Synthesis of Potential Antineoplastic Agents. XXV. Approaches to the Pyridocarbazole System

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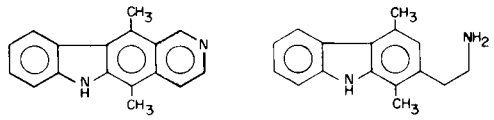
Received February 24, 1975

The indolization of cyanomethylphenylhydrazines provides a convenient route to cyanomethylcarbazoles. These cyanomethylcarbazoles provide an important entry to the pyridocarbazole system including ellipticine.

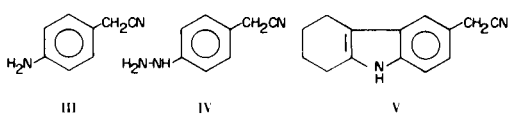
There is continuing interest in the antineoplastic activity of the alkaloid ellipticine (I) (1), and a number of syntheses of this compound have appeared (2). We wish to report on attempts to develop synthetic routes that could be used to readily prepare analogues of this 6*H*-pyrido[4,3-*b*]-carbaozle system.



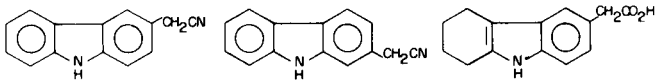
I II

Govindachari and co-workers (3) have synthesized ellipticine (I) by cyclization of the formyl derivative of the β-aminoethylcarbazole II followed by dehydrogenation and Manske and Hulka (4) have reported the conversion of various cyanomethylcarbazoles to the corresponding β-aminoethylcarbazoles. With this in mind we set out to attempt to develop convenient synthetic routes to cyanomethylcarbazoles.

4-Aminobenzylcyanide (III) was converted to the hydrazine IV. Reaction of IV with cyclohexanone in refluxing glacial acetic acid gave 5,6,7,8-tetrahydrocarbazole-3-acetonitrile (V) which was dehydrogenated with palladium on carbon in refluxing xylene to give 3-cyanomethylcarbazole (VI) which had been previously (4) reduced to the corresponding 3-(β-aminoethyl)carbazole. In a similar sequence of reactions 3-aminobenzylcyanide was converted to 2-cyanomethylcarbazole (VII) which had previously (4) been reduced to 2-(β-aminomethyl)carbazole. The acid VIII has been obtained from 4-aminophenylacetic acid in a similar sequence.

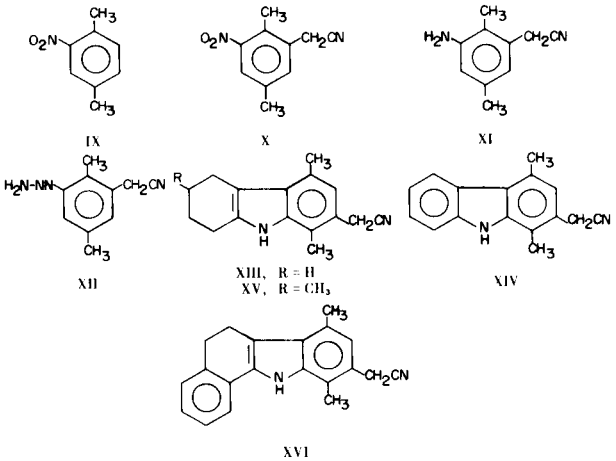


III IV V



VI VII VIII

In view of the convenience of this indolization route to precursors of the pyridocarbazole system, 2,5-dimethylnitrobenzene (IX) was reacted with chlorosulfonic acid and paraformaldehyde to give the cyanomethyl compound X. Catalytic hydrogenation of X gave the amine XI which was converted through its diazonium salt to 3-cyanomethyl-2,5-dimethylphenylhydrazine (XII). This hydrazine was used directly, without purification, in the indole synthesis. Refluxing XII with cyclohexanone in glacial acetic acid saturated with hydrogen chloride gave XIII which was dehydrogenated to the cyanomethylcarbazole XIV which could be reduced (4) to II which had previously (3) been converted to ellipticine (I). The generality of this procedure as a potential route to analogues of ellipticine was demonstrated by the reaction of 4-methylcyclohexanone and α-tetralone with XII to give XV and XVI respectively.

