Carcinogenic Nitrogen Compounds. Part LXXIV.[1] Skraup and Combes–Beyer Reactions with 3-Aminocarbazoles; a New Route to Pyrido-[3,2′-*b*]carbazoles

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3-Amino-9-ethyl- and 3-amino-9-ethyl-6-methyl-carbazole follow Marckwald's rule in the Skraup reaction, to give derivatives of 7*H*-pyrido[2,3-*c*]carbazole; in contrast, the same amines undergo anti-Marckwald cyclisations in the Combes–Beyer reaction, to give derivatives of the linear 6*H*-pyrido[3,2-*b*]carbazole, which are analogues of the carcinostatic alkaloid ellipticine.

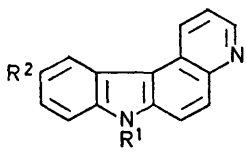
SEVERAL derivatives of the angular benzocarbazoles[2] and benzocarbolines[3] are carcinogenic and it was of interest to prepare, for carcinogenesis studies, the similarly built 7*H*-pyrido[2,3-*c*]carbazole (I) and some of its homologues. If the Skraup reaction were to follow Marckwald's rule (*i.e.* cyclisation on both ends of a

[1] Part LXXIII, N. P. Buu-Hoï, O. Périn-Roussel, and P. Jacquignon, *J.C.S. Perkin I*, 234, 1972.

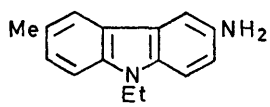
[2] O. Schürch and A. Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79; A. Lacassagne, N. P. Buu-Hoï, R. Royer, and F. Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635.

[3] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, O. Périn-Roussel, P. Jacquignon, F. Périn, and J.-P. Hoeffinger, *Compt. rend.*, 1970, **271** *D*, 1474.

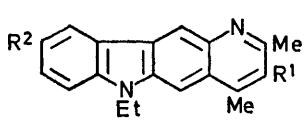
double bond [4]), then 3-aminocarbazoles would be convenient intermediates in these syntheses. 3-Amino-9-ethylcarbazole did indeed afford 7-ethyl-7*H*-pyrido-[2,3-*c*]carbazole (II), and de-ethylation with sulphur at 300° [5] resulted in compound (I), which was identical with the product previously synthesised by Clemo and



(I) $R^1 = R^2 = H$
(II) $R^1 = Et, R^2 = H$
(III) $R^1 = Et, R^2 = Me$

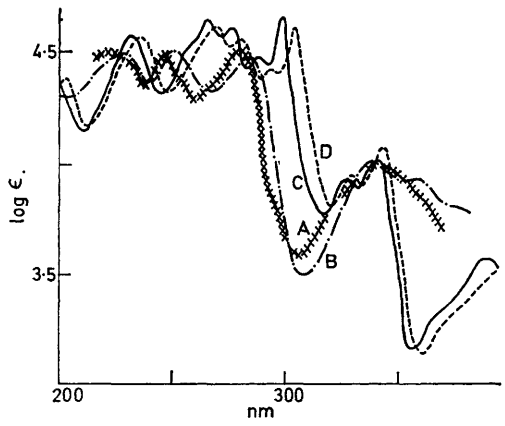


(IV)



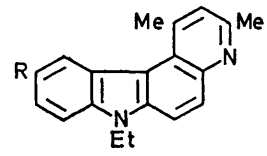
(V) $R^1 = R^2 = H$
(VI) $R^1 = H, R^2 = Me$
(VII) $R^1 = Me, R^2 = H$
(VIII) $R^1 = R^2 = Me$

Felton in two steps from cyclohexanone 6-quinolylhydrazone.[6] The u.v. absorption and n.m.r. spectra also support the angular structures (I) and (II). 3-Amino-9-ethyl-6-methylcarbazole (IV), readily prepared *via* a Beckmann rearrangement of the oxime of 3-acetyl-9-ethyl-6-methylcarbazole, underwent a Skraup reaction to give also the expected angular 7-ethyl-10-methyl-7*H*-pyrido[2,3-*c*]carbazole (III).

