# Carcinogenic Nitrogen Compounds. Part LXXX.[1] [1]Benzopyrano-[4,3-*b*]indoles and 6*H*-[1]Benzopyrano[4,3-*b*]quinolines

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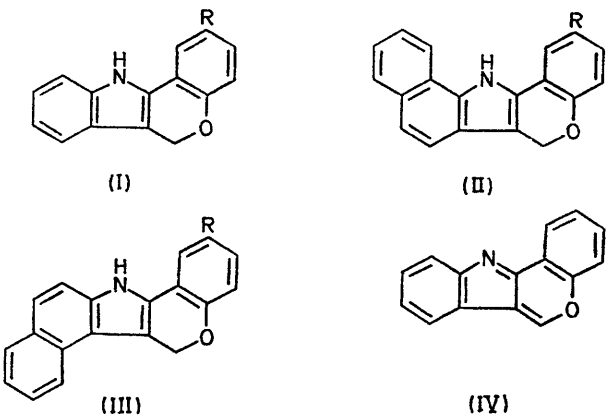
A number of compounds derived from the [1]benzopyrano[4,3-*b*]indole and 6*H*-[1]benzopyrano[4,3-*b*]quinoline systems have been prepared from chroman-4-one and its 6-chloro- and 6-methyl-derivatives, and their physicochemical and biological properties investigated; analogous derivatives of the [1]benzothiopyrano[4,3-*b*]indole system were prepared from 6-chloro- and 6-methoxy-thiochroman-4-one. The majority of the compounds synthesised displayed high zoxazolamine hydroxylase inducing activity.

In previous papers [2] we reported that the dihydro[1]-benzothiopyrano[4,3-*b*]indoles and their benzo-derivatives, which are easily prepared by the Fischer cyclisation of the arylhydrazones of thiochromanones, readily undergo dehydrogenation to the corresponding *pseudo*-azulenes of molecular structure resembling carcinogenic hydrocarbons and benzacridines,[3] while they themselves resemble carcinogenic benzocarbazoles;[4] since then, many of these indoles have themselves exhibited carcinogenic activity.[5] It was therefore of interest to investigate similarly the dihydro[1]benzopyrano[4,3-*b*]-indoles (I) and their benzo-derivatives which are derived from the arylhydrazones of chromanones; so far, only two compounds in this series, *i.e.* (I; R = H) [2,6] and (III; R = H),[6] had been reported in the literature.

The new indoles of general formulae (I)—(III) were readily prepared, though in poor yield, by cyclisation of the appropriate arylhydrazones by means of acetic acid containing hydrogen chloride; the physical data are in Supplementary Publication No. 20351 (4 pp., 1 microfiche *). In no case was it possible to effect dehydrogenation to the corresponding *pseudo*-azulene [*e.g.*, compound (IV)] with picric acid as a mild oxidation agent, a procedure which had proved highly successful for the preparation of the equivalent sulphur *pseudo*-azulenes;[2] nor was perchloric acid (*via* a pyrylium perchlorate)[7] any more satisfactory.

As had previously been observed with the sulphur analogue,[8] the n.m.r. spectrum of 6,11-dihydro[1]benzopyrano[4,3-*b*]indole (I; R = H) in $CDCl_3$ [δ 5·66 (2H, s $CH_2$), 6·75—7·6 (8H, envelope, ArH), and 8·12br p.p.m. (1H, NH)] is greatly different from that in $CF_3CO_2H$, the signal due to the imino-proton disappearing in the latter solvent, through the formation of the tautomeric 3*H*-indole form (V) [δ 4·15—4·73 (1H, m, 6a-H), 4·73—5·61 (2H, m, 6-$H_2$), and 7·15—8·2 p.p.m. (8H, envelope, ArH)]. On the other hand, the mass spectrum of (I; R = H) (Figure 1) differs fundamentally from that of its sulphur analogue, which fragments mainly through extrusion of the sulphur heteroatom. Here, in contrast, the molecule undergoes ready dehydro-




* For details of Supplementary Publications, see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1971, Issue No. 20 (items less than 10 pp. will be supplied as full page copies).

