Carcinogenic Nitrogen Compounds. Part LXX.[1] Polycyclic Naphthyridines By Means of the Ullmann–Fetvadjian Reaction

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The Ullmann–Fetvadjian condensation of arylamines with β-naphthol and paraformaldehyde has been successfully applied to 5-amino-2-methoxypyridine and 3-aminoquinoline, cyclisation taking place at positions 6 and 4, respectively, to give 10-methoxynaphtho[2,1-*b*][1,5]naphthyridine and benzo[*f*]naphtho[2,1-*b*][1,7]naphthyridine; 4-hydroxycoumarin gave with 5-amino-2-methoxypyridine and with 4-amino-2-methylquinoline the corresponding benzopyranonaphthyridines.

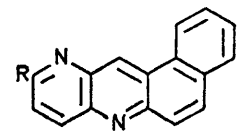
NAPHTHO[2,1-*b*][1,5]NAPHTHYRIDINE (I) and its derivatives are hitherto unknown; in view of the possibility that such compounds, which are isosteric with both benz[*a*]anthracenes and the angular benzacridines, are carcinogenic,[2] a synthesis of this new heterocyclic system was sought. An extension of the Ullmann-Fetvadjian benzacridine synthesis [3] to 5-amino-2-methoxypyridine proved successful. The aminopyridine reacted with β-naphthol and paraformaldehyde to furnish a product homogeneous on g.l.c. and t.l.c., which showed a u.v. spectrum resembling that of benz[*a*]acridine. Proof that this compound was 10-methoxynaphtho[2,1-*b*][1,5]-naphthyridine (II) (resulting from cyclisation at the pyridine 6-position) and not the isomeric[1,7]naphthyridine (IV) (cyclisation at the pyridine 4-position) was obtained from the n.m.r. spectrum (Varian A60 spectrometer; solvent CCl_4–$CDCl_3$; internal reference Me_4Si), which featured only one aromatic singlet (Table), corresponding to the *meso*-anthracenic proton; structure (IV) would require three aromatic singlets, corresponding to protons 8, 11, and 12. Although the reaction failed when α-naphthol was used in place of β-naphthol, with 4-hydroxycoumarin and the aminopyridine a normal Ullmann-Fetvadjian condensation product was obtained, which we assigned the structure (V), 9-methoxy-[1]benzopyrano[4,3-*b*][1,5]naphthyridin-6-one, by

[1] Part LXIX, N. P. Buu-Hoï, P. Jacquignon, and M. Mangane, *J. Chem. Soc.* (*C*), 1971, 1109.

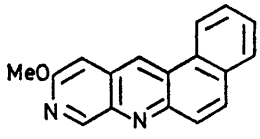
[2] *Cf.* A. Lacassagne, N. P. Buu-Hoï, R. Daudel, and F. Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

[3] F. Ullmann and A. Fetvadjian, *Ber.*, 1903, **36**, 1027; N. P. Buu-Hoï, *J. Chem. Soc.*, 1949, 670; 1950, 1146; 1951, 2871; *J. Chem. Soc.*, (*C*) 1967 213.

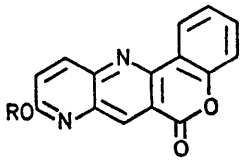
analogy with structure (II).* Both compounds (II) and (V) were readily demethylated by pyridine hydrochloride to give the corresponding hydroxy-compounds



(I) R = H
(II) R = OMe
(III) R = OH



(IV)



(V) R = Me
(VI) R = H

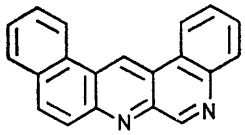
(III) and (VI). An attempt to prepare the unsubstituted heterocycle (I; R = H) from 3-aminopyridine gave no well defined product.

Chemical shifts (p.p.m.) of compound (II)

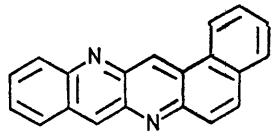
Signal	Protons
4·12 (s)	Me
7·13 (d, $J_{9,8}$ 9 Hz) *	9
7·53—7·9 (complex)	2,3,4,5,6
8·21—8·36 (*d*, $J_{8,9}$ 9 Hz)	8
8·63—8·8 (m)	1
9·23 (s)	12

* Strongly deshielded by MeO and by N in *meta*-position.