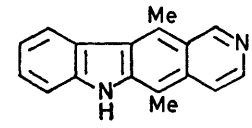


U.v. spectra of pyridocarbazoles in ethanol: (A) (II); (B) (III); (C) (V); (D) (VI)

In order to prepare polymethylated derivatives of compound (I), 3-amino-9-ethylcarbazole and its homologue (IV) were submitted to Combes–Beyer reactions, *i.e.* cyclisation of the intermediary imines obtained with acetylacetone.[7] Whereas sulphuric acid (as used originally) proved unsuitable for these cyclisations because of its sulphonating power, polyphosphoric acid was employed with success, and gave two compounds which, surprisingly, proved to be derivatives (V) and (VI) of the linear pyrido[3,2-*b*]carbazole, as shown by n.m.r. and u.v. spectra. The u.v. absorptions of compounds (V) and (VI) reveal a considerable bathochromic shift compared with the corresponding isomers (II) and (III) (see Figure), as would be expected from the linear structures postulated. The aromatic portion of the n.m.r. spectrum of compound (V) comprised, apart from the 3-proton singlet, a further singlet corresponding to the highly deshielded 11-proton (*peri*-effect exerted by the pyridine nitrogen atom) which would not arise from the alternative angular structure (IX); the same holds for compound (VI), whose spectrum is



(IX) R = H
(X) R = Me



(XI)

consistent with the linear structure (VI) and not with (X). The Table lists the n.m.r. characteristics of these substances and their angular analogues (II) and (III).

Chemical shifts [a] of characteristic protons (δ in p.p.m. from tetramethylsilane)

Compound (II)		Compound (III)	
Signal	Protons	Signal	Protons
1·35 (t)	Me of Et	1·38 (t)	Me of Et
4·28 (q)	CH_2 of Et	2·59 (s)	10-Me
7·12—7·74 (m)	2-, 6-, 8-, 9-, 10-H	4·32 (q)	CH_2 of Et
		7·31—7·80 (m)	2-, 6-, 8-, 9-H
8·03—8·45 (m)	5-, 11-H	8·05—8·20 (m)	5-, 11-H
8·80—8·96 (m)	1-, 3-H [b]	8·83—8·95 (m)	1-, 3-H

Compound (V)		Compound (VI)	
1·41 (t)	Me of Et	1·41 (t)	Me of Et
2·70 (s)	2-, 4-Me	2·58 (s)	9-Me
4·30 (q)	CH_2 of Et	2·70 (s)	2-, 4-Me
7·08 (s)	3-H	4·38 (q)	CH_2 of Et
7·22—7·58 (m)	5-, 7-, 8-, 9-H	7·15—7·60 (m)	3-, 5-, 7-, 8-H
8·20 (m)	10-H	8·05 (s)	10-H
8·75 (s)	11-H	8·70 (s)	11-H

[a] Solutions in $CDCl_3$; Varian 60-T spectrometer. [b] Protons deshielded by the pyridine nitrogen,[8] 1-H being further deshielded by its angular position.[9]

The difference in orientation observed between the Skraup reaction and the Combes–Beyer cyclisation could be ascribed to a steric effect, as molecular models of structures (IX) and (X) show an overlapping of the methyl group at position 1 and the hydrogen atom at

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[8] *Cf.* R. H. Martin and F. Geerts-Evrard, *Tetrahedron*, 1964, **20**, 1495.

[9] *Cf.* N. P. Buu-Hoï, G. Saint-Ruf, and J.-C. Perche, *Bull. Soc. chim. France*, 1967, 4126.

position 11. When 3-methylpentane-2,4-dione was used in the Combes–Beyer reaction this steric effect was further enhanced, and the resulting compounds can be safely assumed to have the linear structures (VII) and (VIII), on the grounds of their u.v. spectra.

The various 6-ethyl-6*H*-pyrido[3,2-*b*]carbazoles reported here are analogues of the alkaloid ellipticine (XI), a derivative of 6*H*-pyrido[4,3-*b*]carbazole known to possess strong anticancer properties. Compounds (V)—(VIII) are being tested for possible carcinostatic activity.

