6,11-Dimethyl-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinoline: a New Aza-analogue of Ellipticine

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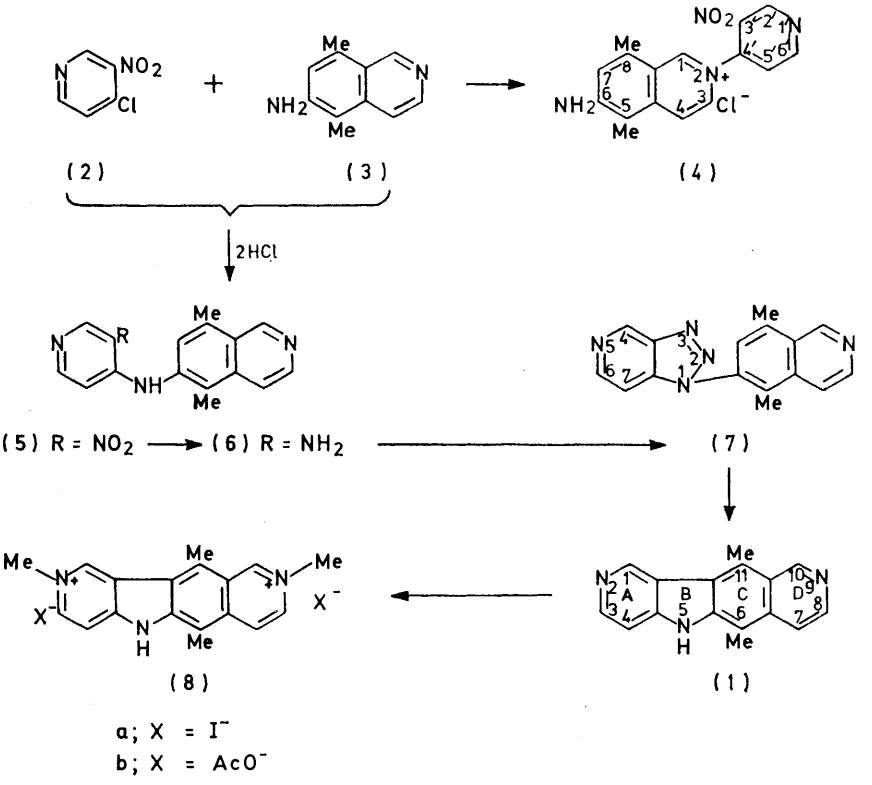
6,11-Dimethyl-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinoline, an aza-analogue of ellipticine, has been prepared in four steps, starting from 4-chloro-3-nitropyridine and 6-amino-5,8-dimethylisoquinoline. Different unsuccessful attempts to prepare various pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinolines by application of methods successfully used in the synthesis of several pyrido[4,3-*b*]carbazoles, are described.

PYRIDO[4,3-*b*]CARBAZOLES (ellipticines) have been obtained by various synthetic procedures [1] and their 6-oxa- and 6-thia-analogues have been described.[2] Surprisingly, pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinolines which are analogous to pyrido[4,3-*b*]carbazoles, with the exception that ring A is replaced by a pyridine nucleus that might increase the pK_a value and therefore the affinity constant towards DNA,[3] have not been described.



We describe here the first synthesis of the ellipticine analogue 6,11-dimethyl-5*H*-pyrido[3′,4′:4,5]pyrrolo-[2,3-*g*]isoquinoline (1) by a method which has not so far been used in the ellipticine series.

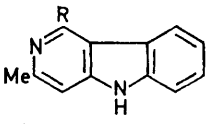
In ethanol or 1,2-dimethoxyethane, 4-chloro-3-nitropyridine (2) [4] reacts with 6-amino-5,8-dimethylisoquinoline (3) [5] to give the quaternary salt (4), but in the presence of hydrochloric acid (2 mol. equiv.) the product (5) is obtained as a result of substitution of the amino group. Hydrogenation with palladium on charcoal afforded the amino-compound (6) which was converted with nitrous acid in acetic acid into the *v*-triazole (7). Heating of (7) in paraffin at 330—350 °C [6] yielded the required product (1).