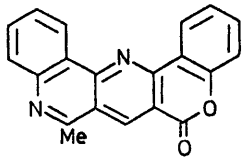
Whereas with 5-amino-2-methoxypyridine the Ullmann-Fetvadjian cyclisation takes place *ortho* to the ring nitrogen atom, with 3-aminoquinoline and β-naphthol it occurred at the *para*-position, to give benzo[*f*]naphtho[2,1-*b*][1,7]naphthyridine (VII),† which showed no band in the visible spectrum; had the reaction occurred at the *ortho*-position, the resulting isomeric compound (VIII) would absorb in the visible at least to the extent [6] of benzo[*a*]naphthacene and dibenz[*a*,*i*]acridine, which are both orange. This cyclisation at position 4 gave however only poor yields, and when 4-hydroxycoumarin was used in place of β-naphthol no trace of a naphthyridine derivative was obtained; the reverse trend was observed with 4-amino-2-methylquinoline, which gave no cyclised product with β-naphthol, whereas with 4-hydroxycoumarin, 8-methylbenzo[*h*][1]benzopyrano[4,3-*b*][1,6]naphthyridine-6-one (IX) was obtained in small yields. α-Naphthol was less reactive than either β-naphthol or 4-hydroxycoumarin, as no naphthyridine derivative was formed either with 3-aminoquinoline or with 4-amino-2-methylquinoline. The difficulty in bringing about Ullmann-Fetvadjian condensations with



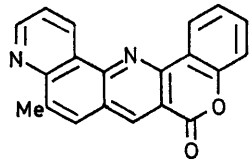
(VII)



(VIII)



(IX)



(X)

a pyridine ring to give naphthyridine derivatives is in sharp contrast with the ease with which such condensations occur with a benzene ring; thus, 5-amino-8-methylquinoline readily afforded 9-methyl[1]benzopyrano[4,3-*b*]pyrido[2,3-*h*]quinolin-6-one (X) with 4-hydroxycoumarin. This supports the notion that the Ullmann-Fedvadjian reaction involves an electrophilic substitution, which would occur more easily at sites of higher electron density.‡

Preliminary biological tests show the naphthyridine (VII) to have strong inducing activity in the biosynthesis of zoxazolamine hydroxylase in rats,§ compound (II) to be only weakly active, and (III) to be completely inactive in this respect. Since carcinogenic compounds are generally excellent enzyme inducers in this test,[9] the naphthyridine (VII) is being assayed for carcinogenicity; results will be reported elsewhere.

EXPERIMENTAL

10-*Methoxynaphtho*[2,1-b][1,5]*naphthyridine* (II).—To a boiling mixture of β-naphthol (1·5 g) and 5-amino-2-methoxypyridine (1·25 g), paraformaldehyde (0·45 g) was added in small portions, and once the vigorous reaction had subsided the product was fractionated *in vacuo*. The portion boiling at *ca.* 250° at 11 mmHg was treated

* The preferential cyclisation at the pyridine 2-position rather than the 4-position is also in line with the higher electron density at the former site.[4]

† Although the unsubstituted compound was not previously known, its 14-chloro-6-phenyl and 14-phenoxy-6-phenyl derivatives had been prepared by a different method.[5]

‡ Nucleophilic substitution on quinolines takes place exclusively at positions 2 and 4 in the pyridine ring, *i.e.* at the positions of lowest π-electron density.[7]

§ The corresponding dibenz[*a*,*j*]acridine is highly active in this test.[8]

[4] *Cf.* C. A. Coulson and H. C. Longuet-Higgins, *Rev. scientifique*, 1947, **85**, 935.
[5] M. Colonna, *Boll. sci. fac. Chim. ind. Bologna*, 1948, **6**, 26.
[6] *Cf.* G. M. Badger, 'Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings,' ed. C. F. H. Allen, Interscience, New York, 1958, p. 551.
[7] See, for instance, R. Daudel, P. Daudel, N. P. Buu-Hoï, and M. Martin, *Bull. soc. chim. France*, 1948, **15**, 1202.
[8] N. P. Buu-Hoï and D.-P. Hien, *Compt. rend.*, 1967, *D*, **264**, 153.
[9] N. P. Buu-Hoï and D.-P. Hien, *Biochem. Pharmacol.*, 1969, **18**, 741.

with ethanol, and a brown insoluble residue was filtered off. The filtrate was concentrated, and the solid obtained on cooling was recrystallised from ethanol, giving the *naphthyridine* (II), as yellowish needles (1 g), m.p. 157°, showing deep yellow halochromism in sulphuric acid (Found: C, 78·2; H, 4·4; N, 10·7. $C_{17}H_{12}N_2O$ requires C, 78·5; H, 4·6; N, 10·7%). The *picrate* formed yellow microprisms, m.p. 249° (decomp. >180°) (from toluene) (Found: N, 14·4. $C_{23}H_{15}N_5O_8$ requires N, 14·3%). The purity of compound (II) was verified by t.l.c. (on silica) and g.l.c.

