Synthesis of 10-Substituted 5*H*-Pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinolines

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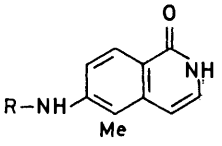
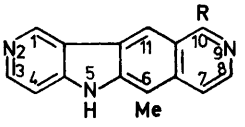
The preparation of 6-amino-5-methyl isoquinolin-1(2*H*)-one is described. Starting from this key intermediate, several derivatives of 5*H*-pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinoline substituted with various alkyl amino-groups at their 10-position have been synthesized.

DURING our investigations on the synthesis of 9-aza-analogues of ellipticine,[1,2] we wished to obtain derivatives substituted by dialkylamino-alkylamine chains similar to those present in antimalarial acridines and quinolines. Such chains might increase the DNA intercalating properties of pyridopyrroloisoquinolines.[3] We report here the synthesis of the key intermediate 6-amino-5-methylisoquinolin-1(2*H*)-one (1a) and some 6-methylpyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinolines (2) derived from it.



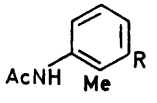
(1)



(2)

a; R = NH_2
b; R = NHCOMe

3-Acetamido-2-methylbenzonitrile (3) was reduced to the corresponding aldehyde (4) by boiling in dilute formic acid with Raney nickel.[4] However, the reaction is incomplete, and purification of the aldehyde (4) difficult. We therefore prepared the cinnamic acid (5) by condensing malonic acid with the mixture of (3) and (4), and separated (5) from the unchanged nitrile. The cinnamic acid (5) was converted into the azide (6) by the mixed anhydrides method.[5] In boiling diphenyl ether [6,7] the azide (6) yielded the isoquinolone (1b), which was then hydrolysed to the free amine (1a).



(3) R = CN ⟶ (4); R = CHO ⟶
(5); R = CH: $CHCO_2H$ ⟶ (6); R = CH: $CHCON_3$ ⟶
(1b) ⟶ (1a)

Substitution of 4-chloro-3-nitropyridine (7) by the amino-isoquinolone (1a) in dimethylformamide at room temperature yielded the nitropyridylamino-isoquinoline (8). However, it is impossible to avoid the formation also of a small quantity of the imine (9).[8]

Starting from compound (8), the following two pathways are available to prepare pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinolines chlorinated at their 10-position: (i) reduction of (8) to the amine (10), diazotisation of (10) to the triazolopyridine (11), thermal cyclisation of (11) to the pyridopyrroloisoquinolone (12), and chlorination of (12) to (16) in boiling phosphorus chloride oxide; (ii) transformation of (8) to the chloro-compound (13), reduction of (13) to the amine (14), diazotisation of (14) to the triazolopyridine (15), and finally thermal cyclisation leading to compound (16).

We have found that only pathway (i) is satisfactory. Two stages in route (ii) are problematic: selective reduction of (13) to (14) at the nitro-group only is not successful with palladium on charcoal and Raney nickel, and succeeds only with reduced iron and with small quantities of the amine (13);[9] thermal cyclisation of (15) to (16) in boiling phenanthrene leads to a mixture in which only a trace of the desired product could be characterized.

Substitution of compound (16) by β-dimethylaminoethylamine and γ-dimethylamino- and γ-diethylaminopropylamine leads to the expected products (17), (18), and (19), respectively.

The structures of the key intermediates in these reactions, as well as the final products, were analysed by high-resolution n.m.r. spectroscopy at 100 MHz using the Fourier transform technique together with homonuclear decoupling and nuclear Overhauser enhancement measurements for unambiguous assignments. These results for compounds (8), (9) (free base and cation), (12), and (16)—(19) are given in Supplementary Publication No. SUP 22348 (3 pp.).† N.m.r. results at 60 MHz for other substances are given in the Experimental section.