[1] Part LXXIX, N. P. Buu-Hoï, O. Périn-Roussel, P. Jacquignon, and A. Cheutin, preceding paper.

[2] N. P. Buu-Hoï, A. Croisy, A. Ricci, P. Jacquignon, and F. Périn, *Chem. Comm.*, 1966, 269; N. P. Buu-Hoï, A. Martani, A. Croisy, P. Jacquignon, and F. Périn, *J. Chem. Soc.* (*C*), 1966, 1787; N. P. Buu-Hoï, P. Jacquignon, A. Croisy, A. Loiseau, F. Périn, A. Ricci, and A. Martani, *ibid.*, 1969, 1422.

[3] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and R. Daudel, *Adv. Cancer Res.*, 1956, **4**, 315.

[4] E. Boyland and A. M. Brues, *Proc. Roy. Soc.*, 1937, **122** [*B*], 429; A. Lacassagne, N. P. Buu-Hoï, R. Royer, and F. Zajdela, *Compt. rend.*, 1947, **141**, 635.

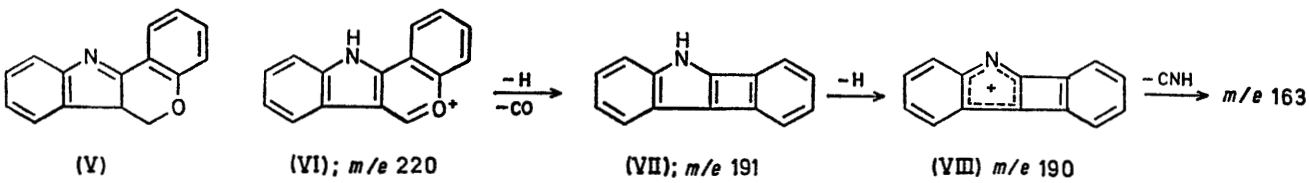
[5] F. Zajdela, N. P. Buu-Hoï, P. Jacquignon, A. Croisy, and F. Périn, *J. Nat. Cancer Inst.*, 1971, **46**, 1257.

[6] N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, *Zhur. obshchei. Khim.*, 1962, **32**, 3640.

[7] T. E. Young and P. H. Scott, *J. Org. Chem.*, 1966, **31**, 343.

[8] N. P. Buu-Hoï, V. Bellavita, G. Grandolini, A. Ricci, and P. Jacquignon, *Compt. rend.*, 1966, **262** [*C*], 1204.

genation to the species (VI), which loses carbon monoxide to give an ion *m/e* 192; this in turn either extrudes hydrogen cyanide, or is dehydrogenated first to the 2,3-phenyleneindole (VII), then to the species (VIII), which, finally, loses HCN to give an ion *m/e* 163. These




transitions are confirmed by the presence of corresponding metastable peaks.

Chroman-4-one and its 6-methyl- and 6-chloro-derivatives underwent Friedländer condensations with *o*-aminobenzaldehyde, although the yields were poor, to