10-*Hydroxynaphtho*[2,1-b][1,5]*naphthyridine* (III).—A mixture of the methoxy-compound (II) (0·5 g) and freshly redistilled anhydrous pyridine hydrochloride (3 g) was heated under reflux for 5 min; the cooled product was treated with 1% aqueous acetic acid, and the precipitate was washed with water, dried, and purified by sublimation *in vacuo*. The *hydroxy-compound* (III) crystallised as pale yellow microneedles (0·3 g), m.p. 370° (from toluene) (Found: C, 78·1; H, 4·9; N, 11·3. $C_{16}H_{10}N_2O$ requires C, 78·1; H, 4·9; N, 11·4%). It gave a greenish yellow halochromism in sulphuric acid, but did not form a picrate.

9-*Methoxy*[1]*benzopyrano*[4,3-*b*][1,5]*naphthyridin*-6-*one* (V).—To a mixture of 4-hydroxycoumarin (3·15 g) and 5-amino-2-methoxypyridine (2·5 g) heated at *ca.* 220°, paraformaldehyde (0·9 g) was added in small portions, and the product was distilled *in vacuo*. The reddish resin obtained, b.p. >300°/11 mm, was triturated with ethanol, and the solid product was recrystallised twice from ethanol–benzene (1 : 1), to give the *naphthyridine* (V) as pale yellow needles (1 g), m.p. 231°, showing yellow halochromism in sulphuric acid, and giving no picrate (Found: C, 68·4; H, 3·8; N, 9·8. $C_{16}H_{10}N_2O_3$ requires C, 68·6; H, 4·0; N, 10·0%). 9-*Hydroxy*[1]*benzopyrano*[4,3-b][1,5]*naphthyridin*-6-*one*, (VI), prepared in almost quantitative yield from the foregoing methoxy-compound with pyridine hydrochloride, was purified by sublimation *in vacuo*, and formed pale yellow needles, m.p. >370° (Found: C, 68·2; H, 3·8; N, 10·5. $C_{15}H_8N_2O_3$ requires C, 68·2; H, 3·8; N, 10·6%).

Benzo[f]*naphtho*[2,1-b][1,7]*naphthyridine* (VII).—An Ullmann-Fetvadjian reaction with 3-aminoquinoline (3 g), β-naphthol (3 g), and paraformaldehyde (0·9 g) afforded a product which, on distillation *in vacuo*, gave a yellow resin, b.p. >300° at 0·1 mmHg. This solidified on trituration with butanol; the solid was recrystallised from benzene–butanol (1 : 1) to give the *naphthyridine* (VII) [10] as pale yellow needles (0·9 g), m.p. 215°, showing orange halochromism in sulphuric acid (Found: C, 85·5; H, 4·5; N, 9·7. $C_{20}H_{12}N_2$ requires C, 85·7; H, 4·3; N, 10·0%), $\nu_{max.}$ (EtOH) 228 (ε 24,700), 296 (29,411), 360 (5882), 380 (6470), and 400 nm (7058); *picrate*, yellow prisms, m.p. 245° (decomp. >210°) (from toluene) (Found: N, 13·5. $C_{26}H_{15}N_5O_7$ requires N, 13·8%).

8-*Methylbenzo*[h][1]*benzopyrano*[4,3-b][1,6]*naphthyridin*-6-*one* (IX).—The Ullmann-Fetvadjian reaction with 4-amino-2-methylquinoline (3 g), 4-hydroxycoumarin (3·2 g), and paraformaldehyde (0·45 g) furnished, on distillation of the product *in vacuo*, a portion boiling at *ca.* 320° at 0·5 mmHg, which gave the *naphthyridine* (IX) as yellow, sublimable needles (1 g), m.p. 306° (from butanol), showing greenish-yellow halochromism in sulphuric acid (Found: C, 76·7; H, 3·9; N, 8·7. $C_{20}H_{12}N_2O_2$ requires C, 76·9; H, 3·9; N, 9·0%). This compound did not give a picrate.

9-*Methyl*[1]*benzopyrano*[4,3-b]*pyrido*[2,3-*h*]*quinolin*-6-*one* (X).—Similarly prepared from 5-amino-8-methylquinoline (1·5 g), 4-hydroxycoumarin (1·6 g), and paraformaldehyde (0·4 g), this *quinoline*, b.p. >360° at 11 mmHg, crystallised from butanol–xylene (1 : 1) as pale yellow needles (0·7 g), m.p. 327°, giving a yellow halochromism in sulphuric acid (Found: C, 76·6; H, 4·2; N, 9·3%).

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[10] For orientation in the Skraup cyclisation of 3-aminoquinoline, see N. P. Buu-Hoï, R. Royer, and M. Hubert-Habart, *J. Chem. Soc.*, 1956, 2048.