biadduct derivatives).[5,6]

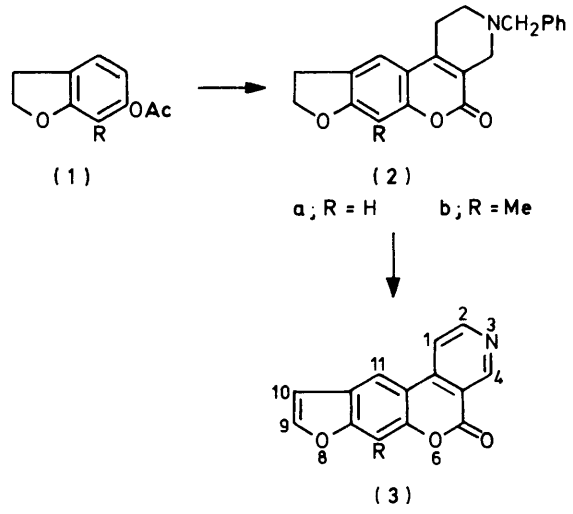
However, in the photoreaction with biological substrates the so-called bifunctional psoralens (which have two photoreactive double bonds), give rise to monoadducts [7] which correspond to the first step of the reaction. Consequently, some of the photobiological properties of furocoumarins may result from the monoadducts.

This assumption has been exemplified by various studies on 3-ethoxycarbonylpsoralen, a compound which photoreacts with DNA only by its 4',5' double bond.[8,9] It exhibits low mutagenicity, lethal effects on yeast, absence of carcinogenicity, and therapeutic properties in psoriasis.[9] Moreover, 4,5'-dimethylangelicin, another 'monofunctional derivative' with angular structure which does not allow interstrand DNA cross-links for steric reasons, has also shown interesting biological properties.[10] It cannot be excluded, however, that under UVA irradiation these two furocoumarins bind to biological substrates other than DNA by their second double bond.

This point being very important for an interpretation of various photobiological properties of furocoumarins, it seemed of interest to perform further studies with new monofunctional psoralen derivatives whose structures ruled out the possibility of their being involved in a double photoaddition reaction.

For this purpose, pyridopsoralens having a fused pyridine ring (*a priori* capable of increasing the DNA intercalating binding ability of the psoralen) on the 3,4 or 4',5' sites should be compounds of choice. As part of a program developed in this Institute concerning photobiological properties of new monofunctional psoralen derivatives, we describe here the synthesis of 5*H*-furo[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-ones and 8*H*-pyrano[3',2':5,6]benzofuro[3,2-*c*]pyridin-8-ones.

5H-*Furo*[3',2':6,7][1]*benzopyrano*[3,4-*c*]*pyridin-5-ones* (3).—5*H*-3-Benzyl-1,2,3,4,9,10-hexahydrofuro[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-ones (2) were obtained by condensation of 1-benzyl-3-ethoxycarbonylpiperidin-4-one with 6-hydroxycoumaran acetates (1a and b) according to the von Pechmann reaction. Aromatization with palladium on charcoal in boiling diphenyl ether then afforded the expected 5*H*-furo[3',2':6,7]-[1]benzopyrano[3,4-*c*]pyridin-5-ones (3a and b).