The least satisfactory stage of the synthesis is the preparation of (5) but efforts to improve the yield have been unsuccessful. Compound (1) forms a dimethiodide (8a) and a dimethoacetate (8b).

Alternative attempts to prepare the pyrido[3′,4′:4,5]-pyrrolo[2,3-*g*]isoquinolines (1) by methods used already for the preparation of ellipticines failed; details are as follows.

(i) Our first attempts used methods which consisted of building the D ring on 3-formyl-1,4-dimethylcarbazole [7] or 2-formyl-1,4-dimethylcarbazole [8] as intermediates. In contrast to carbazoles which are formylated at their 3-positions the pyrido[4,3-b]indoles (9), like

5,8-dimethylcarbolines,[9] do not undergo the Vilsmeier–Haack reaction, or react by the method of Rieche.[10]

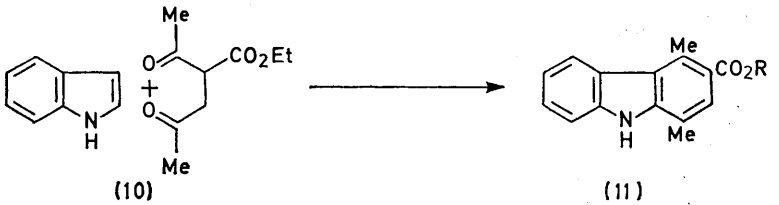


(9)

a ; R = OH
b ; R = Cl

(ii) Attempts to synthesize pyrido[4,3-*b*]indoles carrying a functional group on their C_6 ring, either by the Fischer reaction between 6-methylpyridine-2,4-diol and 3-hydrazino-2-methylbenzonitrile,[11,12] or by the method of Besselievre and Husson [13] applied to pyrrolo[3,2-*c*]-pyridine, were unsuccessful.

(iii) In a similar approach, we attempted to synthesize ethyl pyrido[4,3-*b*]indole-6- or -7-carboxylate by condensation of pyrrolo[3,2-*c*]pyridine with ethyl 2,5-dioxohexane-3-carboxylate (10) by the Cranwell–Saxton technique.[7] Whereas the reaction between indole and the dione (10) leads to the carbazole (11a) and then to the corresponding acid (11b) by a route which is easier than the method of Govindachari *et al.*,[8] under the same conditions, pyrrolo[3,2-*c*]pyridine [14] or 4-chloro-1-methylpyrrolo[3,2-*c*]pyridine [15] do not react with hexane-2,5-dione or with ethyl 2,5-dioxohexane-3-carboxylate.



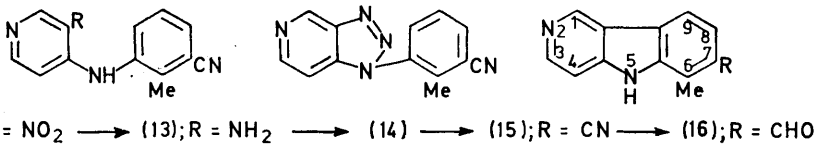
(10) (11)

a ; R = Et
b ; R = H

These results are most likely due to the lower reactivity of the five-membered ring in pyrrolo[3,2-*c*]pyridine.

Following these unsuccessful attempts, a 7-substituted pyrido[4,3-*b*]indole was obtained by reduction of the 3-nitropyridine (12) [16] to the corresponding amine (13), followed by diazotisation to provide the triazolopyridine (14) which was then pyrolysed in boiling phenanthrene to give a good yield of 7-cyano-6-methyl-5*H*-pyrido-[4,3-*b*]indole (15).

Despite attempts to reduce the nitrile (15) directly under various conditions, we only succeeded in making a few milligrams of the aldehyde (16) following Staskun and Backeberg's technique [17] and we have accordingly abandoned this route.