Compounds (16)—(19) lack a methyl group at position 11; an 11-methyl group has been recognized to be necessary for biological activity in the ellipticine series.[10] The cytotoxic properties on cells *in vitro* and the antitumour activity toward leukaemia L1210 and other experimental murine tumours of these new compounds, particularly (19), are nevertheless much higher than those of the previously studied 6,11-dimethyl-5*H*-pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinoline.[1]

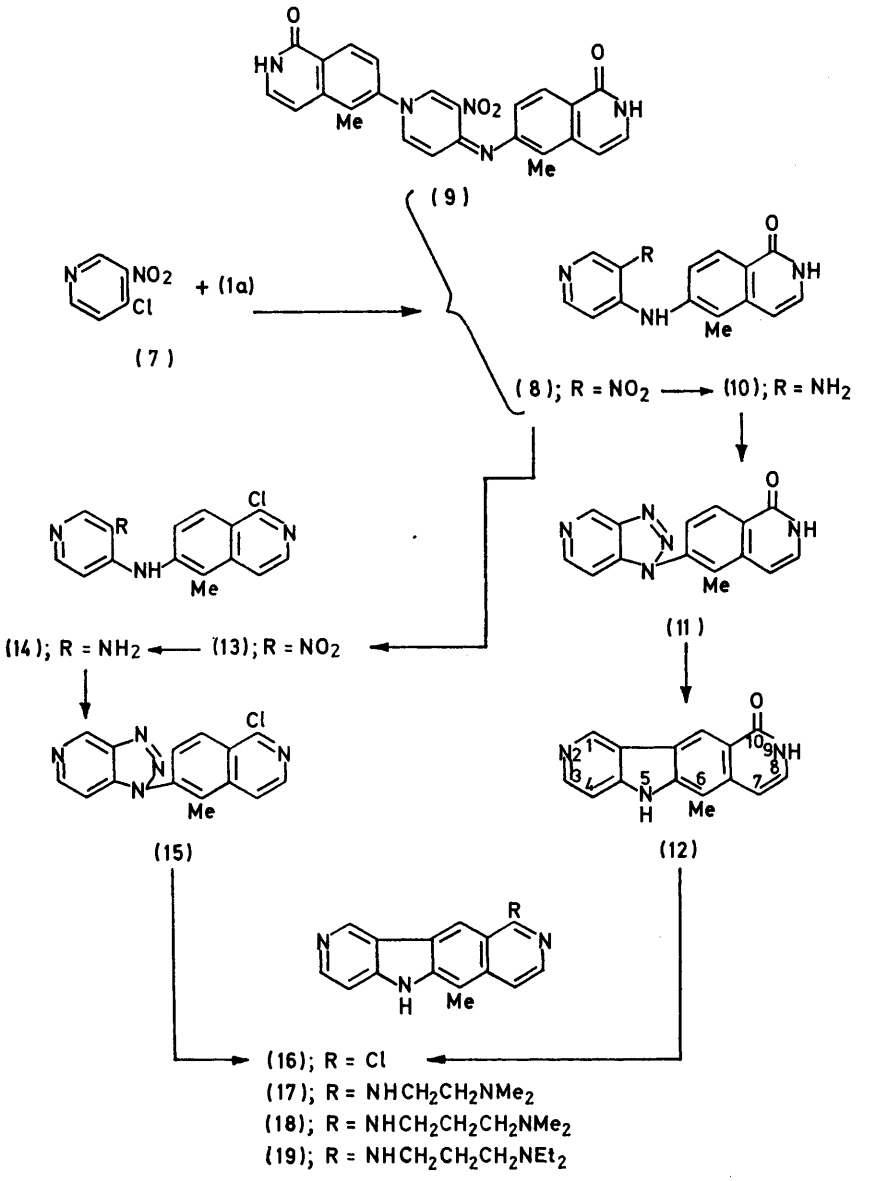
The increase in antitumour activity of the DNA intercalating compounds of the ellipticine type afforded by the presence of the dialkylamino- alkylamine side chains is thus demonstrated. Consequently, it would

† Details of Supplementary Publications are given in *J.C.S. Perkin I*, 1978, Index issue.

be useful to study analogues of (17)—(19), derived from pyrido[4,3-*b*]carbazoles, and we are now investigating their synthesis.

EXPERIMENTAL

M.p.s were determined with a Kofler or 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 spectrometer [solvent $(CD_3)_2SO$; Me_4Si as internal standard].