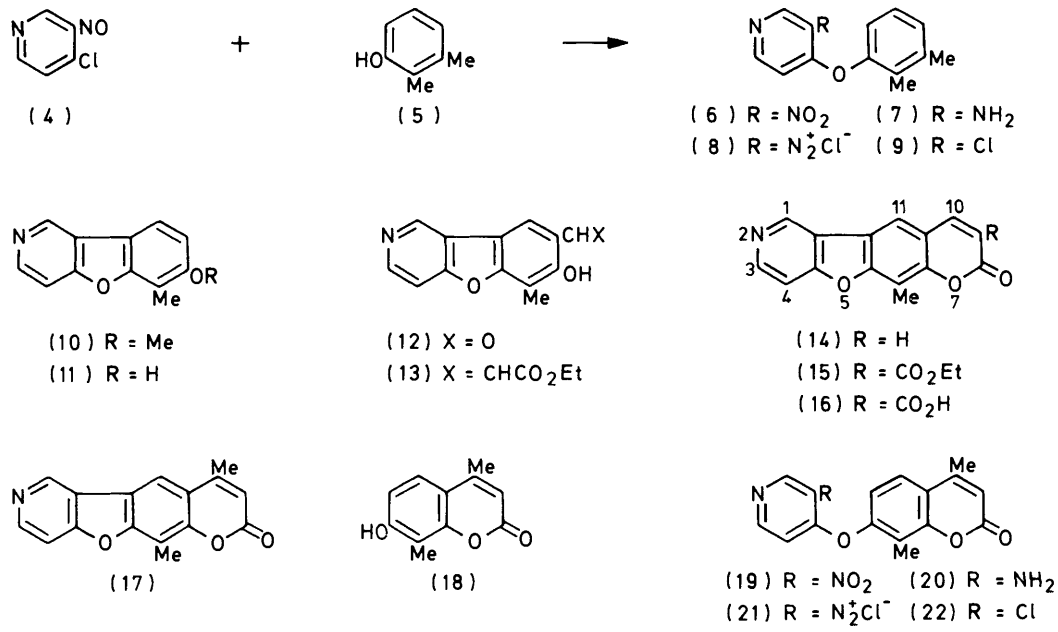


Scheme 1

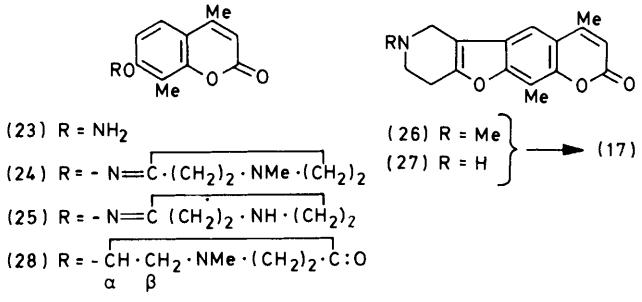
8H-*Pyrano*[3',2':5,6]*benzofuro*[3,2-c]*pyridin-8-ones*.—For the synthesis of 8*H*-pyrano[3',2':5,6]benzofuro[3,2-*c*]pyridin-8-one system, two ways were investigated.

(a) *By cyclisation of aryloxypyridinediazonium chlorides.* Condensation of 4-chloro-3-nitropyridine (4) with 3-methoxy-2-methylphenol (5),[11] gave the diaryl oxide (6). After reduction to the corresponding amine (7) and diazotization to (8), decomposition of this last compound occurs in the presence of cupric chloride giving 7-methoxy-6-methylbenzofuro[3,2-*c*]-pyridine (10) in low yield (17%) and traces of 3-chloro-4-(3-methoxy-2-methylphenoxy)pyridine (9). Demethylation of compound (10) in boiling pyridine hydrochloride then led to 7-hydroxy-6-methylbenzofuro[3,2-*c*]pyridine (11), which failed to condense with ethyl acetoacetate under a variety of von Pechmann reaction conditions.

Nevertheless, formylation at the 8-position took place with hexamethylenetetra-amine in boiling acetic acid and, starting from the resulting aldehyde (12), we obtained the expected pyridopsoralen (14) by two ways: (i) *via* the *trans*-acrylic ethyl ester (13) which was transformed into (14) in boiling toluene or xylene. Under these conditions, however, pyridopsoralen (14) was accompanied by a by-product (probably a dimeric compound on the basis of ^{1}H n.m.r.) and it was difficult to purify; (ii) by condensation with diethyl malonate which gave the ethoxycarbonyl-pyridopsoralen (15). After hydrolysis, the corresponding acid (16) was decarboxylated,



Scheme 2



Scheme 3

leading to 8*H*-6-methylpyrano[3′,2′:5,6]benzofuro[3,2-*c*]-pyridin-8-one (14) which was then easily purified.

In order to obtain 6,10-dimethyl8-*H*-pyrano[3′,2′:5,6]benzo-pyrano[3,2-*c*]pyridin-8-one (17), we tried to apply the first part of the reaction in Scheme 2 starting from 7-hydroxy-4,8-dimethylcoumarin (18). Thus, the nitro-compound (19) and the corresponding amine (20) were obtained in good yields but decomposition of the diazo-derivative (21) gave only 7-(3-chloro-4-pyridyloxy)-4,8-dimethylcoumarin (22) and no trace of the pyridopsoralen (17) (Scheme 2).

(b) *By a Fischer indole type reaction.* 7-Hydroxy-4,8-dimethylcoumarin (18) gave the already described *O*-aryl-hydroxylamine (23) [12] which was condensed with 1-methyl-piperidin-4-one and piperidin-4-one to the oximes (24) and (25) respectively. As expected, acidic Fischer cyclisation of these oximes provided tetrahydropyridopsoralens (26) and (27). In the *N*-methyl series, a second product was isolated and identified as being compound (28) on the basis of mass, i.r. and ^{1}H n.m.r. spectral results, elemental analysis, and analogy with a derivative resulting from the parent acetone oxime derivative.[12] Aromatization of compounds (26) and (27) in boiling decalin in the presence of palladium on charcoal then led to 6,10-dimethyl-8*H*-pyrano[3′,2′:5,6]benzofuro-[3,2-*c*]pyridin-8-one (17) (Scheme 3). This three-step synthesis to this new heterocyclic ring system appears to be more convenient than the preceding one.

Results of the biological studies performed with the new psoralen derivatives described in this paper will be reported elsewhere.[13]

Experimental

M.p.s were determined with a Reichert hot-stage microscope. I.r. spectra were obtained in KBr pellets with a Perkin-Elmer double-beam spectrometer model 21. Unless otherwise stated, n.m.r. spectra were recorded with a Varian T60 apparatus, with $SiMe_4$ as internal standard.