EXPERIMENTAL

7-Ethyl-7H-pyrido[2,3-c]*carbazole* (II).—To a stirred mixture of freshly redistilled nitrobenzene (37·5 g), glycerol (44·5 g), and 3-amino-9-ethylcarbazole (20 g), heated at 160°, sulphuric acid (25 g) was added in portions. The deep green mixture thus obtained was maintained at the same temperature for 4½ h more, then left to cool and poured on ice. The nitrobenzene was removed by steam-distillation, and the residue was made basic with ammonia and extracted into toluene. The solid obtained after removal of the toluene was purified by distillation *in vacuo*, and the portion boiling at 293° and 27 mmHg was recrystallised from ethanol, giving *compound* (II) (16%), as prisms, m.p. 125—126° (Found: C, 82·8; H, 5·8; N, 11·4. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%). The *picrate* formed brown microprisms, m.p. 279° (decomp. >250°) (from *o*-dichlorobenzene) (Found: N, 14·9. $C_{23}H_{17}N_5O_7$ requires N, 14·7%).

7H-Pyrido[2,3-c]*carbazole* (I).—An intimate mixture of compound (II) (1 g) and sulphur (1 g) was heated for 1 h at 300° in a metal bath. Copper powder (0·5 g) was then added, and heating was continued for a further 15 min. Sublimation *in vacuo* of the product afforded compound (I), crystallising as needles (0·3 g), m.p. 211° (from benzene), identical with a sample (m.p. 211°) prepared by Clemo and Felton's method.[6] The *picrate* formed yellow prisms, m.p. 276° (lit.,[6] 275°) (from aqueous ethanol).

3-Amino-9-ethyl-6-methylcarbazole (IV).—A solution in a mixture of anhydrous benzene and pyridine (9 : 1) of the oxime of 3-acetyl-9-ethylcarbazole[10] (m.p. 215°; 50 g) was treated in portions during 1 h with finely powdered phosphorus pentachloride (55 g), with vigorous stirring and at 0°. After 30 min at room temperature, the mixture was poured on ice and left overnight. The solid which formed was washed with dilute aqueous sodium carbonate, then with water, dried, and recrystallised from acetic acid to give *3-acetamido-9-ethyl-6-methylcarbazole* (41 g), needles, m.p. 211° (Found: N, 10·6. $C_{17}H_{18}N_2O$ requires N, 10·5%). A suspension of this amide (30 g) in ethanolic 10% potassium hydroxide (300 ml) was heated under reflux for 10 h. The ethanol was distilled off, and the residue was treated with water; the solid obtained was recrystallised from ethanol to give the *amine* (IV) as cream-coloured needles (22 g), m.p. 106° (Found: C, 80·0; H, 7·2; N, 12·8. $C_{15}H_{16}N_2$ requires C, 80·3; H, 7·2; N, 12·5%).

7-Ethyl-10-methyl-7H-pyrido[2,3-c]*carbazole* (III).—This compound, obtained from the foregoing amine (36 g) as for (II) and in excellent yield, had b.p. 283—284° at 17 mmHg, and crystallised as microprisms, m.p. 146° (from ethanol) (Found: C, 82·9; H, 6·2; N, 10·8. $C_{18}H_{16}N_2$ requires C, 83·0; H, 6·2; N, 10·8%); *picrate*, brick red microprisms, m.p. 275° (from *o*-dichlorobenzene) (Found: C, 59·1; H, 4·0; N, 13·9. $C_{24}H_{19}N_5O_7$ requires C, 58·9; H, 3·9; N, 14·3%).

Combes–Beyer Reactions with 3-Amino-9-ethylcarbazole.—(a) *In sulphuric acid.* The amine (10 g) was heated for 3 h with pentane-2,4-dione (5·2 g) and the resulting anil was treated with sulphuric acid (85 g) at 5°. The mixture was heated at 95° (30 min) and then treated with ice; the precipitate was washed with dilute aqueous sodium hydroxide and recrystallised from pyridine to give a yellow microcrystalline powder (10 g), m.p. >370°, probably a sulphonation product of (V).