3-Acetamido-2-methylbenzonitrile (3).—Acetylation of 3-amino-2-methylbenzonitrile gives the *acetamide* (3), as plates, m.p. 160 °C (from toluene) (Found: C, 68.8; H, 5.8; N, 16.0. $C_{10}H_{10}N_2O$ requires C, 68.95; H, 5.8; N, 16.1%); ν(C≡N) 2 200; ν(N–H) 3 160; ν(C=O) 1 660 cm^{-1}; δ 2.1 and 2.4 (Me), 7.2—7.9 (ArH), and 9.6 (NH).

3-Acetamido-2-methylcinnamic Acid (5).—A mixture of the nitrile (3) (60 g, 0.34 mol) and 50% aqueous formic acid (1 l) in a 6 l vessel was heated under reflux, and five portions of Raney nickel (120 g in total) were added at intervals of 30 min. The mixture was then left for a further 30 min and filtered, the insoluble material washed with hot water. Extraction of the filtrate plus washings with chloroform and evaporation yielded a residue which was distilled to give a product (39 g), b.p. 210—225 °C at 11 mmHg, corresponding to a mixture of the initial nitrile and the aldehyde (4). Fractional recrystallization from benzene or toluene, gave, first, needles of the *aldehyde* (4), m.p. 124—128 °C (Found: C, 68.1; H, 6.3; N, 8.05. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); ν(C=O) 1 690 cm^{-1}; δ($CDCl_3$) 8.1 (NH) and 10.5 (CHO).

A solution of the foregoing mixture (38 g), after distillation, in dry pyridine (50 ml) was added to a solution of malonic acid (22.5 g) and piperidine (1 ml) in pyridine (300 ml) and the mixture was heated under reflux for 90 min. After evaporation under reduced pressure, the residue was

dissolved in water, and the solution made alkaline with 1M sodium hydroxide, and extracted with chloroform. Evaporation of the chloroform left a residue composed of the initial untransformed nitrile (3). Acidification of the aqueous phase with hydrochloric acid precipitated the *acrylic acid* (5) as needles, m.p. 265—267 °C (from acetic acid) [25 g, 34% with respect to the nitrile (3)] (Found: C, 65.6; H, 6.1; N, 6.5. $C_{12}N_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%); ν(C=O) 1 695 and 1 715; ν(OH) 2 400—3 000 cm^{-1}; δ 6.3 and 7.85 (C*H*=C*H*CO_2H, *J* 17 Hz).

3-*Acetamido*-2-*methylcinnamoyl Azide* (6).—The acrylic acid (5) (36 g) was added to a solution of triethylamine (17 g) in acetone (150 ml). The mixture was maintained below 0 °C and a solution of ethyl chloroformate (24.3 g) in acetone (150 ml) was added dropwise. The mixture was then shaken at 0 °C for 1 h and a solution of sodium azide (16 g) in water (40 ml) was added in portions. The cold mixture was shaken for a further 1 h and filtered to yield the azide (6). Evaporation of the mother liquor on a water-bath at 30 °C under reduced pressure gave a further quantity of (6). The two fractions were washed with water and dried, and used in the following synthesis, m.p. 150 °C (decomp.) (27.8 g, 71%); ν(N_3) 2 120 cm^{-1}.

6-*Acetamido*-5-*methylisoquinolin*-1(2H)-*one* (1b).—To a vigorously stirred solution of tributylamine (33 g) in diphenyl ether (500 ml) maintained at 240 °C, a suspension of the azide (6) (41 g) in diphenyl ether (500 ml) was added as quickly as possible. The mixture was kept at 240 °C for a further 20 min, concentrated to half volume, then allowed to cool. The precipitate which formed was filtered off, washed with benzene, and recrystallized from dimethylformamide to give the *isoquinolone* (1b), m.p. >320 °C (25 g, 69%) (Found: C, 67.0; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%); ν(C=O) 1 645 and 1 675; ν(NH) 3 100 cm^{-1}; δ 2.1 and 2.3 (Me), 6.7 (d, $J_{4.3}$ 7 Hz, 4-H), 7.2 (3-H), 7.55 (d, $J_{7.8}$ 9 Hz, 7-H), 8.1 (8-H), 9.7 (N*H*COMe), and 12.0 (lactam NH).