3-*Benzyl*-1,2,3,4,9,10-*hexahydro*-5H-*furo*[3′,2′:6,7][1]*benzo-pyrano*[3,2-c]*pyridin*-5-*one* (2a).—A solution of 6-acetoxy-2,3-dihydrobenzofuran (1a) (2.5 g, 14 mmol) and 1-benzyl-3-ethoxycarbonylpiperidin-4-one hydrochloride (4 g, 13.5 mmol) in glacial acetic acid containing 6% of hydrogen chloride (25 ml) was stirred at room temperature for 5 days. The resulting precipitate was filtered off and washed with acetic acid and with dry ether to yield (2a). HCl (3.78 g, 75%), m.p. 234—236 °C. The foregoing hydrochloride (310 mg) was suspended in water (20 ml) and aqueous sodium hydrogen carbonate was added to make the solution alkaline. After the mixture had been stirred for 30 min, the solid was filtered off, washed with water, dried, and crystallized from ethanol to give (2a) (206 mg), m.p. 163—165 °C, δ ($CDCl_3$) 2.73 (4 H, br s, 1,2-CH_2), 3.16 (2 H, t, *J* 8.5 Hz, 10-CH_2), 3.4 (2 H, br s, 4-CH_2), 3.65 (2 H, s, $C_6H_5CH_2$), 4.56 (2 H, t, *J* 8.5 Hz, 9-CH_2), 6.53 (1 H, s, 7-H), 7.16 (6 H, br s, $C_6H_5CH_2$ and 11-H) (Found: C, 75.3; H, 5.65; N, 4.15. $C_{21}H_{19}NO_3$ requires C, 75.65; H, 5.7; N, 4.2%).

3-*Benzyl*-7-*methyl*-1,2,3,4,9,10-*hexahydro*-5H-*furo*[3′,2′:6,7]-[1]*benzopyrano*[3,4-c]*pyridin*-5-*one* (2b).—This compound was synthesized as described for the preparation of (2a). 6-Acetoxy-7-methyl-2,3-dihydrobenzofuran (1b) (3.90 g, 20 mmol) gave (2b). HCl (5.85 g, 75%), m.p. 260 °C. Compound (2b) free base was crystallized twice from ethanol to give white crystals, m.p. 208 °C, δ ($CDCl_3$) 2.25 (3 H, s, 7-Me), 2.77 (4 H, br s, 1,2-CH_2), 3.23 (2 H, t, *J* 8.5 Hz, 10-CH_2), 3.5

(2 H, br s, 4-CH_2), 3.70 (2 H, s, $C_6H_5CH_2$), 4.66 (2 H, t, *J* 8.5 Hz, 9-CH_2), 7.16 (1 H, s, 11-H), and 7.35 (5 H, s, $C_6H_5CH_2$) (Found: C, 75.9; H, 6.1; N, 4.2. $C_{22}H_{21}NO_3$ requires C, 76.05; H, 6.05; N, 4.0%).

5H-*Furo*[3′,2′:5,6][1]*benzopyrano*[3,4-c]*pyridin*-5-*one* (3a).—A mixture of the hydrochloride of compound (2a) (2.33 g, 6.31 mmol), 10% palladium on charcoal (2.1 g), and diphenyl ether (30 ml) was refluxed for 5 h; it was then filtered whilst hot and the catalyst washed with hot diphenyl ether (5 ml). The solution was cooled to room temperature and hexane (500 ml) was added. The precipitate (573 mg) was collected and crystallized twice from methylene chloride–ethanol to give white needles (375 mg, 25%), m.p. 284—288 °C, δ ($CDCl_3$, 100 MHz) 6.90 (1 H, dd, *J* 2.3 Hz, *J* 0.2 Hz, 10-H), 7.54 (1 H, d, *J* 1 Hz, 7-H), 7.73 (1 H, d, *J* 2.3 Hz, 9-H), 7.95 (1 H, d, *J* 5.5 Hz, 1-H), 8.30 (1 H, d, *J* 0.2 Hz, 11-H), 8.95 (1 H, d, *J* 5.5 Hz, 2-H), 9.57 (1 H, s, 4-H); *m/z* 237 (M^+), $\lambda_{max.}$ (EtOH) 240 (ε 27 700), 280 (ε 8 400), and 325 nm (ε 6 700) (Found: C, 70.8; H, 3.0; N, 5.9. $C_{14}H_7NO_3$ requires C, 70.9; H. 2.9; N, 5.9%).

7-*Methyl*-5H-*furo*[3′,2′:5,6][1]*benzopyrano*[3,4-c]*pyridin*-5-*one* (3b).—The hydrochloride of compound (2b) (3 g, 7.83 mmol) was converted into (3b) as described above. The crude product (928 mg) was crystallized twice from methylene chloride–ethanol to give white crystals (478 mg, 25%), m.p. 272—274 °C, δ ($CDCl_3$, 100 MHz) 2.65 (3 H, s, 7-Me), 6.87 (1 H, d, *J* 2.2 Hz, 10-H), 7.74 (1 H, d, *J* 2.2 Hz, 9-H), 7.93 (1 H, d, *J* 5.5 Hz, 1-H), 8.15 (1 H, s, 11-H), 8.92 (1 H, d, *J* 5.5 Hz, 2-H), and 9.56 (1 H, s, 4-H); *m/z* 251 (M^+); $\lambda_{max.}$ (EtOH) 240 (ε 24 400), 285 (ε 10 300), 310sh (ε 8 300), and 330sh nm (ε 6 600) (Found: C, 71.6; H, 3.7, N, 5.35. $C_{15}H_9NO_3$ requires C, 71.7; H, 3.6; N, 5.55%).

