The Synthesis of Polycyclic Benz-Fused Pyrroles (1)

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Pyrrolo[1,2-*f*]phenanthridine (**2**), benzo[*f*]pyrrolo[2,1-*a*]isoquinoline (**3**), 5,6,7,8,9,10,11-hexahydrobenzo[g]pyrrolo[2,1-*a*]isoquinoline (**5**), and pyrrolo[2,1-*a*]isoquinoline (**6**) dicarboxylic acid diesters were prepared in 1,3-dipolar cycloaddition reactions between dimethyl acetylenedicarboxylate and the hydrofluoroborate salt of the appropriate Reissert compound. Several of the different methods to prepare Reissert compounds are compared and the carbon-13 nmr spectra for the Reissert compounds are reported. Carbon-13 nmr was used to assign the structures of isomers **10** and **11**; the latter compounds arose from a prior reaction in which the cyclization of β-(5,6,7,8-tetrahydro-2-naphthyl)ethylamine *N*-formate which gave a mixture of hexahydroisoquinolines, **8a** and **9a**. Pyrrolo[1,2-*b*]isoquinoline (**12**) and pyrrolo[2,1-*a*]isoquinoline dicarboxylic acid diesters were made in münchnone cycloaddition reactions. The latter compound was made from tetrahydroisoquinoline-1-carboxylic acid which was readily prepared from isoquinaldic acid by catalytic reduction. The dehydrogenation of several of the partially saturated compounds is also discussed.

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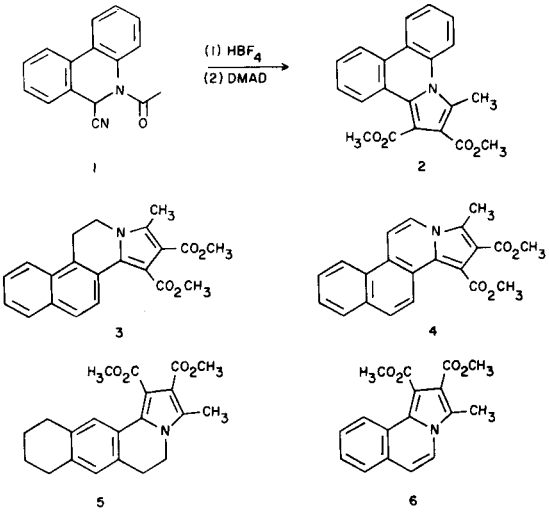
We have recently reported the synthesis and antileukemic activity of a number of *N*-alkylcarbamate derivatives of *bis*(hydroxymethyl)pyrroles (**2-4**) and 6,7-*bis*-(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine (5). The significant reproducible antineoplastic activity which these agents have shown in a number of different *in vivo* test systems has led us to design a series of polycyclic benz-fused pyrroles. This report describes the synthesis of a series of dicarboxylic esters which will ultimately serve as key intermediates in the synthesis of potential antineoplastic agents based on these heterocycles.

Two approaches were used to synthesize the benz-fused pyrrole systems: 1,3-dipolar cycloadditions of alkynes to hydrofluoroborate salts of Reissert compounds (6-8) or with mesoionic oxazolones (münchnones) (9-11). The Reissert compounds used in this study were prepared by one of four different methods which may be compared to analogous reactions reported in the literature.

Method A, which is largely outmoded, involves the use of toxic liquid hydrogen cyanide, an acid chloride, and the nitrogen heterocycle (12). In method B the acid chloride is added to a rapidly stirred mixture of the nitrogen heterocycle in dichloromethane-aqueous potassium cyanide (13); addition of a phase transfer catalyst (method C) represents an improvement over method B (14-16). The method of choice in our work, method D, involved the use of trimethylsilylcyanide in dichloromethane containing a trace of anhydrous aluminum chloride (17). The Reissert compound from phenanthridine and acetyl chloride was prepared in 7, 39, and 91 percent yield by method B, C, and D, respectively; 69, 47 and 0 percent of unreacted phenanthridine was recovered in the respective methods. The yields of other Reissert compounds prepared by the different methods are compared in the appropriate experimental section.