(12); R = NO_2 → (13); R = NH_2 → (14) → (15); R = CN → (16); R = CHO

EXPERIMENTAL

M.p.s were determined with a Kofler or a Reichert hot-stage apparatus. I.r. spectra were obtained with a Perkin-Elmer model 21 double-beam spectrometer. Unless otherwise stated n.m.r. spectra were recorded with a Hitachi–Perkin-Elmer 60 MHz apparatus [solvent $(CD_3)_2SO$; Me_4Si as internal standard].

6-Amino-5,8-dimethyl-2-(3-nitro-4-pyridyl)isoquinolinium Chloride (4).—A mixture of the aminoisoquinoline (3) (0.43 g, 2.5 mmol), 4-chloro-3-nitropyridine (0.40 g, 2.5 mmol), and absolute ethanol (10 ml) was heated under reflux for 3 h. The orange precipitate obtained was dried and washed with warm ethanol, to give the *chloride* (4), m.p. >350 °C (0.45 g, 55%) (Found: C, 57.8; H, 4.7; Cl, 10.7; N, 16.7. $C_{16}H_{14}N_4O_2$,HCl requires C, 58.1; H, 4.5; Cl, 10.7; N, 16.9%); ν(N–H) 3 300 and 3 170; δ(NH_2) 1 645; ν(NO_2) 1 545 and 1 355 cm^{-1}; δ(XL 100): 2.25 (5-Me), 2.61 (8-Me) (assigned by nuclear Overhauser enhancement of the 1- and 4-H resonances upon selective irradiation of the methyl group), 9.08 (1-H), 8.17 (3-H), 7.88 (d, $J_{3,4}$ 7.1 Hz, 4-H) 7.16 (q, $J_{7\text{-H},8\text{-Me}}$ 1 Hz, 7-H), 9.03 (2′-H), 8.70 (6′-H), and 7.50 (d, $J_{6',5'}$ 6.2, 5-H). Compound (4) is unchanged by treatment with sodium carbonate or triethylamine.

5,8-Dimethyl-6-(3-nitro-4-pyridylamino)isoquinoline (5).—4-Chloro-3-nitropyridine (2) (33.14 g) and a solution of dry hydrogen chloride in ether [2 mol. equiv. with respect to (3)] was added to a solution of 6-amino-5,8-dimethylisoquinoline (3) (36 g) in 1,2-dimethoxyethane (1.5 l). The mixture was heated for 8 days under reflux, solvent was evaporated off, the residue was stirred with water (1.5 l) for 1 h, and the precipitate filtered off to give 3-nitropyridin-4-ol (1.7 g). The pH of the aqueous solution was adjusted by addition of potassium carbonate to 5.5; the *nitro-compound* (5) which precipitated was filtered off and recrystallized from benzene as yellow prisms, m.p. 206 °C (17.6 g, 28.6%) (Found: C, 65.1; H, 4.8; N, 18.9. $C_{16}H_{14}N_4O_3$ requires C, 65.3; H, 4.3; N, 19.0%); ν(N–H) 3 320; ν(NO_2) 1 490 and 1 370; δ(NH_2) 1 635 and 1 610 cm^{-1}; δ 2.55 and 2.73 (Me), 6.7 (d, $J_{4,3}$ 7 Hz, 4-H), 7.61 (7-H), 8.15 (d, $J_{5',6'}$ 6 Hz, 5′-H), 8.41 (3-H), 8.86

(6′-H), 9.40 (1-H), 9.74 (2′-H), and 10.8 (N–H) (primed numbers refer to the pyridyl ring). When the pH of the aqueous solution was increased to 10, the aminoisoquinoline (3) (13 g, 36%) was obtained.