6-*Amino*-5-*methylisoquinolin*-1(2H)-*one* (1a).—A solution of compound (1b) (25 g) in ethanol (500 ml)–hydrochloric acid (100 ml) was heated under reflux for 2.5 h. Evaporation left a residue which was dissolved in hot water and filtered. The filtrate was basified with 1M sodium hydroxide to give needles of the *amine* (1a) m.p. 260—285 °C (decomp.) (from ethanol) (16.3 g, 81%) (Found: C, 69.0; H, 5.8; N, 15.85. $C_{10}H_{10}N_2O$ requires C, 68.95; H, 5.8; N, 16.1%); ν(NH_2) 3 200—3 350; ν(NH) 3 120; ν(C=O) and δ(NH_2) 1 650—1 610 cm^{-1}; δ 5.65 (NH_2), 6.6 (d, $J_{4.3}$ 7 Hz, 4-H), 6.95 (d, $J_{7.8}$ 8 Hz, 7-H), 7.15 (3-H), and 8.0 (8-H).

5-*Methyl*-6-(3-*nitro*-4-*pyridylamino*)*isoquinolin*-1(2H)-*one* (8).—4-Chloro-3-nitropyridine (7) (15.9 g) was added to a solution of compound (1b) (17.4 g) in dimethylformamide (DMF) (500 ml) and the mixture was left at room temperature for 12 days. Evaporation under reduced pressure gave a residue which was dissolved in hot water, and this solution was made alkaline with 1M sodium hydroxide. The precipitate was recrystallized from DMF to afford the *amino-compound* (8) ,as yellow prisms, m.p. >330 °C (21.3 g, 72%) Found: C, 60.5; H, 4.1; N, 18.6. $C_{15}H_{12}N_4O_3$ requires C, 60.8; H, 4.0; N, 18.9%); ν(C=O) 1 640; ν(NO_2) 1 540 and 1 350 cm^{-1}. 1-(5-*Methyl*-1-*oxo*-1,2-*dihydroisoquinolin*-6-*yl*)-4-(5-*methyl*-1-*oxo*-1,2-*dihydroisoquinolin*-6-*yl*-*imino*)-3-*nitro*-1,4-*dihydropyridine* (9) was obtained as a secondary product, as red prisms (from DMF), m.p. >330 °C (Found: C, 64.7; H, 4.2; N, 14.3. $C_{25}H_{19}N_5O_4,0.5H_2O$ requires C, 64.95; H, 4.35; N, 14.4%).

5-*Methyl*-6-(3-*amino*-4-*pyridylamino*)*isoquinolin*-1(2H)-*one* (10).—10% Palladium on charcoal (0.6 g) was added to a solution of the nitro-compound (8) (12.6 g) in acetic acid (500 ml) and the mixture was stirred under hydrogen at atmospheric pressure until the calculated quantity of hydrogen had been absorbed. After filtration and evaporation, the residue was dissolved in water, and the pH adjusted to 9; the *amine* (10) precipitated as cream crystals (10.3 g, 84.3%), m.p. 164 and 267 °C (decomp.) (Found: C, 63.8; H, 5.4; N, 19.5. $C_{15}H_{14}N_4O,H_2O$ requires C, 63.9; H, 5.7; N, 19.7%); ν(NH_2) 3 200 and 3 140; ν(C=O) 1 635; δ(NH_2) 1 620 cm^{-1}; δ 4.0 (NH_2), 6.55 (5′-H), 6.65 (d, $J_{3.4}$ 7 Hz, 4-H), 7.25 (3-H), 7.7 (6′-H), 7.7 (d, $J_{7.8}$ 9 Hz, 7-H), 8.05 (2′-H), and 8.1 (8-H), (primed numbers refer to the pyridyl ring).