4-(3-*Methoxy*-2-*methylphenoxy*)-3-*nitropyridine* (6).—3-Methoxy-2-methylphenol (5) (4.35 g, 31.5 mmol) was added to a solution of potassium hydroxide (1.76 g) in alcohol (40 ml) and the resulting dark solution was evaporated to dryness. To the residue dissolved in dimethylformamide (50 ml) a solution of 4-chloro-3-nitropyridine (4) (5 g, 31.5 mmol) in the same solvent (30 ml) was added at once at room temperature with stirring. The mixture was stirred for 1 h, then heated at 60 °C for a further hour, and finally evaporated to dryness under reduced pressure. The residue was taken up in water and extracted with chloroform; after work-up of the extract removal of solvent afforded a solid which was recrystallized from alcohol (charcoal) to give yellow crystals (5 g, 61%), m.p. 115—117 °C, δ ($CDCl_3$) 2.02 (3 H, s, 2-Me), 3.9 (2 H, s, 3′-OMe), 6.7 (1 H, d, *J* 6 Hz, 5-H), 6.86—6.89 (2 H, 2 d, *J* 8 and 9 Hz, 4′-H and 6′-H), 7.25 (1 H, t, 5′-H), 8.5 (1 H, d, 6-H), and 9.12 (1 H, s, 2-H) (Found: C, 59.8; H, 4.6; N, 10.7. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.6; N, 10.7%).

3-*Amino*-4-(3-*methoxy*-2-*methylphenoxy*)*pyridine* (7).—The nitro-compound (6) (5 g, 19.2 mmol) was dissolved in absolute ethanol (100 ml) and hydrogenated by stirring in the presence of Raney nickel (5 g) at ambient temperature and atmospheric pressure until absorption of the theoretical volume of hydrogen. The catalyst was then filtered off and the ethanol removed to give a solid residue which was recrystallized from ethanol with charcoal to afford white crystals (3.1 g, 70%), m.p. 143 °C, δ ($CDCl_3$) 2.05 (3 H, s, 2′-Me), 3.81 (3 H, s, 3′-OMe), 6.35 (1 H, d, *J* 6 Hz, 5-H), 6.6 and 6.7 (2 H, 2 d, *J* 8 and 9 Hz, 4′ and 6′-H), 7.15 (1 H, t, 5′-H), 7.85 (1 H, d, 6-H), and 8.5 (1 H, s, 2 H) (Found: C, 67.6; H, 5.9; N, 11.9. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.0; N, 12.1%).

7-*Methoxy*-6-*methylbenzofuro*[3,2-c]*pyridine* (10) *and* 3-*Chloro*-4-(3-*methoxy*-2-*methylphenoxy*)*pyridine* (9).—The preceding aminopyridine (7) (2.3 g, 10 mmol) in 0.66N-hydrochloric acid (30 ml) was stirred at 0 °C and the mixture was treated dropwise with aqueous sodium nitrite (0.7 g) below 0 °C. After a further 15 min of stirring at 0 °C, this solution was added dropwise to a well stirred mixture of acetone (50 ml), water (12.5 ml), and cupric chloride (3.3 g) heated at 35—40 °C. This temperature was maintained for a further 15 min after completion of addition; the mixture was then refluxed for 5 min and cooled. After basification by addition of sodium hydroxide, extraction with chloroform, and work-up of the extract, a solid residue was obtained; this was recrystallized twice from hexane (once with charcoal) to give (10) as white needles, m.p. 141—143 °C (360 mg, 16.9%), δ ($CDCl_3$, 100 MHz) 2.37 (3 H, s, 6-Me), 7.15 (1 H, d, *J* 8.4 Hz, 8-H), 8.0 (1 H, d, *J* 8.4 Hz, 9-H), 8.29 (1 H, d, *J* 6.5 Hz, 4-H), 8.86 (1 H, d, *J* 6.5 Hz, 3-H), and 9.65 (1 H, d, 1-H) (Found: C, 72.9; H, 5.2; N, 6.3. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.5%).

The combined hexane solutions from the recrystallization of (10) were evaporated and the residue was chromatographed over silica gel (190 g) with chloroform–ethanol (9 : 1) as eluant to give the chloropyridine (9) (50 mg, 2%), m.p. 72—75 °C (from hexane), δ ($CHCl_3$) 2.04 (3 H, s, 2′-Me), 3.86 (3 H, s, 3′-OMe), 6.46 (1 H, d, 5-H), 6.65 and 6.80 (2 H, 2 d, *J* 8 and 9 Hz, 4′-H and 6′-H), 7.25 (1 H, 2 d, 5′-H), 8.25 (1 H, d, 6-H), and 8.56 (1 H, s, 2-H) (Found: C, 62.8; H, 4.9; N, 5.8. $C_{13}H_{12}ClNO_2$ requires C, 62.5; H, 4.8; N, 5.6%).

7-*Hydroxy*-6-*methylbenzofuro*[3,2-c]*pyridine* (11).—The benzofuropyridine (10) (2.5 g) and anhydrous pyridine hydrochloride (25 g) were heated to reflux (220—230 °C) for 15 min; the mixture was then poured into ice–water. The resulting solid was filtered off and recrystallized from ethanol to give the hydrochloride of the expected compound (11) (1.8 g, 77%), m.p. > 300 °C (Found: C, 60.8; H, 4.5; N, 5.6. $C_{12}H_{10}ClNO_2$ requires C, 61.1; H, 4.2; N, 5.9%).