6-(3-*Amino*-4-*pyridylamino*)-5,8-*dimethylisoquinoline* (6).—10% Palladium on charcoal (2 g) was added to a solution of the nitro-compound (5) (20 g) in absolute ethanol (1 l) and the mixture was stirred at ambient temperature and pressure under hydrogen until the theoretical quantity of hydrogen had been absorbed. The catalyst was filtered off, the solution was evaporated, and the residue was recrystallized from ethanol affording the *amino-compound* (6) as beige crystals, m.p. 235—250 °C (decomp.) (16.9 g, 93.7%) (Found: C, 70.8; H, 6.8; N, 19.2. $C_{16}H_{16}N_4$, 0.5 EtOH requires C, 71.05; H, 6.7; N, 19.5%); ν(N–H) 3 300—3 150 cm^{-1}; δ 2.42 and 2.70 (5- and 8-Me), 5.04 (NH_2), 6.50 (d, $J_{4,3}$ 5 Hz, 4-H), 7.28 (7-H), 7.40 (NH), 7.66 (3-H), 7.85 (d, $J_{5',6'}$ 6 Hz, 5′-H), 8.0 (2′-H), 8.54 (6′-H), and 9.38 (1-H) (primed numbers refer to the pyridyl ring).

1-(5,8-*Dimethyl*-6-*isoquinolyl*)-1H-v-*triazolo*[4,5-c]*pyridine* (7).—A solution of sodium nitrite (4.83 g) in water (150 ml) was added dropwise to a solution of the amine (6) (16.8 g) in acetic acid (300 ml) at *ca.* 0 °C. The mixture was stirred at this temperature for 2 h, then allowed to reach room temperature during 1 h. After evaporation, the residue was shaken with water (300 ml) and the resulting residue was filtered off, to give the *triazolo-pyridine* (7) as pale yellow crystals (from ethanol), m.p. 215—220 °C (14.8 g, 84.5%) (Found: C, 69.7; H, 4.8; N, 25.2. $C_{16}H_{13}N_5$ requires C, 69.8; H, 4.8; N, 25.4%); δ 2.38 and 2.86 (5- and 8-Me), 7.63 (7-H), 7.67 (d, $J_{4,3}$ 6 Hz, 4-H), 8.08 (d, $J_{7',6'}$ 6 Hz, 7′-H), 8.65 (3-H), 8.75 (6-H), 9.65 (4′-H), and 9.70 (1-H) (primed numbers refer to the isoquinoline ring).

6,11-*Dimethyl*-5H-*pyrido*[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinoline* (1).—The triazolopyridine (7) (12 g) was mixed with paraffin, m.p. 54—56 °C (36 g), and the mixture heated at 320—340° C until the release of gas has ceased (20—25 min).

The mixture was cooled, the paraffin was removed with light petroleum (b.p. 100—140 °C) (100 ml), and the insoluble black solid was dissolved in ethanol in the presence of animal charcoal; this solution was then filtered, concentrated, and filtered while cold, and the residue was recrystallized from pyridine to give the *dimethyl compound* (1) as yellow crystals, m.p. >350 °C (5.4 g, 40.6%) (Found: C, 77.5; H ,5.3; N, 17.0. $C_{16}H_{13}N_3$ requires C, 77.7; H, 5.3; N, 17.0%); ν(N–H) 3 050 cm^{-1}; δ(XL 100) 2.82 [6-Me, assigned, together with the 7-H resonance by nuclear Overhauser enhancement of the methine proton (30%) upon selective irradiation of the methyl group], 3.29 (q, $J_{Me,Me'}$ 0.6 Hz, 11-Me), 9.75 (10-H), 8.49 (d, $J_{7,8}$ 6.1 Hz, 8-H), 7.97 (d, $J_{7,10}$ 0.75 Hz, 7-H), 7.53 (4-H), 8.56 (d, $J_{3,4}$ 5.6 Hz, 3-H), 9.53 (d, $J_{1,4}$ 0.9 Hz, 1-H), and 11.81 (NH).

Acetate Salt of Compound (1).—Compound (1) was heated, in boiling acetic acid; the excess of acid was evaporated off, and the residue was washed with acetone, to give yellow-ochre crystals, of the *acetate salt* of (1), m.p. >310 °C (Found: C, 66.6; H, 5.8; N, 12.8. $C_{18}H_{17}N_3O_2,H_2O$ requires C, 66.4; H, 5.9; N, 12.9%).