5-Acetyl-5,6-dihydro-6-phenanthridinecarbonitrile (**1**) was converted to a colorless hydrofluoroborate salt and treated with dimethyl acetylenedicarboxylate (DMAD) in either dichloromethane-absolute ethanol or DMF to give dimethyl 3-methylpyrrolo[1,2-*f*]phenanthridine-1,2-dicarboxylate (**2**) in 48 and 68 percent yield, respectively. We have found that the cycloadditions in DMF usually give higher yields than the reactions in dichloromethane-ethanol but that purification of the product is more facile when the latter solvent system is used. In a similar manner, dimethyl 5,6-dihydro-8-methylbenzo[*f*]pyrrolo[2,1-*a*]-isoquinoline-9,10-dicarboxylate (**3**), dimethyl 8-methylbenzo[*f*]pyrrolo[2,1-*a*]isoquinoline-9,10-dicarboxylate (**4**), dimethyl 3-methyl-5,6,7,8,9,10,11-hexahydrobenzo[*g*]pyr-

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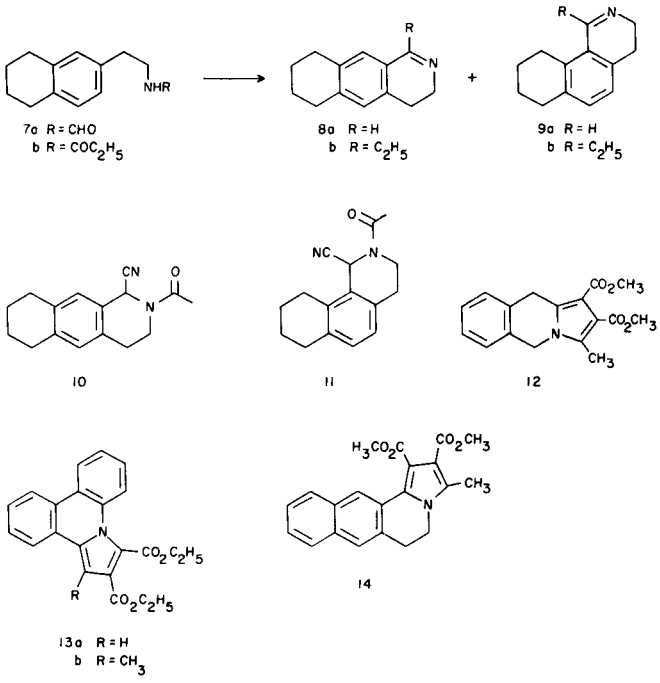

rolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**5**), and the known (18,19) dimethyl 3-methylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**6**) were prepared from the hydrofluoroborate salt of the corresponding Reissert compound.

The tetracyclic diester **5** was prepared in a reaction sequence starting with 5,6,7,8-tetrahydronaphthalene-2-acetamide which was dehydrated (thionyl chloride) to give the nitrile which was reduced (lithium aluminum hydride) and formylated to give **7a**. Treatment of **7a** with polyphosphoric acid gave a mixture (approximately 1:1 as judged by pmr) of **8a** and **9a**. Similarly, phosphorus oxychloride cyclization of **7b** yielded a mixture of **8b** and **9b**. These results were unexpected since previous reports on the ring closure of derivatives of **7a** described exclusive formation of linear compounds (20,22).

The mixture of **8a** and **9a** proved difficult to separate, so the Reissert reaction was run with the mixture. The Reissert compounds, **10** and **11**, were separable and the higher melting adduct was assigned the linear structure, **10**. The assignments were based on the proton- and carbon-13 nmr spectra of **10** and **11**. The pmr spectrum of **10** contained two singlets (one proton each) at δ 6.90 and 7.00 ppm while the spectrum of **11** contained a two-proton multiplet at δ 6.99 which was characteristic of an AB type signal where $\Delta\nu_{AB}$ was small. A comparison of the cmr spectra for **10** and **11** revealed that C-1 was shifted upfield in the angular isomer, **11**, by 2.41 ppm. This upfield shift is presumably due to a γ-gauche effect. A comparison of some cmr data for several Reissert compounds is given in Table I.

The proton-coupled cmr spectra showed the nitrile carbon coupled to the C-1 proton in each Reissert compound and the the coupling constants ranged between 9.3 and 10.3 Hz (23). The coupling constants observed in the cmr spectrum of 1,2-dihydro-2-acetylisoquinoline-1-carbonitrile were typical (24): ^1J (C-1, H-1) = 151.1 Hz, ^3J (C-1, H-3; or C-1, H-8) = 2.4 Hz, ^1J (C-4, H-4) = 168.5 Hz, ^2J (C-4, H-3; or C-4, H-5) = ~ 2.3 Hz. The pmr spectra of several isoquinoline Reissert compounds have been reported (25).

