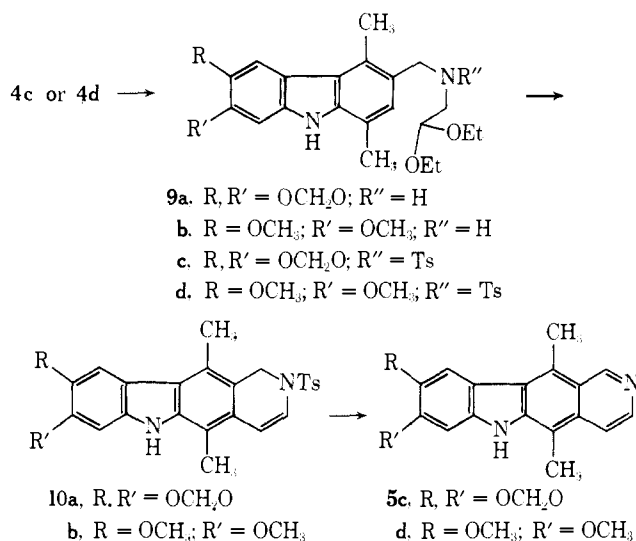
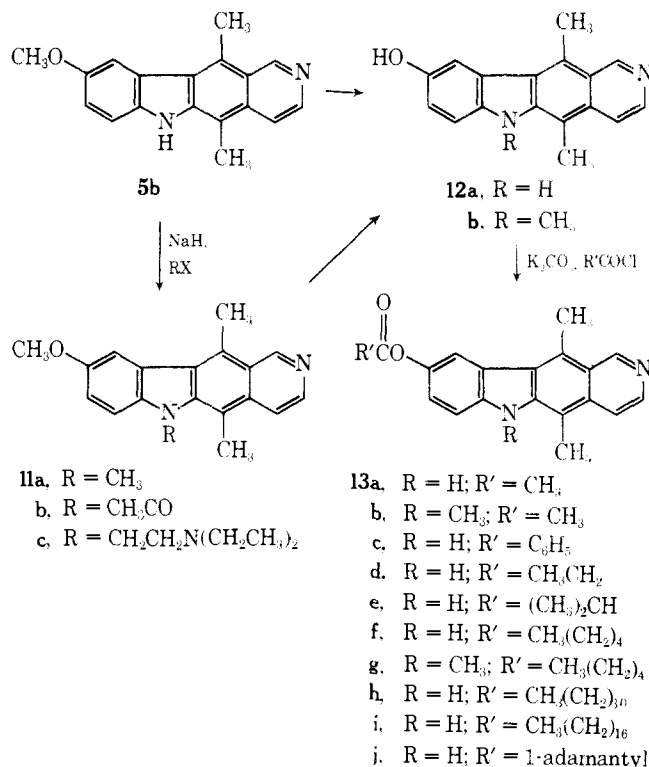


with a mixture of 6 *N* HCl in dioxane at room temperature resulted in the rapid (within 15 min) formation of a colorless precipitate which subsequently redissolved and was replaced after several hours by the gradual precipitation of 8,9-methylenedioxyellipticine (5c) as its hydrochloride. The intermediate compound was shown to be the expected *N*-tosyldihydroellipticine derivative 10a. Contrary to expectations¹⁵ this material could not be transformed into 5c under the strongly basic conditions that had converted 7 into 8. However, as is evident from the result described above, 10a readily lost *p*-toluenesulfonic acid to give 5c when treated with HCl in dioxane. 5,6-Dimethoxyindole 1d was also converted into 8,9-dimethoxyellipticine by this modified procedure. It has been reported¹⁶ recently that *N*-tosyl derivatives related to 6 can be converted directly to the corresponding isoquinolines using similar acidic conditions.