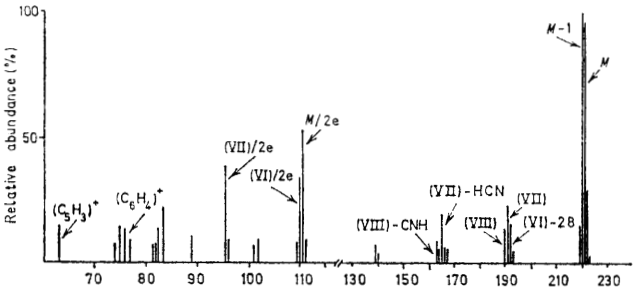
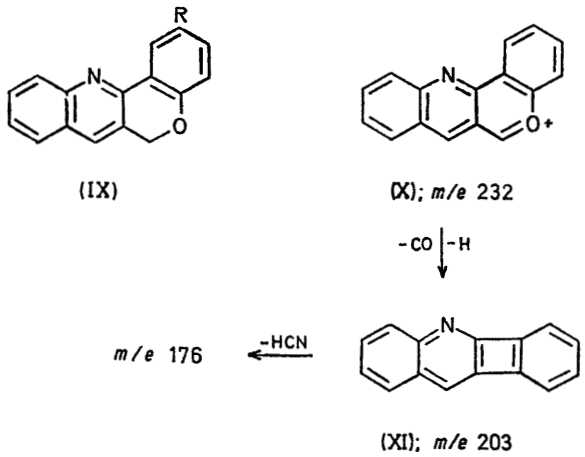



FIGURE 1 Mass spectrum of 6*H*-[1]benzopyrano[4,3-*b*]indole (I; R = H) (*M*, 221)

give 6*H*-[1]benzopyrano[4,3-*b*]quinolines (IX) [see Supplementary Publication No. 20351 (4 pp., 1 microfiche *)],




which are of interest in view of their structural analogy with benz[*c*]acridines. The differences between the n.m.r. spectrum of (IX; R = H) in $CDCl_3$ and that in $CF_3CO_2H$ (in which protonation of the nitrogen heteroatom occurs) are given in the Experimental section. The pattern of fragmentation of (IX; R = H) under electron impact (Figure 2) is remarkably similar to that of the indole (I; R = H). Here again, the molecule

* See footnote, p. 1266.

is first dehydrogenated to the species (X), which then extrudes carbon monoxide to an ion *m/e* 204; this either eliminates HCN to give an ion *m/e* 177, or is dehydrogenated to the species (XI), which in turn extrudes HCN to give the hydrocarbon species *m/e* 176.

For purposes of comparison, two new sulphur analogues of the [1]benzopyrano[4,3-*b*]benzo[*e*]indoles (III) were also prepared, from 6-chloro- and 6-methoxy-thiochroman-4-one. The two dihydro-compounds (XII), at variance with their pyrano-analogues, readily underwent dehydrogenation with picric acid to give the *pseudo*-azulenes (XIII). It should be noted that in the indolisation of the β-naphthylhydrazones reported, cyclisation was taken to involve the α-position of the naphthalene system rather than the less reactive β-position; this was now proven by features in the n.m.r. spectra of compounds (III; R = H) and (XII; R = H). Whereas in

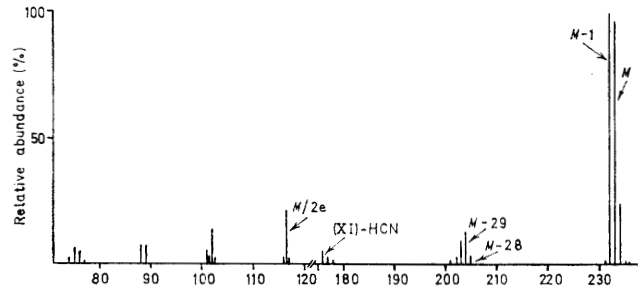
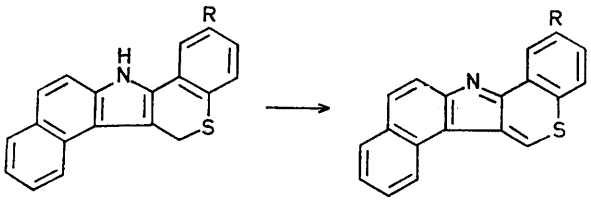



FIGURE 2 Mass spectrum of 6*H*-[1]benzopyrano[4,3-*b*]quinoline (IX; R = H) (*M*, 233)