1-(5-*Methyl*-1-*oxo*-1,2-*dihydroisoquinolin*-6-*yl*)-1H-v-*triazolo*[4,5-c]*pyridine* (11).—An aqueous solution of sodium nitrite (3 g) was added dropwise to a solution of the amine (10) (10.2 g) in acetic acid (70 ml) cooled below 5 °C. The mixture was stirred for 1 h, during which time it reached ambient temperature; the *triazolo-pyridine* (15) crystallized, was filtered off, and washed with water, m.p. 309—310 °C (8.3 g, 83.5%) (Found: C, 60.9; H, 4.15; N, 23.4. $C_{15}H_{13}N_5O_2$ requires C, 61.0; H, 4.4; N, 23.7%); δ(Varian XL100) 9.65 (d, $J_{4.7}$ 1.2 Hz, 4-H), 7.65 (d, $J_{6.7}$ 5.8 Hz, 7-H), 8.64 (6-H), 11.61 (2′-NH), 7.40 (d, $J_{3'.4'}$ 7.5 Hz, 3′-H), 6.77 (d, $J_{4'.8'}$ 0.6 Hz, 4′-H), 2.19 (5′-Me), 7.61 (d, $J_{7.9''}$ 8.5 Hz, 7′-H), and 8.32 (8′-H) (primed numbers refer to the isoquinoline ring).

6-*Methyl*-5H-*pyrido*[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinolin*-10(9H)-*one* (12).—A stirred mixture of the triazolopyridine (11) (8 g) and phenanthrene (60 g) was heated at 340 °C until the release of gas ceased (30 min). The phenanthrene was removed with hexane, and the methyl compound (12) was obtained as grey crystals (from DMF), m.p. >310 °C (4.2 g, 58%) (Found: C, 70.0; H, 4.4; N, 16.1. $C_{15}H_{11}N_3O,0.5H_2O$ requires C, 69.75; H, 4.7; N, 16.3%); ν(C=O) 1 665 cm^{-1}.

1-*Chloro*-5-*methyl*-6-(3-*nitro*-4-*pyridylamino*)*isoquinoline* (13).—The amine (8) (3 g, 10 mmol) and phosphorus chloride oxide (150 ml) were heated in a water-bath for 7 h; after evaporation under reduced pressure, chloroform (50 ml) and water were added, and the pH was adjusted to 7, with stirring, with 1M sodium hydroxide. Evaporation of the chloroform extracts under reduced pressure afforded the *chloro-compound* (13), yellow prisms (from xylene), m.p. 245 °C (1.8 g, 57%) (Found: C, 57.0; H, 3.65; Cl, 11.35; N, 17.3. $C_{15}H_{11}ClN_4O_2$ requires C, 57.2; H, 3.5; Cl, 11.26; N, 17.8%); δ($CDCl_3$) 2.6 (Me), 6.1 (d, $J_{4.3}$ 6 Hz, 4-H), 7.6 (d, $J_{7.8}$ 9 Hz, 7-H), 8.3 (3-H), 8.4 (8-H), 7.8 (d, $J_{5'6'}$ 6 Hz, 5′-H), 8.4 (6′-H), and 9.3 (2′-H) (primed numbers refer to the pyridyl ring).

6-(3-*Amino*-4-*pyridylamino*)-1-*chloro*-5-*methylisoquinoline* (14).—The nitro-compound (13) remains unchanged under hydrogen in the presence of Raney nickel. With palladium on charcoal, the reduction is not selective, and separation of the products leads to poor yields of the desired amine. As with the previous method [9] it only gives good yields with <2 mmol of substrate. Use of larger quantities leads to incomplete reduction. To a solution of the nitro-compound (13) (628 mg, 2 mmol) in ethanol (20 ml) were added reduced iron (1.2 g), water (0.4 g), water (0.4 ml), and conc. hydrochloric acid (0.02 ml). The mixture was heated under reflux for 2.5 h, the catalyst was filtered off and washed, and solvent was removed under reduced pressure. The

residue was dissolved in water and treated with 1M sodium hydroxide to precipitate the *amine* (14), yellow prisms (from xylene or ethanol), m.p. 256—257 °C (325 mg, 57%) (Found: C, 63.1; H, 4.7; Cl, 12.6; N, 19.7. $C_{15}H_{13}ClN_4$ requires C, 63.3; H, 4.6; Cl, 12.45; N, 19.7%); δ 5.0 (NH_2).