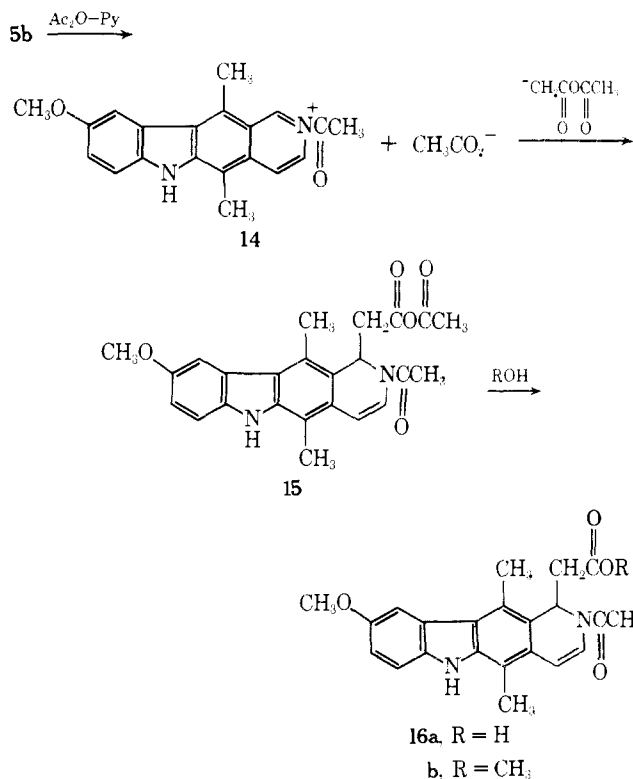


Several acyl derivatives of ellipticine were prepared using 9-methoxyellipticine 5b or 9-methoxy-6-methylellipticine 11a as starting materials. Demethylation of 5b or 11a with pyridine hydrochloride furnished the corresponding 9-hydroxyellipticine 12a or its *N*-methyl analog 12b, respectively. Treatment of 12 with the appropriate acyl halide in the presence of Na₂CO₃ or K₂CO₃ furnished the corresponding 9-acyloxy derivative 13 (a-j). A representative *N*-acylated analog 11b was made by treating 5b with sodium hydride in THF, followed by the addition of acetyl chloride.

Parentetically, treatment of 9-methoxyellipticine 5b under mild acetylating conditions, i.e., Ac₂O and pyridine at room temperature, resulted in the formation of the anhydride 15 which was characterized by the typical infrared absorptions. This product, depending on the work-up used, furnished the corresponding acid 16a or its methyl ester 16b. Compound 15 presumably arises from a condensation of the anion of acetic anhydride (from acetate ion and ace-



tic anhydride) with the *N*-acetylpyridinium intermediate 14. The identity of these compounds is fully supported by physical-chemical data. While such a reaction to our knowledge is unprecedented in isoquinoline chemistry, the isolation of *N*-acetyl-1,2-dihydro-2-pyridylacetic acid, albeit in low yield, has been reported¹⁷ as an artifact during an acetylation reaction using Ac₂O and pyridine. The authors showed that the formation of the *N*-acetyl compound was due to the reaction of Ac₂O with pyridine presumably by a mechanism similar to that postulated for the formation of 16a.



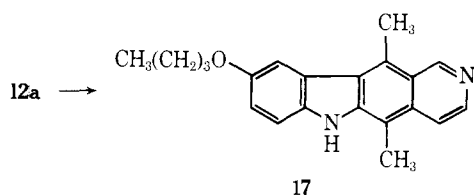
Several *O*- and *N*-alkylated analogs of ellipticine were also prepared. 9-*n*-Butoxyellipticine 17 was obtained by

Table I. Antitumor Activity of Ellipticine and Its Derivatives^a

Compd	Sarcoma 180			Ehrlich carcinoma					
	Dose, mg/kg	Survivors	Index C/T	Dose, mg/kg	Survivors	Index C/T	Dose, mg/kg	Survivors	Index C/T
5a	125 ip ^b	8/16	8.65				125 ip	8/16	18.78
	62.5	13/16	5.45				62.5	16/16	5.74
	31.2	14/16	2.56				31.2	8/8	1.85
	15.6	14/16	1.54				15.6	8/8	1.68
5b	125 ip	7/8	5.99				125 ip	5/8	5.98
	62.5	8/8	2.96	80 po ^b	7/8	4.80	62.5	8/8	2.13
	31.2	8/8	2.79	40	8/8	2.18	31.2	8/8	1.18
	15.6	8/8	2.46				15.6	8/8	1.46
10a	80 ip	5/8	3.87				40 ip	7/8	1.85
	40	8/8	4.24				80 ip	6/8	2.42
11b	80 ip	8/8	2.80						
	40	8/8	1.47						
11c	10 ip	7/8	1.18	125 po	6/8	4.47	125 po	7/8	4.96
				62.5	8/8	1.65	62.5	7/8	1.06
12a	20 ip	8/8	4.06				20 ip	9/24	1.77
							10	8/8	0.81
13a	80 ip	4/8	10.20				40 ip	7/8	12.50
	20	7/8	2.87				20	8/8	2.11
13d	80 ip	8/8	2.25	80 po	7/8	2.40			
	40	8/8	1.74	40	7/8	1.43			
13e	80 ip	6/8	3.83	80 po	7/8	8.55			
	40	8/8	2.75	40	6/8	1.70			
13f	80 ip	8/8	2.18	80 po	7/8	1.45			
	40	8/8	1.19	40	7/8	1.23			
13j	80 ip	4/8	5.56	80 po	7/8	1.61			
	40	7/8	2.53	40	7/8	1.89			
18	80 ip	7/8	5.14				80 ip	4/8	3.84
	40	8/8	2.87				40	8/8	2.14
	20	8/8	1.70				20	8/8	1.66
20a	80 ip	8/8	2.58				80 ip	8/8	3.29
	40	8/8	1.94				40	8/8	1.70

