Carcinogenic Nitrogen Compounds. Part XLIX.[1] Analogues of Benzacridines and Benzocarbazoles Having an α-Pyrone Ring

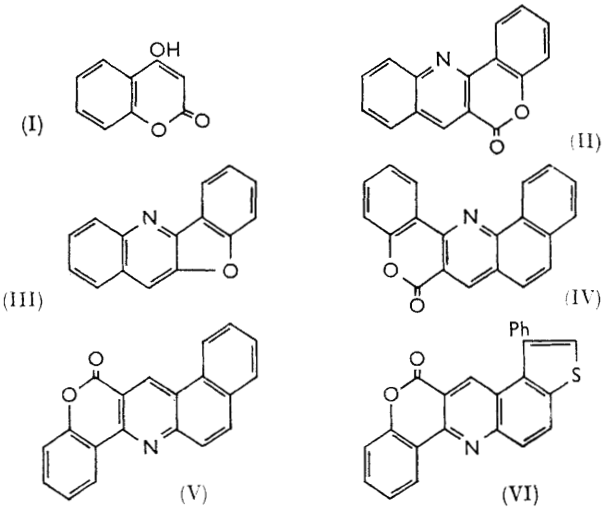
By N. P. Buu-Hoï, M. Mangane, and P. Jacquignon

4-Hydroxycoumarin is shown to undergo a novel reaction with primary arylamines and paraformaldehyde to give chromenoquinolines, which are analogues of the carcinogenic benzacridines and dibenzacridines. Isochromenoindoles, analogous to mono- and di-benzocarbazoles, were prepared by indolisation of aryl- and quinolyl-hydrazones of isochroman-1,4-dione. The electron-impact fragmentation of these compounds is discussed.

It has been established recently[2] that certain simple synthetic (*e.g.*, β-propiolactone) and complex natural (*e.g.*, aflatoxin) compounds with lactone functions possess considerable carcinogenic activity. Hence, it was of interest to prepare for investigation compounds of molecular structure akin to those of confirmed nitrogen heterocyclic carcinogens (*i.e.*, the angular benzacridines and benzocarbazoles), but with a lactone ring.

An attractive synthetic approach was to build a nitrogen-containing heterocycle on the coumarin or isocoumarin nucleus. 4-Hydroxycoumarin (I) was found to be a convenient starting material, behaving like an α-naphthol with a very reactive *ortho*-position, *i.e.*, readily undergoing an Ullmann–Fetvadjian-type condensation reaction with aniline and paraformaldehyde to furnish, in excellent yield, 6-oxo-6*H*-chromeno-[4,3-*b*]quinoline (II). This compound showed a remarkable stability, and could be distilled *in vacuo* without decomposition. Further, in the mass spectrometer, it underwent relatively little electron-impact fragmentation, giving the molecular peak ($m/e = 247$) as the main one, and also a significant peak corresponding to the doubly charged molecular ion (123·5). The most prominent feature of the fragmentation was the loss of carbon dioxide, corresponding to the formation of the ion $m/e = 219$ which, by analogy with the thermal decarbonylation of coumarin to benzofuran,[3] must correspond to the molecular species (III). The structure of this last molecule is very close to that of many alkaloids such as dictamnine, maculine, and acronycidine, which also are furoquinolines.[4] The loss of oxygen from compound (II), giving rise to the fluorenone-type ion $m/e = 231$, is on the other hand negligible (only 0·9% of the base peak).

The reaction leading to compound (II) can be extended to more complex primary arylamines. For instance, *p*-anisidine and 3,4-dimethylaniline afforded, respectively, 9-methoxy- and 9,10-dimethyl-6-oxo-6*H*-chromeno[4,3-*b*]quinoline; compounds (IV) and (V), analogues of the carcinogenic dibenzo[*c*,*h*]- and dibenzo[*a*,*h*]-acridine, were obtained from α- and β-naphthylamine, and compound (VI), a derivative of a thiophen isostere of (V), was obtained from 5-amino-3-phenylthianaphthen. All these coumarins are remarkably stable, and the very low degree of basicity is shown by their inability to form stable picrates, and by the fact that they crystallise unchanged from acetic acid.