(b) *In polyphosphoric acid.* A mixture of the crude anil obtained as in (a) (10 g) and polyphosphoric acid [from 85% orthophosphoric acid (35 ml) and phosphorus pentoxide (40 g)] was stirred at 110° for 45 min; cooling and treatment with ice gave a solid, which was washed with aqueous ammonia and extracted into benzene. The residue from evaporation of the extract was distilled *in vacuo*. *6-Ethyl-2,4-dimethyl-6H-pyrido*[3,2-b]*carbazole* (V) (b.p. *ca.* 283° at 17 mmHg) formed faintly yellow prisms (4 g), m.p. 149° (from hexane) (Found: C, 82·9; H, 6·7; N, 9·9. $C_{19}H_{18}N_2$ requires C, 83·2; H, 6·6; N, 10·2%). The *picrate* formed yellow prisms, m.p. 295° (from chlorobenzene) (Found: C, 59·8; H, 4·3; N, 13·6. $C_{25}H_{21}N_5O_7$ requires C, 59·7; H, 4·2; N, 13·9%). *6-Ethyl-2,3,4-trimethyl-6H-pyrido*[3,2-b]*carbazole* (VII) was similarly prepared from the anil (m.p. 103°; 4·5 g) obtained from 3-methylpentane-2,4-dione[11] (2·7 g) and 3-amino-9-ethylcarbazole (5 g); it former prisms (3·2 g), m.p. 169—170° (from cyclohexane) (Found: C, 83·2; H, 7·1; N, 9·9. $C_{20}H_{20}N_2$ requires C, 83·3; H, 7·0; N, 9·7%) $\lambda_{max.}$ 235 (ε 41,690), 265 (42,170), 276 (35,890), 288 (29,180), 299 (48,980), 329 (8512), 342 (10,470), 384 (3589), and 403 (3126) nm; *picrate*, ochre yellow microprisms, m.p. 293° (from chlorobenzene) (Found: N, 13·8. $C_{26}H_{23}N_5O_7$ requires N, 13·5%).

Combes–Beyer Reactions with 3-Amino-9-ethyl-6-methylcarbazole (IV).—Only technique (b) was used here. With pentane-2,4-dione, a 65% yield was obtained of *6-ethyl-2,4,9-trimethyl-6H-pyrido*[3,2-b]*carbazole* (VI), b.p. 302° at 22 mmHg, needles, m.p. 138° (from cyclohexane) (Found: C, 83·6; H, 6·9; N, 9·4%); *picrate*, yellow microprisms, m.p. 295° (from chlorobenzene) (Found: N, 13·5%). With 3-methylpentane-2,4-dione [corresponding anil, needles, m.p. 131° (from benzene)], *6-ethyl-2,3,4,9-tetramethyl-6H-pyrido*[3,2-b]*carbazole* (VIII) * was obtained as needles, m.p. 192° (from cyclohexane) (Found: C, 83·2; H, 7·3; N, 9·2. $C_{21}H_{22}N_2$ requires C, 83·4; H, 7·3; N, 9·3%) $\lambda_{max.}$ 237 (ε 46,240), 268 (44,670), 280 (33,890), 292 (28,510), 304 (47,870), 330 (25,120), 345 (13,650), 391 (3389), and 409 (2951) nm; *picrate*, yellow microprisms, m.p. 309—310° (from chlorobenzene) (Found: N, 13·4. $C_{27}H_{25}N_5O_7$ requires N, 13·2%).

This work was supported by l'Institut National de la Santé et de la Recherche Médicale (Director Prof. C. Burg) and by the Régie Nationale des Tabacs (S.E.I.T.A.).

[1/1505 *Received, August 18th*, 1971]

* The non-substituted heterocyclic system from which this and the previous compounds are derived was synthesised *via* an elaborate method by M. Kulka and R. H. F. Manske (*Canad. J. Chem.*, 1952, **30**, 712).

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