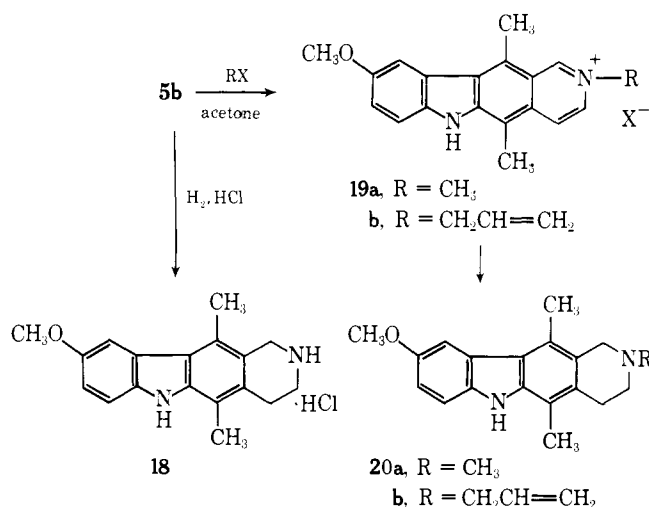
^aFor test methodologies, see E. Grunberg, H. N. Prince, E. Titsworth, G. Beskid, and M. D. Tendler, *Chemotherapy*, 11, 249 (1966). A compound is considered to show significant antitumor activity if the ratio of the average tumor weight of the treated (T) animals is 50% or less of the average tumor weight of the untreated control (C) animals (C/T index ≥ 2.0). ^bip = intraperitoneally; po = orally.

the reaction of 12a with 1-butanol in the presence of the di-nepentyl acetal of DMF.¹⁸ Treatment of 5b with sodium hydride in a suitable aprotic solvent (THF or DMF) followed by the addition of the appropriate alkyl halide led to the 6-alkylated ellipticines 11a and 11c.



Hydrogenation of 5b in the presence of HCl furnished the 1,2,3,4-tetrahydro derivative as its stable hydrochloride 18. The instability of the parent amine has been documented by Büchi et al.⁵ The corresponding N-alkylated tetrahydroellipticines 20a and 20b were prepared according to the published procedure,¹⁹ i.e., via reduction of the intermediate quaternary ammonium salts 19a and 19b, respectively.

Biological Results. Ellipticine 5a, 9-methoxyellipticine 5b, and 19 derivatives (5c, 5d, 10a, 11b, 11c, 12a, 13a, 13c-f, 13h-j, 16a, 16b, 18, 20a, and 20b) were tested for antitumor activity against the solid form of Sarcoma 180 and



all but 13d-f and 13j were tested against the solid form of Ehrlich carcinoma in mice. The results of the tests with those compounds which exerted antitumor activity are shown in Table I. The activity of ellipticine and 9-methoxyellipticine was confirmed.¹⁻⁴ Eleven derivatives (10a, 11b, 11c, 12a, 13a, 13d-f, 13j, 18, and 20a) were active by the in-

traperitoneal and/or oral route against Sarcoma 180 and five derivatives (11b, 11c, 13a, 18, and 20a) were also active against Ehrlich carcinoma. However, none of the derivatives showed activity superior to that of ellipticine or 9-methoxyellipticine. Eight derivatives (5c, 5d, 13c, 13h, 13i, 16a, 16b, and 20b) failed to exhibit antitumor activity.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within 0.4% of the theoretical values. The NMR spectra were determined using a Varian A-60 or HA-100 spectrometer and the chemical shifts are given in parts per million downfield from Me₄Si. Only those resonance signals necessary for differentiating the various compounds are given.