1,3-Dipolar cycloaddition reactions with DMAD and the appropriate münchnone (generated *in situ*) were also used to prepare benz-fused pyrroles. Thus, treatment of the hydrochloride salt of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (26) with acetic anhydride-DMAD gave dimethyl 4,9-dihydro-1-methylpyrrolo[1,2-*b*]isoquinoline-1,2-dicarboxylate (**12**). The known (10) dimethyl 5,6-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-1,2-dicarboxylate was prepared in a similar manner from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid. This starting acid was prepared in a sequence starting with the Reissrt compound, 1,2-dihydro-2-acetylisoquinoline-1-carbonitrile: hydrolysis (27) of the Reissert compound (ethanol-sulfuric acid) gave isoquinaldic acid [purified as the copper(II) salt (28)]; catalytic reduction of isoquinaldic acid

Table I

Carbon-13 Nmr Data for Reissert Compounds (a)

Compound	C-1	C-3	C-4	*C*N	*C*OCH$_3$	CO*C*H$_3$	$^2J_{CN,CH}$(Hz)
(c)	43.50	(b)	110.59	116.54	168.35	20.96	9.3
(d)	44.07	(b)	(b)	116.44	168.44	21.92	9.8
(e)	44.04	41.58	25.23	117.72	169.32	21.17	(b)
(f)	44.28	(b)	106.62	116.62	168.41	20.89	9.2
10	43.36	42.47	(b)	118.12	169.57	21.34	9.6
11	40.95	42.01	(b)	117.24	169.36	21.13	10.1
(g)	43.51	42.14	28.45	117.94	169.65	21.29	10.3

(a) Spectra were determined for deuteriochloroform solutions containing tetramethylsilane as an internal standard; chemical shift values are in ppm. (b) Not determined. (c-g) These are the Reissert compounds derived from: (c) isoquinoline; (d) phenanthridine; (e) 3,4-dihydrobenzo[*f*]isoquinoline; (f) benzo[*f*]isoquinoline; and (g) 3,4-dihydroisoquinoline (reference 36).

(Adams' catalyst in acetic acid; 50 psi of hydrogen for 3.5 hours). The ease of reduction was surprising in view of an earlier report in which the same reduction required 13 days for completion at 50° and atmospheric pressure (29).

Two additional pyrrolo[1,2-*f*]phenanthridines, **13a** and **13b**, were synthesized in low yields from 6-methyl- and 6-ethylphenanthridine, respectively, by treatment with diethyl chlorooxaloacetate and sodium bicarbonate in absolute ethanol (30). The corresponding methyl esters were reportedly prepared by a different method (31-33).

Dehydrogenation of **5** (palladium on charcoal in mineral oil) at 180-190° gave the colorless tetracycle, **14**. More vigorous conditions (240°) led to complete aromatization with the concomitant loss of one carbomethoxy group to give a single yellow monoester. A trace of the desired fully aromatic diester could be detected at intermediate temperatures but the decarboxylated material still predominated. Dehydrogenation of **3** (palladium on charocal) in mineral oil at 240° gave **4** in low yield along with some uncharacterized material. Attempts to dehydrogenate **12** failed (34).

EXPERIMENTAL

Melting points, which were determined in open capillary tubes in a Thomas-Hoover Uni-melt apparatus, and boiling points are uncorrected. Infrared spectra were determined either for mineral oil mulls (on sodium chloride plates) or for potassium bromide pellets with a Perkin-Elmer model 237 spectrophotometer. Proton and carbon-13 nmr spectra were determined for deuteriochloroform solutions containing tetramethylsilane as internal standard, with Varian T-60A and FT-80 spectrometers, respectively. Microanalyses were performed by Atlantic Microlabs, Inc., Atlanta, Georgia.

5-Acetyl-5,6-dihydrophenanthridine-6-carbonitrile (**1**).

Method. B.

The procedure of Popp and Soto (13) was used to give **1** (7%) from phenanthridine, acetyl chloride, aqueous potassium cyanide, and dichloromethane. Phenanthridine (68%) was recovered from the acidic washings.

Method C.

The above procedure was repeated with the addition of 2% (by weight based on potassium cyanide) of benzyltriethylammonium chloride to give **1** (39%) along with recovered phenanthridine (47%). In either method B or C, whenever the mixture turned dark and gelatinous and the yields dropped considerably.

Method D.