As isochroman-1,4-dione (VII) (tautomeric with 4-hydroxyisocoumarin) was readily accessible through Knott's procedure,[5] it was used as starting material for preparing a number of isocoumarin analogues of the bisangular dibenzocarbazoles by indolisation of its naphthyl-, quinolyl-, and isoquinolyl-hydrazones. Compounds (VIII), (X), (XI), and (XII) are analogues both of dibenzo[*a*,*i*]carbazoles, and of benzopyridocarbazoles (several of which are potent carcinogens[6]), whilst compound (XIII) is an analogue of dibenzo[*a*,*g*]-carbazole. All these isochromenoindoles are stable, high-melting, insoluble compounds, which could be purified only by sublimation and, like the chromenoquinolines, failed to give stable picrates; they are particularly difficult to burn, and therefore, in several instances, gave poor carbon analyses. The behaviour of 5-oxo-5*H*-benzo[*g*]isochromeno[4,3-*b*]indole (VIII) in mass spectrometry closely resembles that of 6-oxo-6*H*-chromeno[4,3-*b*]quinoline (II), featuring a large molecular peak ($m/e = 285$), and a pattern of electron-impact fragmentation characterised by little loss of oxygen

[1] Part XLVIII, N. P. Buu-Hoï and G. Saint-Ruf, *J. Chem. Soc.*, 1965, 5464.

[2] Cf. A. L. Walpole, D. C. Roberts, F. L. Rose, J. A. Hendry, and R. F. Homer, *Brit. J. Pharmacol.*, 1954, **9**, 306; F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, 1961, **15**, 85; R. Allcroft and G. Lewis, *Biochem. J.*, 1963, **88**, 58P.

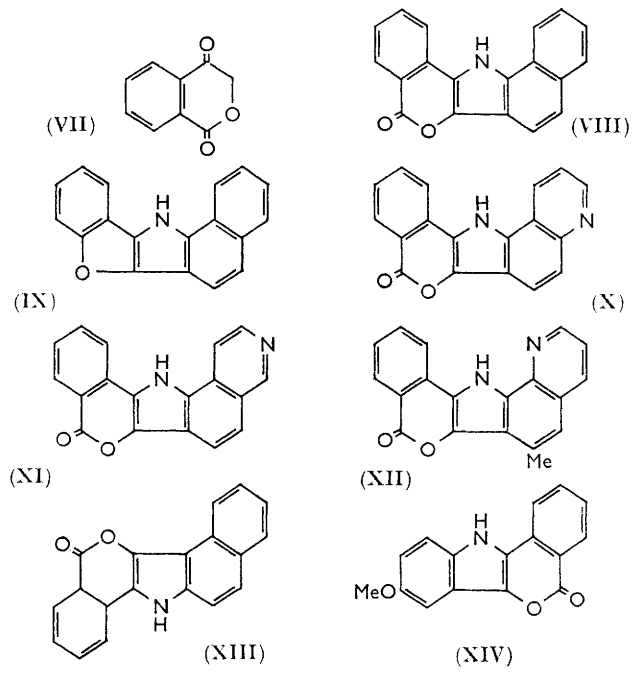
[3] Cf. H. Meyer, "Synthese der Kohlenstoffverbindungen," vol. 2, Springer-Verlag, Vienna, 1940, p. 27.

[4] See literature in F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, p. 536.

[5] E. B. Knott, *J. Chem. Soc.*, 1963, 402.

[6] N. P. Buu-Hoï, F. Périn, and P. Jacquignon, *J. Chem. Soc.*, 1960, 4500; 1962, 146; A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, P. Jacquignon, and F. Périn, *Nature*, 1961, **191**, 1005; *Compt. rend.*, 1963, **257**, 817.

(ion $m/e = 269$) and, contrariwise, a very important contribution of the ion corresponding to the species (IX) resulting from a decarbonylation reaction. The other isochromenoindoles, including the tetracyclic compound



(XIV) prepared from *p*-methoxyphenylhyrazine, showed similar patterns of electron-impact decomposition.

Tests for carcinogenesis are under way, and results will be reported elsewhere.