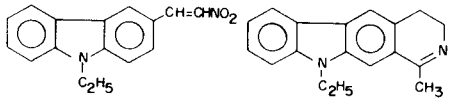


IX X XI

XII XIII, R = H XV, R = CH_3 XIV

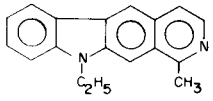
XVI

In another synthesis of a pyridocarbazole, *N*-ethyl-3-carbazolecarboxaldehyde was reacted with nitromethane to give the nitrovinylcarbazole XVII. Compound XVII was reduced, acetylated, and the amide formed cyclized with phosphorus oxychloride. Structure XVIII rather than the isomeric, non-linear, structure is assigned to XVIII on the basis of analogy to earlier work (5). Dehydrogenation of XVIII gave the pyridocarbazole XIX.



XVII

XVIII



XIX

EXPERIMENTAL (6)

4-Hydrazinophenylacetonitrile (IV).

A solution of 5.61 g. of 4-aminobenzyl cyanide (III) in 105 ml. of concentrated hydrochloric acid and 150 ml. of water was cooled and 3.30 g. of sodium nitrite in 35 ml. of water was added dropwise with stirring at 0-5°. After the addition was complete, the diazonium salt was added to 37.0 g. of stannous chloride dihydrate in an ice-water slurry. After standing overnight in the cold the mixture was saturated with hydrogen sulfide and filtered and the residue washed with warm water. The wash and filtrate were made basic with potassium hydroxide and extracted with methylene chloride. The dried (magnesium sulfate) extract was evaporated to give 3.94 g. of IV, m.p. 68-70° from ethanol-hexane; ir (potassium bromide): 3390, 3360, 2250 cm^{-1}.

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16. Found: C, 65.26; H, 6.17.

5,6,7,8-Tetrahydrocarbazole-3-acetonitrile (V).

A mixture of 2.50 g. of IV, 1.67 of cyclohexanone, and 40 ml. of glacial acetic acid was refluxed with stirring for 1 hour, cooled, and diluted with water. Filtration gave 3.05 g. of V, m.p. 85-86° from carbon tetrachloride; ir (potassium bromide): 3400, 2260 cm^{-1}; nmr (deuteriochloroform); 1.86 (4H), 2.66 (4H), 3.76 (2H), 6.86-7.52 (3H), 7.96 δ (1H).

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.98; H, 6.67; N, 13.37.

3-Cyanomethylcarbazole (VI).

A mixture of 4.08 g. of V, 0.60 g. of 10% palladium on carbon and 80 ml. of decahydronaphthalene was refluxed under nitrogen with stirring for 17 hours and filtered hot. The residue was washed with hot decalin and on cooling 2.45 g. of material were collected by filtration, m.p. 164-166° (after chromatography); reported (4) m.p. 168-169°.

2-Cyanomethylcarbazole (VII).

This compound, m.p. 190-191°, reported (4) m.p. 193-194° was prepared by a procedure similar to the preparation of VI but without purification of the intermediates.

5,6,7,8-Tetrahydrocarbazole-3-acetic Acid (VIII).

A mixture of 2.25 g. of 4-hydrazinophenylacetic acid hydrochloride, 1.09 g. of cyclohexanone, and 80 ml. of glacial acetic acid was stirred at reflux for 3 hours, allowed to cool and poured into water. Filtration gave 1.91 g. of VIII (7), m.p. 145-150° (sealed capillary) from ethanol; ir (potassium bromide): 3415, 1700 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.60; N, 6.11. Found: C, 73.02; H, 6.74; N, 6.00.

3-Cyanomethyl-2,5-dimethylnitrobenzene (X).

To a mixture of 25.0 g. of 2,5-dimethylnitrobenzene (IX) and 25.0 g. of paraformaldehyde was added with stirring at 10°, 56 ml. of chlorosulfonic acid. Sodium chloride (10 g.) was added and the mixture was allowed to stir overnight. The mixture was cautiously added to ice-water and extracted with chloroform. The washed (aqueous sodium bicarbonate) and dried (potassium carbonate) extract was distilled to give 13.8 g. of product, b.p. (2 mm) 140-142°; ir (potassium bromide): 1535, 1350, 730 cm^{-1}; mass spectrum; 201 and 199. This compound was also prepared in poorer yield, from IX, bis(chloromethyl) ether and chlorosulfonic acid.