A solution of trimethylsilylcyanide (7.0 ml., 0.056 mole) in dichloromethane (5 ml.) was added (one minute) to a stirred mixture of phenanthridine (5.00 g., 0.027 mole) and anhydrous aluminum chloride (0.050 g.) in dichloromethane (50 ml.). Acetyl chloride (3.8 ml., 0.053 mole) in dichloromethane (5 ml.) was added dropwise (10 minutes). The mixture was stirred for 4 hours, and poured into cold water; the organic layer was separated and washed successively with water, 5% aqueous sodium hydroxide, water, 2*N* hydrochloric acid (no phenanthridine precipitated when the acid washings were made alkaline), and water. The dried (sodium sulfate) extract was filtered and concentrated until crystallization began. The mixture was diluted with ethanol, heated, and left to cool; **1** (6.33 g., 91%) was obtained as a white powder which was recrystallized from chloroform-petroleum ether, m.p. 172-173°; ir (potassium bromide): 3140 w, 3000 w, 2970, 2250, 1660, 1600 sh, 1590 sh, 1480, 1435, 1345, 1300, 1285, 1255, 1180, 1160, 1090, 1035, 980, 920, and 730 cm^{-1}; cmr: δ 168.84 (CO), 134.27 (C), 131.00 (C), 130.31 (CH), 130.02 (C), 128.83 (2CH), 128.07 (C), 127.48 (CH), 126.69 (CH), 125.43 (CH), 124.99 (CH), 124.21 (CH), 116.44 [CN, ^2J (CN,CH) = 9.8 Hz], 44.07 (CH, $^1J_{CH}$ = 149.4 Hz), and 21.95 (CH_3, $^1J_{CH}$ = 129.9 Hz).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.45; H, 4.94; N, 11.27.

Dimethyl 3-Methylpyrrolo[1,2-*f*]phenanthridine-1,2-dicarboxylate (**2**).

Fluoroboric acid (48%, 23 ml.) was added to a warm solution of **1** (28.5 g., 0.115 mole) in hot acetic acid (700 ml.). The mixture was allowed to stand for 20 minutes, cooled, and filtered; the solid was washed with dry ether to give 23.79 g. (62%) of the hydrofluoroborate salt as colorless needles, m.p. 217-220° dec. The filtrate was concentrated *in vacuo* to give an additional 10.54 g. (27%) of the salt. A stirred mixture of the hydrofluoroborate salt (32.79 g., 0.098 mole), dimethyl acetylenedicarboxylate (27.0 ml., 0.22 mole), and dry dimethylformamide (50 ml.) was heated at 95-100° for 14 hours. The solution was cooled and poured into a large volume of water; the gummy yellow precipitate was extracted with chloroform and the extract was washed successively with water, 5% sodium bicarbonate solution, and water. The dried (sodium sulfate) extract was concentrated, until crystals began to appear, and diluted with hot methanol; **2** was obtained as small yellow granules (68%, m.p. 145-147°) which were recrystallized from chloroform-methanol to give colorless needles, m.p. 147-148°; ir (mineral oil): 1725, 1705, 1605 w, 1560 w, 1530, 1500, 1480, 1405, 1275, 1245, 1205, 1120, 1105, 1080, 1020, 945, 860 w, 835 w, 785 w, 760, 740, and 715 w cm^{-1}; pmr: δ 2.95 (s, CH_3), 3.87 (s, CH_3), 4.00 (s, CH_3), 7.1-7.4 (m, H-5, H-8, H-9, and H-12), and 7.7-8.1 (m, H-6, H-7, H-10, and H-11).

Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.55; H, 4.96; N, 3.99.

2-Acetyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline-1-carbonitrile.

3,4-Dihydrobenzo[*f*]isoquinoline [prepared from α-naphthylacetonitrile (35)] was converted to the Reissert compound (method B, 65%; method D, 70%), m.p. 186-187° (chloroform-methanol); ir (potassium bromide): 3060, 3020, 2950, 1650, 1600, 1510, 1440, 1360, 1320, 1310, 1280, 1255, 1220, 1175 w, 1095 w, 1035, 990 w, 970, 910 w, 890 w, 865 w, 815, 760, and 745 cm^{-1}; pmr: δ 1.93 (s, CH_3), 3.26 (m, CH_2), 3.60-4.40 (m, CH_2), 6.60 (s, H-1), and 7.28.0 (m, 6H); cmr δ 169.32 (CO), 128.85 (CH), 128.21 (CH), 127.15 (CH), 126.82 (CH), 124.12 (CH), 122.85 (CH), 117.72 (CN), 44.04 (CH), 41.58 (3-CH_2), 25.23 (4-CH_2), and 21.17 (CH_3). Quaternary carbons were not unambiguously assigned, and the solution was too dilute to determine accurate coupling constants in the proton coupled spectrum.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.19. Found: C, 76.70; H, 5.66; N, 11.12.

Dimethyl 5,6-Dihydro-8-methylbenzo[*f*]pyrrolo[1,2-*b*]isoquinoline-9,10-dicarboxylate (**3**).