This hydrochloride was dissolved in boiling water (50 ml) and basified with aqueous ammonia. The resulting white solid was filtered off, air dried, and recrystallized from toluene to afford (11) (quantitative yield) as colourless needles, m.p. 260—263 °C, δ [$(CD_3)_2SO$, 100 MHz] 2.44 (3 H, s, 6-Me), 3.94 (3 H, s, 7-OMe), 6.96 (1 H, d, *J* 8.6 Hz, 8-H), 7.46 (1 H, dd, *J* 5.5 and 1 Hz, 4-H), 7.77 (1 H, d, *J* 8.5 Hz, 9-H), 8.57 (1 H, d, *J* 5.5 Hz, 3-H), and 9.14 (1 H, d, *J* 1 Hz, 1-H) (Found: C, 72.5; H, 4.7; N, 7.0. $C_{12}H_9NO_2$ requires C, 72.3; H, 4.5; N, 7.0%).

8-*Formyl*-7-*hydroxy*-6-*methylbenzofuro*[3,2-c]*pyridine* (12).—The preceding compound (11) (5 g) and hexamethylenetetramine (5.25 g) were heated at reflux in acetic acid (75 ml) for 3 h. After addition of 3M-hydrochloric acid (100 ml) and a further 3 h period under reflux, evaporation of the solvent afforded a residue which was taken up in water and neutralized with saturated aqueous sodium hydrogen carbonate. The resulting precipitate was collected and recrystallized from methanol to give yellow needles (2.1 g, 36%), m.p. 212 °C, δ [$(CD_3)_2SO$, 100 MHz] 2.37 (3 H, s, 6-Me), 7.76 (1 H, d, *J* 6.5 Hz, 4-H), 8.48 (1 H, s, 9-H), 8.63 (1 H, d, *J* 6.5 Hz, 3-H), 9.34 (1 H, s, 1-H), and 10.15 (1 H, s, 8-CHO) (Found: C, 65.9; H, 4.0; N, 5.8. $C_{13}H_9NO_3 \cdot 0.5H_2O$ requires C, 66.1; H, 4.2; N, 5.9%).

Ethyl β-(7-*Hydroxy*-6-*methylbenzofuro*[3,2-c]*pyridin*-8-*yl*)-trans-*acrylate* (13).—A mixture of the aldehyde (12) (1.0 g) and ethoxycarbonylmethylenetriphenylphosphorane (3.05 g) (prepared from triphenylphosphine and ethyl bromoacetate as described [14]) in toluene (80 ml) was heated under reflux for 6 h. The solvent was removed and the residue was taken up

in ethanol (20 ml) and filtered to provide a solid (750 mg) which corresponded to a mixture of the expected compound (13) and the pyridopsoralen (14). This mixture was washed with chloroform (4 × 15 ml) and the remaining solid was recrystallized from toluene to give pure (13) (313 mg, 24%), m.p. 268—270 °C, δ [$(CD_3)_2SO$, 100 MHz] 1.28 (3 H, t, *J* 7 Hz, 8-Me), 2.42 (3 H, s, 6-Me), 4.21 (2 H, q, *J* 7 Hz, 8-CH_2), 6.68 (1 H, d, *J* 16 Hz, 8-H), 7.72 (1 H, d, *J* 5.4 Hz, 4-H), 8.12 (1 H, d, *J* 16 Hz, 8-H), 8.47 (1 H, s, 9-H), 8.57 (1 H, d, *J* 5.4 Hz, 3-H), and 9.27 (1 H, s, 1-H) (Found: C, 69.0; H, 5.2; N, 4.5. $C_{17}H_{15}NO_4$ requires C, 68.6; H, 5.0; N, 4.7%).

The chloroform from the washings was evaporated to give a residue (436 mg) which was taken up in ethanol and again corresponded to a mixture of (13) + (14), used in the next step (a) without further purification.

6-*Methyl*-8H-*pyrano*[3′,2′:5,6]*benzofuro*[3,2-c]*pyridin*-8-*one* (14).—(a) *From the mixture of the preceding reaction.* The mixture mentioned above (436 mg) was refluxed in diphenyl oxide (3 ml) for 5 h; after the mixture had been cooled hexane (30 ml) was added. The resulting solid was collected and recrystallized from toluene to afford colourless crystals, m.p. 295—302 °C. This compound gave a single spot by t.l.c. on silica gel (elution with ethyl acetate–ethanol 3 : 1 mixture) (Found: C, 71.5; H, 3.7; N, 5.4. $C_{15}H_9NO_3$ requires C, 71.7; H, 3.6; N, 5.5%) which was satisfactory. However, ^1H n.m.r. spectroscopy showed that, besides the signals of the expected compound (14), it contained a by-product δ [$(CD_3)_2SO$, 100 MHz] 2.13 (6 H, s, 6′- and 6″-Me), 4.28 and 4.50 (4 H, AA′-BB′ system, 9′, 9″- and 10′, 10″-H), 7.56 (2 H, s, 11′ and 11″-H), 7.69 (2 H, dd, *J* 5.8 and 0.8 Hz, 4′- and 4″-H), 8.56 (2 H, d, *J* 5.8 Hz, 3′- and 3″-H), 8.89 (2 H, d, *J* 0.8 Hz, 1′ and 1″-H) which probably corresponded to a cyclo-dimer since the signals of the AA′-BB′ system which appeared at 4.28 and 4.50 p.p.m. could be assigned to the protons of a tetra-substituted cyclobutane derivative resulting from the dimerization of compound (14).