A mixture of 10.0 g. of the above chloromethyl compound, 6.50 g. of potassium cyanide, 100 ml. of ethanol, and 30 ml. of water was refluxed for 2.5 hours, allowed to cool and poured into 200 ml. of water. The solution was extracted with chloroform and the dried (potassium carbonate) extract evaporated to give 8.63 g. of X, m.p. 93-97° from carbon tetrachloride; ir (potassium bromide): 2250, 1525, 1340 cm^{-1}; nmr (deuteriochloroform): 2.4 (6H), 3.8 (2H), 7.5-7.76 δ (2H).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.33; H, 5.17; N, 14.61.

3-Cyanomethyl-2,5-dimethylaniline (XI).

A solution of 8.5 g. of crude X in 150 ml. of absolute methanol was hydrogenated at 45 psi in the presence of 0.30 g. of platinum oxide (the catalyst being added in 3 portions during the reduction). The methanol was evaporated and the residue dissolved in chloroform. The chloroform was extracted with dilute hydrochloric acid and the acid extracts made basic with ammonium hydrochloride. The basic solution was extracted iwth chloroform and the dried (potassium carbonate) extracts were evaporated to give 5.35 g. of XI, m.p. 94-100° from carbon tetrachloride; ir (potassium bromide): 3500, 3400, 3250 cm^{-1}; nmr (deuteriochloroform): 2.06(3), 2.25(3), 3.64(4), 6.54-6.88 (2H).

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55. Found: C, 75.05; H, 7.46.

2-Cyanomethyl-1,4-dimethyl-5,6,7,8-tetrahydrocarbazole (XIII).

To a solution of 4.82 g. of crude XI in 105 ml. of concentrated hydrochloric acid and 150 ml. of water was added dropwise with stirring at 0-5°, 3.30 g. of sodium nitrite in 35 ml. of water. After the addition was complete the diazonium salt was added to 37.0 g. of stannous chloride dihydrate. This was worked up as described for the preparation of IV to give 2.36 g. of XII, m.p. 100-106°; ir (potassium bromide): 3330, 2250 cm^{-1}.

A mixture of 2.53 g. of crude freshly prepared XII, 1.42 g. of cyclohexanone and 59 ml. of glacial acetic acid was saturated with hydrogen chloride and refluxed for ten minutes. After cooling the mixture was poured in cold water and filtered to give 1.73 g. of XIII, m.p. 185-204° from benzene; ir (potassium bromide): 3400, 2280 cm^{-1}; nmr (DMSO-d_6 and deuteriochloroform): 1.68-3.26 (14), 3.8 (2H), 6.76 (1H), 10.35 δ (1H).

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.77; H, 7.52; N, 11.85.

2-Cyanomethyl-1,4,6-trimethyl-5,6,7,8-tetrahydrocarbazole (XV).

Using the same procedure as for the preparation of XIII, 2.50 g. of crude freshly prepared XII, 1.60 g. of 4-methylcyclohexanone and 65 ml. of glacial acetic acid saturated with hydrogen chloride gave 2.10 g. of XV, m.p. 228-237° from benzene; ir (potassium bromide): 3370, 2250 cm^{-1}.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.94; H, 7.92; N, 11.08.

9-Cyanomethyl-7,10-dimethyl-5,6-dihydro-11*H*-benzo[*a*]carbazole (XVI).

Using the same procedure as for the preparation of XIII, 2.14 g. of crude freshly prepared XII, 1.80 g. of α-tetralone, and 48 ml. of glacial acetic acid gave after chromatography on alumina (benzene chloroform 1:3) 0.97 g. of XVI, m.p. 187-188° from benzene; ir (potassium bromide): 3440, 2260 cm^{-1}; nmr (deuteriochloroform): 2.46 (3H), 2.68 (3H), 3.16 (4H), 3.78 (2H), 6.88-7.66 (5H), 8.0-8.64 δ (1H).

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.02; H, 6.26; N, 9.68.

2-Cyanomethyl-1,4-dimethylcarbazole (XIV).