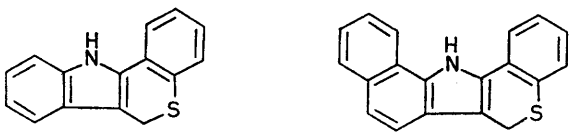
passing from 6,11-dihydro[1]benzothiopyrano[4,3-*b*]-indole (XIV) to its *cis*-bisangular benzo-derivative (XV), the chemical shift of the methylene protons is barely affected (δ 4·16 and 4·23 p.p.m. respectively), a significant displacement is observed with the *trans*-bisangular compound (XII; R = H) (δ 4·7 p.p.m.), due to the angular effect exerted by the proximate ring B. Similarly, in the pyran series, a significant displacement was observed in passing from compound (I; R = H) to its *trans*-bisangular benzo-derivative (III; R = H) (δ 5·66 and 5·9 p.p.m. respectively). Compounds (XVI), which would result were cyclisation to occur at β-position, could safely be expected to show chemical shifts for their methylene protons barely different from those for compound (I; R = H) and (XIV), and furthermore, to show aromatic singlets (7- and 12-H), a feature notably lacking in the spectra of (III; R = H) and (XII; R = H).

Compound (XIII; R = Cl), like the unsubstituted compound (XIII; R = H), displays carcinogenic activity [deposited in Supplementary Publication No.

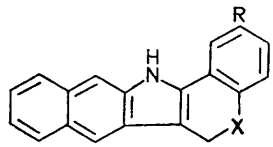
20351 (4 pp., 1 microfiche *)];[5] all the benzopyranoindoles (I)—(III) and the benzopyranoquinolines (IX) are inducers of the *in vivo* biosynthesis of zoxazolamine hydroxylase, maximum activity being encountered in compounds with the *trans*-bisangular structure (III), as



(XII) (XIII)



(XIV) (XV)



(XVI); X = O, S

was also the case with the corresponding thiopyranoindoles.[9,10] As all the polycyclic carcinogens, with only rare exceptions, are inducers of zoxazolamine hydroxylase,[10] carcinogenesis tests are currently being conducted with compounds (II) and (III).

## EXPERIMENTAL

*Preparation of Compounds* (I)—(III).—The arylhydrazones of chromanones were prepared from the corresponding hydrazines and the appropriate ketone in boiling ethanol, and recrystallised from methanol as colourless or yellowish prisms: chroman-4-one α-naphthylhydrazone, m.p. 156—157°; 6-methylchroman-4-one phenylhydrazone, m.p. 83—84°; 6-methylchroman-4-one β-naphthylhydrazone, m.p. 164°; 6-chlorochroman-4-one phenylhydrazone, m.p. 115°; 6-chlorochroman-4-one α-naphthylhydrazone, m.p. 188—189°, and its β-isomer, m.p. 155—156°. Indolisation of the hydrazone (1 part) was achieved instantaneously with a boiling solution (5 parts) of acetic acid saturated with hydrogen chloride. After dilution with water, the indole was taken up in benzene, the benzene solution washed with dilute aqueous sodium hydroxide, then with water, the solvent was distilled off, and the residue was recrystallised. All the indoles (yields were low, *ca.* 20—40%) gave blackish brown picrates.

*Preparation of the Quinolines* (IX).—An equimolar mixture (1 part) of the chroman-4-one and freshly prepared *o*-aminobenzaldehyde was stirred in ethanol (20 parts) containing EtONa (5%) at 20° for 2 h. The brown solution obtained was diluted with water, and the product was taken up in ether; the extracts were washed with water and dried, and the solvent was distilled off. The residue was purified first by chromatography on silica (elution with cyclohexane–benzene), then by crystallisation (yields, 20—30%).