6,7-Methylenedioxy-1,4-dimethylcarbazole (2c). A solution of 5,6-methylenedioxyindole 1c (30 g, 0.186 mol), hexane-2,5-dione (25.0 ml), and BF₃ etherate (30 ml) in dioxane (250 ml) was heated at reflux for 5 hr. The solution was concentrated to dryness and the residue was dissolved in MeOH (100 ml) and diluted with Et₂O (500 ml). The resulting solution was washed with 0.5 N NaOH solution and with H₂O (2 × 100 ml) and the aqueous layers were backwashed with Et₂O (2 × 250 ml). Some solid material was removed and discarded, and the combined organic layers were dried (Na₂SO₄) and evaporated. Crystallization of the residue from benzene gave 17.2 g of the carbazole, mp 157–158° (reported¹⁴ 158–160°).

6,7-Dimethoxy-1,4-dimethylcarbazole (2d). A solution of 5,6-dimethoxyindole 1d (5.5 g, 31 mmol) in dioxane (75 ml) containing hexane-2,5-dione (4.0 g, 35 mmol) and BF₃ etherate (5 ml) was heated at reflux for 6 hr and worked up as in the previous example except that the dried (Na₂SO₄) Et₂O extract was concentrated to ~20 ml. The resulting crystals were filtered off to give 1.1 g of the carbazole 2d, mp 177–179°. The analytical sample was recrystallized from C₆H₆: mp 179–180.5°; NMR (CDCl₃) δ 2.47 (s, 3 H, CH₃-), 2.66 (s, 3 H, CH₃-), 3.90 (s, 3 H, CH₃O-), and 4.0 (s, 3 H, CH₃O-). Anal. (C₁₆H₁₇NO₂) C, H, N.

3-Formyl-6,7-methylenedioxy-1,4-dimethylcarbazole (3c). A mixture of 2c (11.3 g, 47.2 mmol), *N*-methylformanilide (11.0 g, 81 mmol), and POCl₃ (10.2 g) in *o*-dichlorobenzene (55 ml) was heated without stirring on steam bath for 4 hr. A solution of NaOAc (30 g) in H₂O (400 ml) was added and the mixture was steam distilled. The resulting solid was collected by filtration and dried in vacuo. It was placed in a Soxhlet extractor and extracted using PhCH₃ (2 l.) over 2 days. The hot extract was decolorized (charcoal) and quickly filtered through Celite. The filtrate was allowed to cool and the resulting crystalline material was collected to give 10.3 g of 3c, mp 278–280° (reported¹⁴ 278–279°). Concentration of the mother liquors to ~200 ml afforded an additional 0.8 g of material, mp 245–260°.

3-Formyl-6,7-dimethoxy-1,4-dimethylcarbazole (3d). 2d (13.5 g, 52.9 mmol) was formylated as above using *N*-methylformanilide (12 g, 89 mmol) and POCl₃ (11.2 g) in *o*-dichlorobenzene (60 ml). The product was isolated by concentration of the PhCH₃ extract to ~400 ml to give 8.6 g of crystalline 3d, mp 252–256°. The analytically pure material obtained from MeOH–H₂O: mp 261.5–263°; NMR (DMSO) δ 10.27 (s, 1 H, -CHO). Anal. (C₁₇H₁₇NO₃) C, H, N.

3-(2,2-Diethoxyethyliminomethyl)-6,7-methylenedioxy-1,4-dimethylcarbazole (4c). A slurry of 3c (15.0 g, 56.1 mmol) in aminoacetaldehyde diethyl acetal (27.5 ml) was heated on the steam bath with occasional mixing for 2.5 hr. The mixture was evaporated to dryness; then it was dissolved in CHCl₃ (~150 ml) and filtered to remove a trace amount of starting material. The solvent was again removed in vacuo to give 19.9 g of the solid azomethine. Crystallization of a small portion from C₆H₆ furnished the analytically pure material: mp 150–151°; NMR (CDCl₃) δ 8.77 (s, 1 H, -CH=N-). Anal. (C₂₂H₂₆N₂O₄) C, H, N.