A mixture of 3.22 g. of XIII, 1.10 g. of 10% palladium on carbon, and 70 ml. of distilled quinoline was heated under nitrogen with stirring at 210° for 24.5 hours. The mixture was filtered warm and the residue washed with a large volume of chloroform. The filtrate and washings were combined, washed (dilute hydrochloric acid), dried (potassium carbonate) and evaporated. Chromatography on alumina (benzene-chloroform 1:1) of the residue gave 1.11 g. of XIV, 226-231° from benzene; ir (potassium bromide): 3340 cm^{-1}; nmr (DMSO-d_6): 2.72 (3H), 2.96 (3H), 4.30 (2H), 7.0-8.8 (5H), 11.68 δ (1H).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.21; H, 6.02; N, 11.79.

Compound XIV was reduced (4) to II which had previously (3) been converted to ellipticine (I).

N-Ethyl-3(β-nitrovinyl)carbazole (XVII).

A mixture of 5.00 g. of *N*-ethyl-3-carbazolecarboxaldehyde, 2.50 g. of ammonium acetate, and 10 ml. of nitromethane was refluxed for 1.75 hours. The warm mixture was poured into water and filtered to give after recrystallization from benzene ethanol 2.75 g. of XVII, m.p. 135-137°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: N, 10.52. Found: N, 10.41.

10-Ethyl-1-methyl-3,4-dihydropyrido[3,4-*b*]carbazole (XVIII).

A solution of 5.50 g. of XVII in 90 ml. of tetrahydrofuran was added gradually with stirring to 6.0 g. of lithium aluminum hydride in 135 ml. of tetrahydrofuran. The mixture was refluxed for 5.5 hours and ethyl acetate and then water added. Following filtration, the dried (potassium carbonate) solvent was evaporated to give 3.88 g. of *N*-ethyl-3(β-aminoethyl)carbazole.

A mixture of 3.88 g. of the aminoethyl compound, 10 ml. of acetic anhydride, and 4 ml. of glacial acetic acid was heated on the steam bath for 1.25 hours. After addition of 100 ml. of water heating was continued for 3 hours, the mixture was cooled and 15 g. of potassium hydroxide in water was added. The mixture was extracted with chloroform and the extract washed (water), dried (potassium carbonate), and evaporated to give 4.03 g. of the acetyl derivative; ir (potassium bromide): 3275, 1640 cm^{-1}.

To a solution of 4.0 g. of the acetyl derivative in 175 ml. of warm anhydrous toluene was added 15 ml. of phosphorus oxychloride and the solution was refluxed for 20 minutes. After distillation of the solvent, the residue was extracted with boiling dilute hydrochloric acid. The extracts were made basic and extracted with chloroform. Evaporation of the dried (potassium carbonate) chloroform extract gave after chromatography on alumina (ethyl acetate) 0.94 g., m.p. 149-152° from benzene; nmr (deuteriochloroform): 1.2-1.66 (3H), 2.5-2.68 (3H), 2.68-3.14 (2H), 3.6-4.0 (2H), 4.0-4.68 (2H), 7.14-8.32 δ (6H).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.32; H, 6.85; N, 10.69.

10-Ethyl-1-methylpyrido-3,4-*b*]carbazole (XIX).

A thoroughly powdered 0.45 g. of XVIII and 0.45 g. of 10% palladium on carbon were mixed and heated under nitrogen to 200° for 65 minutes. Vacuum sublimation at 200° gave 0.22 g. of XIX, m.p. 180-182° from benzene; nmr (deuteriochloroform): 1.2-1.6 (3H), 3.08 (3H), 4.0-4.6 (2H), 7.24-8.56 δ (8H). Mass Spect. 260.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.02; H, 6.19; N, 10.82.

Acknowledgments.

This work was supported in part by a grant (Cl-90A) from the American Cancer Society.

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(2) See F. LeGoffic, A. Gouyette, and A. Ahond, *Tetrahedron*, 29, 3357 (1973) and references therein.

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(5) R. H. F. Manske and M. Kulka, *J. Am. Chem. Soc.*, 72, 4997 (1950).

(6) All melting points were determined in capillary tubes and are corrected. Analyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan 48106.

(7) This compound is reported in the literature (D. Poynter, S. Selway, and N. W. Spurling, *Proc. Eur. Soc. Study Drug Toxicity*, 10, 191 (1969) without physical constants. Reported (D. E. Bays, private communication) m.p. 138-140°. We thank Dr. Bays of Allen and Hanburys Ltd. for this information.