EXPERIMENTAL

6-*Oxo*-6H-*chromeno*[4,3-b]*quinoline* (II).—To a boiling mixture of 4-hydroxycoumarin (3·3 g.) and aniline (2 g.), in a Claisen flask with a wide lateral tube, paraformaldehyde (0·9 g.) was added in small portions, and the product then distilled *in vacuo*; the portion boiling at *ca.* 240°/0·5 mm. was recrystallised from a mixture of toluene and butanol, to furnish fine yellowish prisms (3·5 g.), m. p. 224°, giving a greenish-yellow halochromism in sulphuric acid (Found: C, 77·3; H, 3·7; N, 5·5. $C_{16}H_9NO_2$ requires C, 77·7; H, 3·7; N, 5·7%). This compound could be recrystallised unchanged from acetic acid, and no isolable picrate could be obtained. 9-*Methoxy*-6-*oxo*-6H-*chromeno*[4,3-b]*quinoline* was similarly prepared from *p*-anisidine (2·5 g.), and crystallised as pale yellow prisms (3 g.), m. p. 229°, from acetic acid (Found: C, 73·2; H, 4·2; N, 5·2; O, 17·5. $C_{17}H_{11}NO_3$ requires C, 73·6; H, 4·0; N, 5·1; O, 17·3%); 9,10-*dimethyl*-6-*oxo*-6H-*chromeno*[4,3-b]*quinoline*, obtained from 3,4-dimethylaniline (2·6 g.), was pale yellow needles (3·5 g.), m. p. 214°, from toluene (Found: C, 78·2; H, 5·0; N, 5·2. $C_{18}H_{13}NO_2$ requires C, 78·5; H, 4·8; N, 5·1%).

6-*Oxo*-6H-*benzo*[h]*chromeno*[4,3-b]*quinoline* (IV).—Prepared from 4-hydroxycoumarin (2·8 g.), α-naphthylamine (2·9 g.), and paraformaldehyde (0·65 g.), this *compound* could also be distilled *in vacuo* without decomposition, and formed yellowish prisms (3·8 g.), m. p. 279°, from acetic acid, giving an orange-yellow halochromism in sulphuric acid (Found: C, 80·4; H, 4·0; N, 5·0. $C_{20}H_{11}NO_2$ requires C, 80·8; H, 3·7; N, 4·7%).

6-*Oxo*-6H-*benzo*[f]*chromeno*[4,3-b]*quinoline* (V).—This *compound*, prepared as for the above using β-naphthylamine, boiled without decomposition at *ca.* 270—275°/0·5 mm., and formed yellowish needles (4·2 g.), m. p. 281°, from acetic acid (Found: C, 80·6; H, 3·9; N, 4·9; O, 10·7. $C_{20}H_{11}NO_2$ requires C, 80·8; H, 3·7; N, 4·7; O, 10·8%).

6-*Oxo*-8-*phenyl*-6H-*chromeno*[4,3-b]*thieno*[3,2-f]*quinoline* (VI).—5-Amino-3-phenylthianaphthen (2·3 g.), prepared according to Angeli,[7] was condensed with 4-hydroxycoumarin (1·6 g.) and paraformaldehyde (0·45 g.), to give *compound* (VI), boiling without decomposition at *ca.* 290—300°/0·5 mm., and crystallising as yellowish prisms (2·5 g.), m. p. 228°, from acetic acid (Found: N, 3·8; S, 8·1. $C_{24}H_{13}NO_2S$ requires N, 3·7; S, 8·4%).

5-*Oxo*-5H-*benzo*[g]*isochromeno*[4,3-b]*indole* (VIII).—A solution of isochroman-1,4-dione (0·5 g.) and α-naphthylhydrazine (0·6 g.) in ethanol (7·5 c.c.) and water (2·5 c.c.) was heated under reflux for 1 hr. with 1 drop of acetic acid; the precipitate of the unstable naphthylhydrazone which formed on cooling was collected, washed with aqueous ammonia, and indolised by heating its solution in acetic acid (10 c.c.) saturated with hydrogen chloride for 5 min. under reflux. After cooling and dilution with water, the yellow precipitate (0·8 g.) obtained was purified by sublimation *in vacuo*, to yield yellowish needles, m. p. 411°, giving a greenish-yellow halochromism in sulphuric acid (Found: N, 4·6; O, 10·9. $C_{19}H_{11}NO_2$ requires N, 4·9; O, 11·2%). This compound gave a brown picrate which decomposed on crystallisation.