Dihydrochloride of Compound (1).—Treatment of a solution of the base (1) (200 mg) in absolute ethanol (20 ml) with hydrogen chloride-saturated ethanol (1 ml) gave the *dihydrochloride* of (1) as ochre crystals (200 mg), m.p. >310 °C (Found: C, 56.3; H, 4.8; Cl, 21.2; N, 12.6. $C_{16}H_{17}Cl_2N_3O$ requires C, 56.8; H, 5.0; Cl, 21.0; N, 12.4%).

2,6,9,11-*Tetramethyl*-5H-*pyrido*[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinolinium Di-iodide* (8a) *and Diacetate* (8b).—A suspension of compound (1) (274 mg) in acetone (750 ml) was heated under reflux for 6 h with methyl iodide (1.42 g). Further methyl iodide (1.42 g) was added and the mixture was left under reflux for a further 14 h, then cooled, and the insoluble di-iodide (8a) (487 mg, 93%) was filtered off. (Found: C, 40.55; H, 3.7; N, 7.9. $C_{18}H_{19}I_2N_3$ requires C, 40.7; H, 3.6; N, 7.9%). A solution of the di-iodide (8a) (450 mg) in water (100 ml) was passed through a column containing Dowex IX2 resin, equilibrated with acetate ions. Removal of solvent, followed by treatment of the residue with isobutyl alcohol, gave the diacetate (8b) as yellow crystals, m.p. 230—235 °C, which showed a single spot on t.l.c. on alumina with methanol–water (4 : 1 v/v) as eluant, and an n.m.r. spectrum which is consistent with this assignment; however its elemental analysis corresponded to a partially hydrated form.

1,4-*Dimethylcarbazole*-3-*carboxylic Acid* (11b).—A solution of indole (11.7 g, 0.1 mol), ethyl 2,5-dioxohexane-3-carboxylate (18.6 g, 0.1 mol), and toluene-*p*-sulphonic acid (0.5 g) in ethanol (50 ml) was heated under reflux for 70 h. After cooling, solvent was removed under reduced pressure; a solution of the residue in chloroform was washed with sodium hydroxide and with water, dried, and then evaporated. Potassium hydroxide (12 g) in water (60 ml) was added to a solution of the residue in ethanol and the mixture was heated under reflux for 3 h. The solution was cooled, and, following chloroform extraction, the aqueous phase was acidified with hydrochloric acid. A black oil was formed, which slowly crystallized. The dried solid was washed with the minimum amount of benzene and then recrystallized from benzene–acetone (1 : 1 v/v) to give *the acid* (11b) as beige crystals, m.p. 220—232 °C (3.1 g, 13%) (Found: C, 75.4; H, 5.65; N, 6.0. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.85%), ν(C=O) 1 675; ν(O–H) 3 390 and 3 430 cm^{-1}; δ 2.85 and 2.9 (Me), 7.2—8.5 (ArH), and 11.35 (NH).

A solution of the foregoing acid (11b) (1.2 g, 5 mmol) in ethanol (10 ml) with one drop of concentrated sulphuric acid was heated under reflux overnight; the usual work-up yielded the ethyl ester (11a), m.p. 149—150 °C (lit.,[8] m.p. 150 °C).

4-(3-*Cyano*-2-*methylanilino*)-3-*nitropyridine* (12).—This compound was described in the preceding paper.[18]

3-*Amino*-4-(3-*cyano*-2-*methylanilino*)*pyridine* (13).—10% Palladium on charcoal (0.25 g) was added to a solution of the nitro-compound (12) (2.55 g, 10 mmol) in ethanol (120 ml) under hydrogen. The mixture was stirred until the calculated quantity of hydrogen had been absorbed (2 h), the catalyst was then filtered off, solvent removed under reduced pressure, and the residue recrystallized from xylene to give the *amine* (13), m.p. 185—186 °C (1.8 g, 80%) (Found: C, 69.6; H, 5.4; N, 25.0. $C_{13}H_{12}N_4$ requires C, 69.6; H, 5.4; N, 25.0%), ν(C≡N) 2 200; ν(NH_2) 3 240 and 3 430; δ(NH_2) 1 580 and 1 650 cm^{-1}; δ 2.4 (Me), 4.9 (NH_2), 6.4 (d, $J_{5,6}$ 5 Hz, 5-H), 7.65 (6-H), 8.0 (2-H), and 7.2—7.5 (ArH).