The Reissert compound, 2-acetyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline-1-carbonitrile, was converted to the bright yellow hydrofluoroborate salt [m.p. 241-243]° dec. in 98% yield. A solution of the salt (29.37 g., 0.087 mole) in dry dimethylformamide (150 ml.) was treated with a solution of dimethyl acetylenedicarboxylate (15.0 ml., 0.12 mole) in dimethylformamide (30 ml.). The stirred mixture was heated at 85-90° for 14 hours, then poured into cold water; the gummy yellow solid was extracted with chloroform and the extract was washed with water, dried (sodium sulfate), concentrated until crystals began to appear, and diluted with hot methanol; the solution was allowed to stand, the product (24.04 g., 79%) was collected and recrystallized (chloroform-methanol) to give **3** as cream-colored needles, m.p. 180-181°; ir (mineral oil): 1720, 1690, 1620 w, 1605 w, 1580 w, 1515 w, 1420, 1400, 1305, 1255, 1210, 1195, 1170, 1130, 1095, 1040, 985 w, 935 w, 840 w, 820, 790 w, 765, and 710 cm^{-1}; pmr: δ 2.46 (s, CH_3), 3.1-3.5 (m, CH_2), 3.80 (s, CH_3), 3.93 (s, CH_3), 3.7-4.1 (m, CH_2), and 7.2-8.0 (m, 6H).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.00. Found: C, 72.05; H, 5.49; N, 4.00.

2-Acetyl-1,2-dihydrobenzo[*f*]isoquinoline-1-carbonitrile.

Benzo[*f*]isoquinoline [prepared from 3,4-dihydrobenzo[*f*]isoquinoline (35)] was converted to the Reissert compound (method A, 22%; method B, 7%; method D, 70%) which was crystallized from chloroform-methanol, m.p. 136.5-138° (dec, darkening); ir (mineral oil): 1680, 1635, 1615, 1590 w, 1570 w, 1515 w, 1335, 1270, 1220, 1195, 1160, w, 1055 w, 1035 w, 980, 905, 890, 865 w, 855 w, 825, and 630 cm^{-1}; pmr: δ 2.25 (s, CH_3), 6.8-7.0 (m, 3H), and 7.2-8.2 (m, 6H); cmr: δ 168.41 (C), 128.98 (CH), 128.78 (CH), 127.33 (CH), 126.99 (CH), 124.65 (CH), 123.69 (CH), 122.80 (CH), 116.42 (CN, $^2J_{CN,CH}$ = 9.2 Hz), 106.62 (4-CH, $^1J_{CH}$ = 168.1 Hz, $^2J_{C\text{-}3,C\text{-}1H}$ or $^3J_{C\text{-}3,C\text{-}4H}$ = *ca.* 2.3 Hz), 44.28 (CH, $^1J_{CH}$ = 151.6, $^3J_{C\text{-}1,C\text{-}3H}$ or $^3J_{C\text{-}1,C\text{-}10H}$ = *ca.* 2.1 Hz), and 20.89 (CH_3, $^1J_{CH}$ = 129.6 Hz). The quaternary carbons were not unambiguously determined.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.43; H, 4.92; N, 11.25.

Dimethyl 8-Methylbenzo[*f*]pyrrolo[1,2-*b*]isoquinoline-9,10-dicarboxylate (**4**).

Method I.

A stirred mixture of **3** and 5% palladium on charcoal in mineral oil was heated at 250° under a nitrogen atmosphere for 1.5 hours. The mixture was cooled and washed with hexane; the residue was extracted with chloroform, the extract was concentrated to dryness, and the residue was purified by chromatography (silica gel/chloroform) to give an unidentified greenish-solid (approximately 15%), m.p. 271-273° and, upon further elution, **4** (26%) as pale yellow needles (from chloroform-ethanol), m.p. 196-197°; ir (mineral oil): 1720, 1700, 1550 w, 1520 w, 1415, 1360, 1295, 1270 w, 1250, 1230 w, 1205, 1190, 1175, 1160, 1145 w, 1135, 1085, 1050 w, 1000 w, 960 w, 940, 815, 800, 780 w, 760, 745, and 720 cm^{-1}; pmr: δ 2.60 (s, CH_3), 3.88 (s, CH_3), 4.03 (s, CH_3), and 7.1-8.4 (m, 8H).

Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.59; H, 4.96; N, 4.00.

Method II.