*N.m.r. and Mass Spectra.*—N.m.r. spectra were recorded with a Varian A-60 spectrometer: 6*H*-[1]benzopyrano[4,3-*b*]quinoline (IX; R = H), δ($CDCl_3$) 5·3 (2H, d, $J_{6,7}$ 1 Hz, 6-$H_2$), 6·9—7·73 (6H, m, 2-, 3-, 4-, 8-, 9-, and 10-H), 7·77 (1H, d, 7-H), 8·0—8·27 (1H, m, 11-H), and 8·35—8·6 p.p.m. (1H, m, $J_{1,2}$ 7·5, $J_{1,3}$ 2 Hz, 1-H), δ ($CF_3$·$CO_2H$) 5·5 (2H, d, 6-$H_2$), 7·1—8·35 (9H, m), and 8·73 p.p.m. (1H, br s, 7-H).

The *mass spectra* were taken with an MS-9 (A.E.I.) spectrometer at 70 eV [direct insertion at 180° for compound (I; R = H) and 200° for compound (IX; R = H)].

2-*Chloro*[1]*benzothiopyrano*[4,3-b]*benzo*[e]*indole* (XIII; R = Cl).—6-Chlorothiochroman-4-one β-naphthylhydrazone [pale yellow needles, m.p. 129—130° (from cyclohexane)] was indolised in over 90% yield as before, to give 2-*chloro*-6,13-*dihydro*[1]*benzothiopyrano*[4,3-b]*benzo*[e]*indole* (XII; R = Cl) as brownish yellow leaflets from methanol, m.p. (inst.) 244° (gradual heating in the air produced a reddening above 190°, indicative of dehydrogenation) (Found: C, 70·9; H, 3·9; N, 4·2; S, 10·0. $C_{19}H_{12}ClNS$ requires C, 70·9; H, 3·8; N, 4·4; S, 10·0%). Dehydrogenation was achieved in 75% yield by briefly heating the blackish brown picrate in ethanol with picric acid in excess; recrystallisation from ethanol gave the *picrate* of (XIII; R = Cl), orange-red needles, m.p. (inst.) 293—295° (decomp. >230°) (Found: N, 10·1. $C_{25}H_{13}ClN_4O_7S$ requires N, 10·2%). The free *base* crystallised from benzene–cyclohexane as brown-red prisms, m.p. (inst.) 302—303° (decomp. >260°) (Found: C, 71·3; H, 3·3; N, 4·2. $C_{19}H_{10}ClNS$ requires C, 71·4; H, 3·2; N, 4·4%).

2-*Methoxy*[1]*benzothiopyrano*[4,3-b]*benzo*[e]*indole* (XIII; R = OMe).— 6-Methoxythiochroman-4-one β-naphthylhydrazone [pale yellow needles, m.p. 184—185° (from cyclohexane)], treated as before, furnished 6,13-*dihydro*-2-*methoxy*[1]*benzothiopyrano*[4,3-b]*benzo*[e]*indole* (XII; R = OMe), light ochre needles from cyclohexane, m.p. (inst.) 205° (gradual heating produced reddening above 185°) (Found: C, 75·7; H, 4·9; N, 4·3; S, 10·2. $C_{20}H_{15}NOS$ requires C, 75·7; H, 4·8; N, 4·4; S, 10·1%); *picrate*, black prisms from cyclohexane, m.p. (inst.) 168—169°; gradual heating produced lightening of the colour, denoting dehydrogenation to the *picrate* of the base (XIII; R = OMe), yellow microprisms, m.p. 296—300° (decomp. >245°) (from butanol) (Found: N, 10·3. $C_{26}H_{16}N_4O_8S$ requires N, 10·3%). The free *base* was obtained as red needles, m.p. 220° (from benzene–cyclohexane) (Found: C, 76·3; H, 4·3; N, 4·3. $C_{20}H_{13}NOS$ requires C, 76·2; H, 4·2; N, 4·4%).

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* See footnote, p. 1266.

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[10] N. P. Buu-Hoï and D.-P. Hien, *Biochem. Pharmacol.*, 1968, **17** 1227; 1969, **18**, 741.