(b) *From acrylic ethyl ester* (13). The pure ethyl ester (13) (0.1 g) in diphenyl oxide (1 ml) was refluxed for 18 h and treated as mentioned above. The resulting colourless crystals (54 mg, 63%), m.p. 285—302 °C, corresponded to the preceding mixture [(14) + by-product].

(c) *Starting from the aldehyde* (12). The aldehyde (12) (1.0 g) and ethoxycarbonylmethylenetriphenylphosphorane (3.06 g) were heated under reflux in xylene (90 ml) for 15 h. Xylene was removed and the residue, taken up in ethanol, afforded a solid which was collected and recrystallized from toluene to provide a mixture (0.33 g, 24%) identical with the preceding one [(14) + by-product].

(d) *Starting from pyridopsoralencarboxylic acid* (16). 9-Ethoxycarbonyl-6-methyl-8*H*-pyrano[3′,2′:5,6]benzofuro-[3,2-*c*]pyridin-8-one (15) (2.6 g) in acetic acid (15.6 ml) and hydrochloric acid (14.3 ml) was heated under reflux for 2 h. The mixture was cooled and the resulting solid was filtered off and dried to provide the acid (16) as a hydrochloride (2.2 g). This compound was dissolved in hot water, basified with aqueous ammonia, and neutralized with acetic acid. The resulting solid was filtered off and well dried to give yellow crystals (1.9 g, 80%), m.p. > 300 °C (Found: C, 68.3; H, 3.8, N, 5.4. $C_{15}H_9NO_3 \cdot 1.5H_2O$ requires C, 68.4; H, 3.9; N, 5.3%). This acid (500 mg) mixed with cupric oxide (5 mg) and *o*-phenanthroline (5 mg) in quinoline (2.7 ml) was heated at 200—220 °C for 20 min. After completion of the reaction by heating at 240 °C for a further 5 min, the mixture was cooled and the solid filtered off. Recrystallization from toluene afforded colourless crystals (210 mg, 49%) corresponding to the expected compound (14), m.p, 295—302 °C, δ [$(CD_3)_2SO$, 100 MHz] 2.58 (3 H, s, 6-Me), 6.52 (1 H, d, *J* 9.6 Hz, 9-H), 7.84 (1 H, d, *J* 5.8 and 0.8 Hz, 4-H), 8.2 (1 H, d, *J* 9.6 Hz, 10-H), 8.41 (1 H, s, 11-H), 8.69 (1 H, d, *J* 5.8 Hz, 3-H), and 9.41 (1 H, d, *J* 0.8 Hz, 1-H) (Found: C, 71.7; H, 3.7; N, 5.3. $C_{15}H_9NO_3$ requires C, 71.7; H, 3.6; N, 5.5%).

9-*Ethoxycarbonyl*-6-*methyl*-8H-*pyrano*[3′,2′:5,6]*benzofuro*-[3,2-c]*pyridin*-8-*one* (15).—The aldehyde (12) (2.0 g) was heated under reflux in ethanol (10 ml) with diethyl malonate (2.28 g) and piperidine (0.2 ml) for 20 min. The well cooled mixture was filtered and the resulting solid was recrystallized from ethanol to provide yellow crystals (2.6 g, 91%), m.p. 256—258 °C (Found: C, 66.6; H, 4.0; N, 3.9. $C_{18}H_{13}NO_5$ requires C, 66.8; H, 4.0; N, 4.3%).

4,8-*Dimethyl*-7-(3-*nitro*-4-*pyridyloxy*)*coumarin* (19).—7-Hydroxy-4,8-dimethylcoumarin (3.8 g) was added to a solution of triethylamine (2.0 g) and 4-chloro-3-nitropyridine (3.16 g) in dimethylformamide (40 ml). The resulting red solution was stirred at room temperature for 78 h and then heated at 60 °C for 1 h; it was then poured into ice–water. The solid was collected and recrystallized from acetic acid to afford yellow crystals (3.7 g, 59%), m.p. 264 °C, δ ($CDCl_3$, 100 MHz) 2.33 (3 H, s, 8-Me), 2.48 (3 H, d, 4-Me, *J* 1.3 Hz), 6.33 (1 H, d, 3-H), 6.67 (1 H, d, *J* 5.8 Hz, 5′-H), 7.01 (1 H, d, *J* 8.8 Hz, 6′-H, 7.54 (1 H, d, 5-H), 8.56 (1 H, d, 6′-H), and 9.16 (1 H, s, 2′-H) (Found: C, 61.8; H, 3.9; N, 8.8. $C_{16}H_{12}N_2O_5$ requires C, 61.5; H, 3.8; N, 8.9%).