2-Acetyl-1,2-dihydrobenzo[*f*]isoquinoline-1-carbonitrile (5.00 g.) was dissolved in acetonitrile (40 ml.) and treated with 48% fluoroboric acid (4.1 g.). The crude salt was warmed briefly in absolute ethanol, the cooled mixture was filtered, and the solid was washed with ether and dried. A mixture of the salt [2.88 g., 0.0086 mole, m.p. 160-165° dec] dimethyl acetylenedicarboxylate (1.6 ml., 0.013 mole), absolute ethanol (30 ml.) and dichloromethane (30 ml.) was slowly heated to 75° (oil bath) and maintained at that temperature for one hour. The red mixture was cooled and partially concentrated *in vacuo*; the paste was filtered and the residue was washed with ethanol. The tan-colored powder (0.67 g., 23%) was crystallized from chloroform-ethanol to give **4** which was identical in all respects to the material obtained by Method I. The use of dimethylformamide as a reaction solvent lead to an intractable mixture.

Dimethyl 5,6,8,9,10,11-Hexahydro-3-methylbenzo[*g*]pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**5**).

The hydrofluoroborate salt (90% yield) of **10** was treated with dimethyl acetylenedicarboxylate (1.5 equivalents) in dimethylformamide at 80° for 6 hours. The product which had m.p. 136-138° (cooled and remelted at 149-151°) was crystallized from dichloromethane-methanol and dried (at 130°/0.2 mm) to give **5** as a colorless solid, m.p. 150.5-151.5°; ir (mineral oil): 1720, 1690, 1620, 1575, 1555, 1525, 1420, 1400, 1340, 1305, 1285, 1240, 1205, 1190, 1160, 1145, 1090, 1050, 1020, 990, 955, 925, 910 w, 880, 840, 820, 780, and 715 cm^{-1}; pmr: δ 1.6-1.9 (m, $CH_2CH_2CH_2$), 2.46 (s, CH_3), 2.5-3.0 (m, 3 × CH_2), 3.78 (s, CH_3), 3.88 (s, CH_3), 3.7-4.0 (m, CH_2N), 6.83 (s, 1H), and 7.27 (s, 1H).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.26; H, 6.57; N, 3.96.

N-Formyl-2-[2-(5,6,7,8-tetrahydronaphthyl)]ethylamine (**7a**).

2-[2-(5,6,7,8-Tetrahydronaphthyl)]ethylamine (b.p. 105-110°/0.1 mm), prepared (88%) by lithium aluminum hydride-aluminium chloride reduction of 5,6,7,8-tetrahydronaphthalene-2-acetonitrile, was heated for 17 hours with ethyl formate. The product, **7a** (98%), was distilled, b.p. 160-164°/0.5 mm, m.p. 70-72°; ir (mineral oil): 3220, 3050, 1650, 1560, 1500, 1440, 1340, 1260, 1240, 1190, 1060, 980, 915, 850, 825, 815, 780 and 740 cm^{-1}; pmr: δ 1.6-2.0 (m, $-CH_2CH_2CH_2$), 2.5-3.0 (m, 3 x CH_2), 3.10 -3.70 (m, CH_2N), 6.4-7.9 (m, 3 aromatic protons and NH), and 8.00 (d, HCO-, J = 2 Hz).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.83; H, 8.45; N, 6.87.

3,4,6,7,8,9-Hexahydrobenzo[*g*]isoquinoline (**8a**) and 3,4,7,8,9,10-Hexahydrobenzo[*h*]isoquinoline (**9a**).

A stirred mixture of **7a** and polyphosphoric acid (approximately 11 times the weight of **7a**) was heated at 190-200° for 2.5 hours. The mixture was cooled to 100°, poured into water, made alkaline with ammonium hydroxide, and extracted with benzene. The benzene extract was washed with water, dried (sodium sulfate) and distilled to give (86%) a colorless liquid, b.p. 116-120°/0.8 mm; ir (prominent bands): 3130, 2940, 2860, 1630, 1560, 1435, 1250, 1095, 1005, and 860 cm^{-1}; the pmr spectrum of the crude product (*ca.* 1:1 ratio of isomers) had signals at δ 1.73 (m, $CH_2CH_2CH_2$), 2.4-3.1 (m, $3CH_2$), 3.4-3.9 (m, CH_2N), 6.7-7.2 (m, 2H), 8.23 (t, 0.5 H, J = 2 Hz), and 8.63 (t, 0.5 H J = 2 Hz)..

2-Acetyl-1,2,3,4,6,7,8,9-octahydrobenzo[*g*]isoquinoline-1-carbonitrile (**10**) and 2-Acetyl-1,2,3,4,7,8,9,10-octahydrobenzo[*h*]isoquinoline-1-carbonitrile (**11**).