5-*Oxo*-5H-*benzo*[e]*isochromeno*[4,3-b]*indole* (XIII).—Isochroman-1,4-dione β-naphthylhydrazone was yellow needles, m. p. 189°, and gave on cyclisation with acetic acid + HCl, the *indole* (XIII) (70% yield) which, after purification by sublimation *in vacuo*, formed pale yellow prisms, m. p. 357° (Found: N, 4·4; O, 10·8%); its brown picrate was unstable and could not be isolated by crystallisation.

8-*Methoxy*-5-*oxo*-5H-*isochromeno*[4,3-b]*indole* (XIV).—*Isochroman*-1,4-*dione* p-*methoxyphenylhydrazone* formed yellow needles, m. p. 206°, from ethanol (Found: N, 9·8. $C_{16}H_{14}N_2O_3$ requires N, 9·9%). Indolisation afforded a 70% yield of the *indole* (XIV), crystallising as yellowish prisms, m. p. 293°, from butanol (Found: N, 5·4; O, 17·8. $C_{16}H_{11}NO_3$ requires N, 5·3; O, 18·1%); the coloration in sulphuric acid was red, turning green, and in an ethanolic solution of picric acid it was red.

8-*Oxo*-8H-*isochromeno*[4′,3′:4,5]*pyrrolo*[2,3-f]*quinoline* (X).—Isochroman-1,4-dione 5-quinolylhydrazone (yellow needles, m. p. 183°, from ethanol) was indolised by heating for 30 min. at 100° with a solution of sulphuric acid (2 c.c.) in acetic acid (10 c.c.); after cooling and dilution with water, the precipitate obtained in 70% yield was washed with aqueous ammonia, then with water, dried, and sublimed *in vacuo*, to furnish the *indole* (X) as bright yellow needles, m. p. 466°, giving a greenish yellow halochromism in sulphuric acid (Found: H, 3·7; N, 9·9. $C_{18}H_{10}N_2O_2$ requires H, 3·5; N, 9·8%).

8-*Oxo*-8H-*isochromeno*[4′,3′:4,5]*pyrrolo*[2,3-f]*isoquinoline* (XI).—Indolisation of isochroman-1,4-dione 5-isoquinolylhydrazone (ochre yellow needles, m. p. 246°), effected as above in 70% yield, afforded the *indole* (XI) which, after sublimation *in vacuo*, formed bright yellow prisms, m. p. 496° (Found: H, 3·8; N, 9·9%).

[7] C. Angeli, *Ann. Chim.* (*Italy*), 1957, **47**, 705.

6-*Methyl*-8-*oxo*-8H-*isochromeno*[4′,3′:4,5]*pyrrolo*[2,3-h]-*quinoline* (XII).—Prepared from 6-methyl-8-quinolylhydrazine,[8] this *indole* formed, after sublimation *in vacuo*, yellow prisms, m. p. 343° (Found: C, 75·9; H, 4·1; N, 9·5. $C_{19}H_{12}N_2O_2$ requires C, 76·0; H, 4·0; N, 9·3%).

Compound (II)			Compound (VIII)		
Ion	*m/e*	%	Ion	*m/e*	%
M^+	247	100	M^+	285	100
$(M + 1)^+$.....	248	20·8	$(M + 1)^+$ ...	286	21·5
$(M - 16)^+$ ...	231	0·9	$(M - 2)^+$ ...	283	3·4
$(M - 28)^+$ ...	219	25·6	$(M - 16)^+$ ...	269	1
$(M - 57)^+$ ...	190[a]	18·5	$(M - 28)^+$ ...	257	39·9
M^{2+}	123·5	6	$(M - 57)^+$ ...	228[a]	6·8
$(M - 28)^{2+}$ ...	109·5	2			

[a] These ions correspond probably to the loss of both carbon monoxide and formaldehyde.

Mass Spectrometric Determinations.—These were performed with a German mark Atlas CH-4 spectrometer, at 70 electron-volts (40 μA). The percentage values for the most significant peaks in the mass spectrograms of two characteristic compounds are shown in the table.

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France. [5/730 *Received*, *July* 12*th*, 1965]

[8] N. P. Buu-Hoï, P. Jacquignon, and J. P. Hoeffinger, *J. Chem. Soc.*, 1963, 4754.