7-(3-*Amino*-4-*pyridyloxy*)-4,8-*dimethylcoumarin* (20).—Hydrogenation of the nitro-derivative (19) (3.5 g) in acetic acid (120 ml) was performed as for the preparation of (7), with Raney nickel (3.5 g). The residue from the evaporation of solvent was taken up in water, basified with aqueous ammonia, and the resulting solid filtered and air-dried; it recrystallized from xylene as colourless needles (1.8 g, 88%), m.p. 186—187 °C, δ [$(CD_3)_2SO$, 100 MHz] 2.26 (3 H, s, 8-Me), 2.45 (3 H, d, *J* 1 Hz, 4-Me), 5.25 (2 H, s, 3′-NH_2), 6.4 (1 H, d, 3-H), 6.6 (1 H, d, *J* 5 Hz, 5′-H), 6.96 (1 H, d, *J* 9 Hz, 6-H), 7.65 (1 H, d, 5-H), 7.74 (1 H, d, 6′-H), and 8.12 (1 H, s, 2′-H) (Found: C, 68.1; H, 5.1; N, 9.8. $C_{16}H_{14}N_2O_3$ requires C, 68.0; H, 5.0; N, 9.9%).

7-(3-*Chloro*-4-*pyridyloxy*)-4,8-*dimethylcoumarin* (22).—The amine (20) (2.82 g) in 0.66M-hydrochloric acid (30 ml) was treated with stirring at 0 °C with aqueous sodium nitrite (0.7 g) and left 15 min at this temperature. The resulting diazonium chloride solution (21) was added dropwise to a well stirred mixture of acetone (50 ml), water (15 ml), and cupric chloride (3.3 g), heated at 35—40 °C. Stirring was maintained for a further 15 min after which the mixture was poured into ice–water. After addition of aqueous ammonia, extraction with chloroform, and work-up of the extract, the residue was chromatographed on silica gel (280 g) with chloroform–ethanol (9 : 1) as eluant. Evaporation of the first and main fraction afforded a solid which recrystallized from ethanol to give (22) as colourless needles (0.95 g, 31.5%), m.p. 188—190 °C, δ ($CDCl_3$) values were comparable with those of the starting amine (20) (Found: C, 63.5; H, 4.1; Cl, 12.0; N, 4.6. $C_{16}H_{12}ClNO_3$ requires C, 63.8; H, 3.9; Cl, 11.7; N, 4.6%).

1-*Methylpiperidin*-4-*one* O-(4,8-*Dimethylcoumarin*-7-*yl*)-*oxime* (24).—7-Amino-oxy-4,8-dimethylcoumarin (23) was prepared according to a literature method.[12] A stirred mixture of this crude compound (850 mg, 2.92 mmol) and 1-methylpiperidin-4-one (500 mg, 4.42 mmol) in absolute ethanol (40 ml) was treated with 15 drops of concentrated hydrochloric acid. After 3.5 h the precipitate was filtered off, washed with ethanol, and dried to yield the hydrochloride of compound (24) (1.24 g, 94%), m.p. 204—205 °C. A suspension of this

hydrochloride (300 mg) in water (6 ml) was adjusted to pH 8—9 with a saturated solution of sodium hydrogen carbonate. After stirring of the mixture for 30 min, the precipitate was filtered off, dried, and crystallized twice from ethanol to afford (24) (120 mg), m.p. 138 °C (decomp.), δ ($CDCl_3$) 2.3, 2.36, 2.35 (3 H, each s, N-Me, 4-Me, 8-Me), 2.50—3.0 and 2.55 [8 H, m and s, $N(CH_2CH_2)_2$], 6.1br (1 H, s, 3-H), and 7.35 (2 H, s, 5-H and 6-H) (Found: C, 67.65; H, 6.7; N, 9.3. $C_{17}H_{20}N_2O_3$ requires C, 67.95; H, 6.7; N, 9.3%).

2,6,10-*Trimethyl*-1,2,3,4-*tetrahydro*-8H-*pyrano*[3′,2′:5,6]-*benzofuro*[3,2-c]*pyridin*-8-*one* (26) *and Compound* (28).—The oxime (24) hydrochloride (2.28 g, 6.78 mmol) in glacial acetic acid containing 6% of hydrogen chloride was stirred at 80 °C and dry hydrogen chloride was passed through the mixture. After 5 h the reaction was cooled, the precipitate was filtered off and washed with acetic acid and with dry ether to yield the hydrochloride of compound (26) (1.6 g, 67%), m.p. 268—271 °C. The base, liberated and crystallized from ethanol, had m.p. 201—202 °C, δ ($CDCl_3$) 2.5 and 2.58 (3 H, s, and 6 H, s, N-Me, 6-Me, 10-Me), 2.9br (4 H, s, 3,4-CH_2), 3.63br (2 H, s, 1-CH_2), 6.26br (1 H, s, 9-H), and 7.43 (1 H, s, 11-H); *m/z* 283 (M^+) (Found: C, 71.85; H, 6.05; N, 4.9. $C_{17}H_{17}NO_3$ requires C, 72.00; H, 6.05; N, 4.95%). Removal of acetic acid from the mother-liquors of (26) left a residue which was dissolved in water.