The mixture of **8a** and **9a** was subjected to the Reissert reaction (method D). The crude product was crystallized (ethanol) to give a nearly quantitative yield (based on one isomer) of **10** as a colorless solid which was recrystallized from ethanol, m.p. 168-5.169.5°; ir (mineral oil): 2250 w, 1650, 1500, 1420, 1350, 1340, 1305, 1290, 1270, 1240, 1200, 1100 w, 1030, 965, 920, 905, 895, 860, 815 w, and 720 cm^{-1}; pmr: δ 1.6-2.0 (m, $-CH_2CH_2CH_2$), 2.18 (s, CH_3), 2.6-3.1 (m, 3 x CH_2), 3.5-4.0 (m, CH_2)N, 6.34 (s, CH), 6.90 (s, 1H), and 7.00 (s, 1H); cmr: δ 169.57 (CO), 138.36 (C), 136.74 (C), 130.69 (C), 129.53 (CH, $^1J_{CH}$ = 155.5 Hz), 127.67 (CH, $^1J_{CH}$ = 156.3 Hz), 125.72 (C), 118.12 (CN, $^2J_{CN,CH}$ = 9.6 Hz), 43.36 (CH, $^1J_{CH}$ = 148.4 Hz), 42.47 (3-CH_2), 29.15 (CH_2), 29.10 (CH_2), 28.16 (CH_2), 23.02 (CH_2), 22.80 (CH_2), and 21.34 (CH_3, $^1J_{CH}$ = 128.8 Hz).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.52; H, 7.13; N, 11.01.

The first ethanol mother liquor was slowly concentrated, with successive removal of additional crops of impure **10**, until succeeding crops contained mainly **11**. The crude **11** was purified by column chromatography (silica gel/benzene-ethyl acetate, 85:15) followed by crystallization (ethanol) to give colorless spars, m.p. 92-93°; ir (mineral oil): 2245 w, 1650, 1510, 1420, 1325, 1270, 1250, 1220, 1200, 1180, 1090, 1030, 995 w, 975, 915, 890, 850, 835 and 815 cm^{-1}; pmr: δ 1.6-2.0 (m, $CH_2CH_2CH_2$), 2.18 (s, CH_3), 2.6-3.1 (m, 3 x CH_3), 3.6-4.1 (m, CH_2N), 6.52 (s, CH), and 6.8-7.2 (AB pattern, H-5 and H-6); cmr: δ 169.36 (CO), 136.57 (C), 134.21 (C), 131.29 (C), 129.99 (CH, $^1J_{CH}$ = 157.2 Hz), 127.12 (C), 126.41 (CH, $^1J_{CH}$ = 158.8 Hz), 117.24 (CN, $^2J_{CN,CH}$ = 10.1 Hz), 42.01 (3-CH_2), 40.95 (CH, $^1J_{CH}$ = 147.7 Hz), 29.78 (CH_2), 28.47 (CH_2), 25.61 (CH_2), 22.94 (CH_2), 22.52 (CH_2), and 21.13 (CH_3, $^1J_{CH}$ = 128.9 Hz).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.61; H, 7.14; N, 10.99.

Dimethyl 4,9-Dihydro-1-methylpyrrolo[1,2-*b*]isoquinoline-2,3-dicarboxylate (**12**).

A mixture of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (1.00 g., 0.0047 mole), dimethyl acetylenedicarboxylate (1.6 g., 0.011 mole), and acetic anhydride (40 ml.) was heated to reflux. After carbon dioxide evolution had appeared to cease, the mixture was heated an additional 20 minutes; the solution was cooled and the volatiles were distilled *in vacuo*. The residue was crystallized (methanol) to give **12** as colorless fluffy crystals (1.11 g., 79%), m.p. 140-142°; ir (mineral oil): 1720, 1690, 1595 w, 1545, 1500, 1410, 1390, 1340, 1320, 1300, 1275, 1200, 1185, 1160, 1080, 1030, 995 w, 960 w, 855, 780, and 750 cm^{-1}; pmr: δ 2.40 (s, CH_3), 3.80 (s, 2 x CH_3), 4.20 (s, CH_2, broadened), 4.88 (s, CH_2, broadened), and 7.20 (4 H, AA'BB' pattern).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.13; H, 5.77; N, 4.66.

Diethyl Pyrrolo[1,2-*f*]phenanthridine-2,3-dicarboxylate (**13a**).