1-(3-*Cyano*-2-*methylphenyl*)-1H-v-*triazolo*[4,5-c]*pyridine* (14).—A solution of sodium nitrite (0.75 g, 11 mmol) in the minimum volume of water was slowly added to a stirred solution of the diamine (13) (2.2 g, 10 mmol) in acetic acid (50 ml) at 0—10 °C. The mixture was then stirred for 30 min at 10 °C and left at room temperature for 1 h. Solvent was then removed under reduced pressure and the residue

was washed (×2) with water and recrystallized from aqueous ethanol to yield the *triazolopyridine* (14) as yellow plates, m.p. 204—206 °C (2.3 g, 98%) (Found: C, 66.2; H, 4.0; N, 30.0. $C_{13}H_9N_5$ requires C, 66.4; H, 3.9; N, 29.8%), ν(C≡N) 2 240 cm^{-1}; δ 2.3 (Me) and 7.6—9.8 (ArH).

7-*Cyano*-6-*methylpyrido*[4,3-b]*indole* (15).—A suspension of compound (14) (3.55 g, 15 mmol) in molten phenanthrene (35 g) was kept at 340 °C for 20 min, until release of gas had ceased. After cooling, the phenanthrene was dissolved in warm light petroleum (b.p. 100—140 °C) and the residue was treated with 1M-hydrochloric acid (100 ml). Insoluble material was filtered off, and the pH of the solution was adjusted to 8. The precipitate obtained was washed with water and recrystallized from 50% aqueous ethanol to give the *pyridoindole* (1.7 g, 54%), which sublimes above 185 °C (Found: C, 75.1; H, 4.5; N, 20.5. $C_{13}H_9N_3$ requires C, 75.3; H, 4.4; N, 20.3%) ν(C≡N) 2 220 cm^{-1}; δ 2.8 (Me), 7.65 (d, $J_{3,4}$ 6 Hz, 4-H), 7.7 (d, $J_{8,9}$ 8 Hz, 9-H), 8.4 (8-H), 8.7 (3-H), 9.65 (1-H), and 12.0 (NH).

6-*Methylpyrido*[4,3-b]*indole*-7-*carbaldehyde* (16).—A mixture of (15) (3.4 g), Raney nickel (6.8 g), formic acid (35 ml), and water (35 ml) was heated under reflux for 5 h, further Raney nickel (6.8 g) being added after 2.5 h. Insoluble material was filtered off from the cold mixture and washed with boiling ethanol. The reaction solution and ethanol extracts were combined and evaporated under reduced pressure, and the residual oil was dissolved in water and the pH adjusted to 11. The precipitate was dried and washed with methanol to give the impure aldehyde (16) (1.5 g), m.p. *ca.* 245 °C.

This aldehyde was purified by preparation of its semicarbazone derivative, which was then hydrolysed with 2M-hydrochloric acid followed by neutralisation. Only 0.2 g of the pure *aldehyde* (16), m.p. 305—310 °C (decomp) (from ethanol), was obtained (Found: C, 74.3; H, 4.8; N, 13.3. $C_{13}H_{10}N_2O$ requires C, 74.1; H, 4.8; N, 13.3%) ν(C=O) 1 660 cm^{-1}; δ 2.9 (Me), 7.5 (d $J_{3,4}$ 5.4 Hz, 3-H), 7.7 (d, $J_{8,9}$ 8.1 Hz, 9-H), 8.3 (8-H), 8.5 (4-H), 9.48 (1-H), 10.4 (CHO), and 12.0 (NH_2).

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