The aqueous solution was made alkaline with a solution of sodium hydrogen carbonate and extracted with methylene chloride. The organic extracts were dried and evaporated to afford a residue which was crystallized from methanol to yield white crystals of (28) (280 mg, 14%), m.p. 200 °C, δ ($CDCl_3$) 2.2—3.58 (15 H, N-Me, 4-Me, 8-Me, O=CCH_2CH_2N, β-CH_2-N), 4.9 (1 H, m, $J_{AX} + J_{BX}$ 20 Hz, α-$CHCH_2$), 6.1br (1 H, s, 3-H), 6.63 (1 H, d, *J* 9 Hz, 6-H), 7.35 (1 H, d, *J* 9 Hz, 5-H); $\nu_{max.}$ ($CHCl_3$) 1 612, 1 715, and 1 725; *m/z* 301 (M^+), 112, and 70 (Found: C, 67.5; H, 6.30; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.75; H, 6.35; N, 4.65%).

6,10-*Dimethyl*-1,2,3,4-*tetrahydro*-8H-*pyrano*[3′,2′:5,6]-*benzofuro*[3,2-c]*pyridin*-8-*one* (27).—This compound was synthesized from piperidin-4-one hydrochloride (1.36 g, 6.63 mmol) and the *O*-aryl hydroxylamine (23) as described for (26); the oxime (25) was not, however, characterized. The hydrochloride of compound (27) (1.150 g, 56.8%) had m.p. 285—290 °C (decomp.). The base, liberated and crystallized from ethanol, had m.p. 211—212 °C, δ ($CDCl_3$) 1.73 (1 H, s, NH), 2.43 (3 H, d, 10-Me), 2.53 (3 H, s, 6-Me), 2.83 (2 H, m, 3-CH_2), 3.2 (2 H, m, 4-CH_2), 3.96 (2 H, m, 1-CH_2), 6.16 (1 H, m, 9-H), and 7.33 (1 H, s, 11-H); *m/z* 269 (M^+) 240, and 212 (Found: C, 68.9; H, 5.9; N, 4.8. $C_{16}H_{15}NO_3 \cdot 0.5H_2O$ requires C, 69.05; H, 5.80; N, 5.03%).

6,10-*Dimethyl*-8H-*pyrano*[3′,2′:5,6]*benzofuro*[3,2-c]*pyridin*-8-*one* (17).—A mixture of the hydrochloride of compound (27) (404 mg, 1.32 mmol), 10% palladium on charcoal (300 mg), and decalin (15 ml) was refluxed for 5 h. The catalyst was filtered off from the hot solution and washed with hot decalin (5 ml). The white crystals of (17), collected after cooling (130 mg, 37%) of the mixture, and recrystallized from methylene chloride–ethanol, had m.p. 270—271 °C, δ ($CDCl_3$, 100 MHz) 2.58 (3 H, d, *J* 1.2 Hz, 10-Me), 2.67 (3 H, d, *J* 0.5 Hz, 6-Me), 6.34 (1 H, d, *J* 1.2 Hz, 9-H), 7.59 (1 H, dd, *J* 0.9 Hz, *J* 5.7 Hz, 4-H), 8.08 (1 H, s, 11-H), 8.70 (1 H, d, *J* 5.7 Hz, 3-H), and 9.29 (1 H, d, *J* 0.9 Hz, 1-H); *m/z* 265 (M^+) 237; $\lambda_{max.}$ (EtOH) 250 (ε 24 700) and 328 nm (ε 13 700) (Found: C, 72.1; H, 4.25; N, 4.7. $C_{16}H_{11}NO_3$ requires C, 72.45; H, 4.2; N, 5.25%).

The hydrochloride of compound (26) (248 mg, 0.77 mmol) was converted into (17) (109 mg) as described above. Recrystallization from methylene chloride–ethanol gave pure (17) (77 mg, 37%).

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References

1 L. Musajo and G. Rodighiero, *Experientia*, 1962, **18**, 153.
2 L. Musajo and G. Rodighiero, in ' Current Topics in Photobiology and Photochemistry,' Academic Press, New York, London, 1972, 115.
3 P. S. Song and J. T. Kenneth, *Photochem. Photobiol.*, 1979, **29**, 1177.
4 B. J. Parsons, *Photochem. Photobiol.*, 1980, **32**, 813.
5 L. Musajo and G. Rodighiero, *Acta Derm. Venereol.*, 1967, **47**, 298.
6 G. Rodighiero, L. Musajo, S. Marciani, G. Caporale, and I. Ciavatta, *Biochim. Biophys. Acta*, 1980, **217**, 40.
7 R. S. Cole, *Biochim. Biophys. Acta*, 1971, **254**, 30.
8 (*a*) D. Averbeck, E. Moustacchi, and E. Bisagni, *Biochim. Biophys. Acta*, 1978, **518**, 464; (*b*) D. Averbeck and E. Moustacchi, *Mutat. Res.*, 1979, **68**, 133.
9 L. Dubertret, D. Averbeck, F. Zajdela, E. Bisagni, E. Moustacchi, R. Touraine, and R. Latarjet, *Br. J. Dermatol.*, 1979, **101**, 379.
10 F. Dall'Acqua, D. Vevaldi, S. Caffini, A. Guitto, P. Rodighiero, F. Baccichetti, F. Carlassase, and F. Bordin, *J. Med. Chem.*, 1981, **24**, 178.
11 R. R. Bishop, E. A. S. Clavell, and N. B. Chapman, *J. Chem. Soc.*, 1952, 437.
12 D. R. Bender, J. E. Hearst, and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 2176.
13 D. Averbeck, to be published.
14 B. Denny and S. T. Ross, *J. Org. Chem.*, 1962, **27**, 998.

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