A stirred mixture of 6-methylphenanthridine (1.96 g., 0.010 mole), sodium bicarbonate (2.53 g.), diethyl chlorooxaloacetate (2.24 g., 0.010 mole), and absolute ethanol (50 ml.) was heated under reflux for 2.5 hours. The mixture was concentrated to dryness *in vacuo* and the residue was diluted with water and extracted with benzene. The benzene extract was washed successively with 10% sodium hydroxide solution, water, 3*N* HCl, and water. The dried (sodium sulfate) extract was evaporated to dryness and the residue was crystallized twice from chloroform-ethanol to give **13a** (0.79 g., 21%) as faintly yellow, hair-like needles, m.p. 106-107°; ir (mineral oil): 3140 w, 1710, 1610 w, 1600 w, 1555, 1515, 1500, 1480, 1420, 1330 w, 1290, 1275, 1210, 1170, 1150, 1135, 1115, 1095, 1055, 955 w, 860, 830, 785, 750, 715, and 690 w cm^{-1}; pmr: δ 1.40 (t, CH_3, J = 7.5 Hz), 1.47 (t, CH_3, J = 7.5 Hz), 4.38 (q, CH_2), 4.58 (q, CH_2), 7.0-7.25 (m, 5H), and 7.25-8.10 (m, 4H).

Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.87. Found: C, 73.06; H, 5.29; N, 3.87.

Diethyl 1-Methylpyrrolo[1,2-*f*]phenanthridine-2,3-dicarboxylate (**13b**).

This compound was obtained as colorless needles (14%) from 6-ethylphenanthridine by the procedure used for **13a** except that the heating period was 14 hours. Compound **3b** had m.p. 112-113° (chloroform-ethanol); ir (mineral oil): 1720, 1690, 1610 w, 1595 w, 1545, 1500, 1420, 1320 w, 1300 w, 1260, 1210, 1155, 1145, 1110, 1080, 1060, 1025, 940 w, 860 w, 790 w, 765, and 750 cm^{-1}; pmr: δ 1.40 (t, 2 × CH_3, J = 7.5 Hz), 2.67 (s, CH_3), 4.40 (q, CH_2, J = 7.5 Hz), 4.50 (q, CH_2, J = 7.5 Hz), 7.1-7.77 (m, 5H), and 7.9-8.20 (m, 3H).

Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.85; H, 5.63; N, 3.73. Found: C, 73.70; H, 5.73; N, 3.69.

Dimethyl 5,6-Dihydro-3-methylbenzo[*g*]pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**14**).

A mixture of the diester **5** (1.67 g.), 5% palladium on charcoal (0.49 g.), and mineral oil (25 ml.) was stirred (nitrogen atmosphere) at 185-200° for 4 hours. The mixture was cooled, diluted with hexane, and filtered. The residue was washed with chloroform and the chloroform solution was evaporated to dyrness. The crude product (m.p. 162-164°, 0.83 g.), which showed a bluish uv fluorescence, was crystallized from ethanol and the needles (m.p. 167-169°) were chromatographed (silica gel/chloroform); the fractions rich in **14** were combined and crystallized to a constant m.p. 171-172° (chloroform-ethanol); ir (mineral oil): 1720, 1690, 1600 w, 1560 w, 1530 w, 1330, 1290, 1235, 1200, 1190 w, 1155, 1090, 1050, 990 w, 950 w, 900, 850 w, 825 w, 780 w, 745, and 700 cm^{-1}; pmr: δ 2.46 (s, CH_3), 2.9-3.2 (m, CH_2), 3.80 (s, CH_3), 3.93 (s, CH_3), 3.7-4.1 (m, CH_2N), 7.2-7.7 (m, 5H), and 8.07 (s, H-12).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.09; H, 5.52; N, 3.98.

Methyl 3-Methylbenzo[*g*]pyrrolo[2,1-*a*]isoquinoline-1-, or 2-carboxylate.

A mixture of **5** (0.54 g.), 10% palladium on charcoal (0.13 g.), and mineral oil (20 ml.) was stirred at 235-250° for one hour under a nitrogen atmosphere. The mixture was cooled, diluted with hexane, and filtered. The residue was washed with chloroform and the yellow chloroform solution was concentrated and chromatographed (silica gel/chloroform); the product was twice crystallized from chloroform-ethanol to give yellow needles, m.p. 189-190°; ir (mineral oil): 1700, 1650 w, 1595 w, 1550, 1525, 1435, 1420, 1230, 1200, 1160, 1145, 1125 w, 1075, 950, 875, 860 w, 805 w, 770, 755, 740, and 725 cm^{-1}; pmr: δ 2.63 (s, CH_3), 3.86 (s, CH_3), 6.60 (d, 1 H, J = 8 Hz), 7.10-7.45 (m, 4H), 7.5-7.9 (m, 3H), and 8.20 (s, H).

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.22; N, 4.84. Found: C, 78.79; H, 5.25; N, 4.84.

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