1-(1-*Chloro*-5-*methylisoquinolin*-6-*yl*)-1H-v-*triazolo*-[4,5-c]*pyridine* (15).—To a stirred solution of the amine (14) (280 mg, 1 mmol) in acetic acid (10 ml) cooled to 3 °C was slowly added aqueous sodium nitrite (100 mg). After 15 min at 3 °C, the solution was left for 1 h to reach room temperature. The *triazolopyridine* (15) which crystallized was filtered off and washed with water, m.p. 259—261 °C (230 mg, 69%) (Found: C, 60.9; H, 3.5; Cl, 12.2; N, 23.5. $C_{15}H_{10}ClN_5$ requires C, 61.0; H, 3.4; Cl, 12.0; N, 23.7%).

10-*Chloro*-6-*methyl*-5H-*pyrido*[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinoline* (16).—A mixture of compound (12) (1.5 g) and phosphorus chloride (375 ml) was heated under reflux for 20 h. Excess of chloride oxide was removed undei reduced pressure, and the residue was washed with cold water and filtered. A filtered solution of the residue in hot water was cooled and the pH adjusted to 7 with aqueous sodium carbonate, giving the *chloro derivative* (16) as yellow crystals (from DMF), m.p. >320 °C (875 mg, 54.4%) (Found: C, 64.8; H, 3.9; Cl, 13.2; N, 15.0. $C_{15}H_{10}ClN_3,0.5H_2O$ requires C, 65.1; H, 4.0; Cl, 12.8; N, 15.2%).

Starting with compound (15), and following the cyclisation technique described for the preparation of compound (12) the chloro-derivative (16) was also obtained; it was characterized by t.l.c. on Merck silica gel, but it was accompanied by several other products, which we have not sought to identify.

Trihydrochloride of 10-(β-*Dimethylaminoethylamino*)-6-*methyl*-5H-*pyrido*[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinoline* (17).—A mixture of the chloro-derivative (16) (440 mg) and β-dimethylaminoethylamine (10 ml) was heated under reflux for 15 h, and the excess of amine removed under reduced pressure. The residue was shaken with water–chloroform, and the chloroform layer was dried and evaporated. The residue was dissolved in ethanol and sufficient ethanolic hydrogen chloride was added to precipitate the product, which was filtered off and recrystallized from ethanol to give the *trihydrochloride* of (17) as prisms, m.p. 262—269 °C (255 mg, 37.5%) (Found: C, 49.9; H, 5.7; Cl, 23.3; N, 14.8. $C_{19}H_{21}N_5,3HCl,2H_2O$ requires C, 49.1; H, 6.0. Cl, 22.9; N, 15.1%).

Trihydrochloride of 10-(γ-*Dimethylaminopropylamino*)-6-*methyl*-5H-*pyrido*[3,′4′:4,5]*pyrrolo*[2,3-g]*isoquinoline* (18).—Use of the foregoing method with γ-dimethylaminopropylamine and a reflux period of 7 h afforded the *trihydrochloride* (18), m.p. 266—268 °C (72%) (Found: C, 51.8; H, 6.2; Cl, 22.9; N, 14.9. $C_{20}H_{23}N_5,3HCl,H_2O$ requires C, 52.1; H, 6.1; Cl, 23.1; N, 15.2%).

10-(γ-*Diethylaminopropylamino*)-6-*methyl*-5H-*pyrido*-[3′,4′:4,5]*pyrrolo*[2,3-g]*isoquinoline* (19).—A mixture of the chloro-compound (16) (1.4 g) and γ-diethylamonopropylamine (50 ml) was warmed at 160 °C in an oil-bath for 4 h. Evaporation followed by chloroform extraction of an aqueous solution of the residue yielded crystals of the *amine* (19) (from benzene), m.p. 215—218 °C (1.45 g, 73%) (Found: C, 70.0; H, 7.4; N, 18.3. $C_{22}H_{27}N_5,H_2O$ requires C, 69.6; H, 7.7; N, 18.5%).

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