3-(2,2-Diethoxyethyliminomethyl)-6,7-dimethoxy-1,4-dimethylcarbazole (4d). A slurry of 8.6 g (30.3 mmol) of 3d in aminoacetaldehyde diethyl acetal (15 ml) was heated on a steam bath for 3.5 hr. A work-up identical with that described above furnished 12.2 g of crude 4d as a solid. Crystallization from C₆H₆ afforded analytically pure material, mp 143–144°. Anal. (C₂₃H₃₀N₂O₄) C, H, N.

3-(2,2-Diethoxyethylaminomethyl)-6,7-methylenedioxy-1,4-dimethylcarbazole (9a). NaBH₄ (7.4 g) was added over a period of 5 min to a stirred solution of 4c (18.3 g, 47.8 mmol) in

methanol at room temperature. After 1 hr the solution was concentrated to dryness. The residue was dissolved in C₆H₆ and washed with H₂O three times. The organic layer was then shaken with sufficient 0.5 N HCl solution so that the mixture remained acidic. A solid formed which was recovered by filtration and combined with the acidic aqueous layer. The resulting mixture was made basic with 10 N NaOH and extracted with CHCl₃ (3 × 200 ml). The extracts were washed with H₂O, dried (Na₂SO₄), and evaporated to give 18 g of the crude amine 9a. Crystallization of the residue (C₆H₆–C₆H₁₄) afforded 10.2 g of material: mp 117–118°; NMR (CDCl₃) δ 3.94 (s, 2 H, ArCH₂N-) and 1.67 (s, 1 H, NH). Anal. (C₂₂H₂₈N₂O₄) C, H, N.

3-(2,2-Diethoxyethylaminomethyl)-6,7-dimethoxy-1,4-dimethylcarbazole (9b). Azomethine 4d (10.2 g, 25.6 mmol) was reduced using NaBH₄ as above to give after work-up 9.0 g of crude amine 9c, mp 100–101°. Crystallization of a small sample from ether–hexane gave the pure amine, mp 106–108°. Anal. (C₂₃H₃₂N₂O₄) C, H, N.

3-[*N*-Tosyl-(2,2-diethoxyethylaminomethyl)]-6,7-methylenedioxy-1,4-dimethylcarbazole (9c). A solution of the amine 9a (14.7 g, 38.2 mmol) in a mixture of THF (150 ml) and H₂O (300 ml) containing Na₂CO₃ (5.0 g) was treated with *p*-toluenesulfonyl chloride (9.5 g, 50 mmol) and stirred at room temperature. A precipitate formed and after 1 hr the reaction mixture was diluted with H₂O (1.5 l.). The solid was recovered by filtration, air-dried, and crystallized from ethyl acetate to give 17.0 g of the *N*-tosylate 9c, mp 216–217°. Anal. (C₂₉H₃₄N₂O₆S) C, H, N, S.

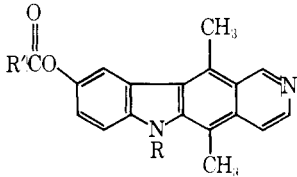
3-[*N*-Tosyl-(2,2-diethoxyethylaminomethyl)]-6,7-dimethoxy-1,4-dimethylcarbazole (9d). A mixture of 8.7 g (21.7 mmol) of the amine 9b, Na₂CO₃ (2.8 g), THF (200 ml), and H₂O (100 ml) was treated as above with tosyl chloride (5.3 g, 27.8 mmol). A noncrystalline material separated from the reaction medium and after 2 hr, the mixture was diluted to ~1 l. with H₂O and extracted with EtOAc (3 × 500 ml). The extracts were washed in turn with 0.1 N HCl (150 ml), water (150 ml), NaHCO₃ solution, and water. Evaporation of the combined, dried (Na₂SO₄) organic layers gave ~12 g of solid *N*-tosylate. Crystallization of the crude material from EtOAc furnished 9.2 g of 9d, mp 168–170°. Concentration of the mother liquors gave an additional 0.6 g of material, mp 165–167°. Recrystallization from EtOAc afforded to pure material, mp 170–172°. Anal. (C₃₀H₃₈N₂O₆S) C, H, N, S.

8,9-Methylenedioxy-5,11-dimethyl-6H-pyrido[4,3-*b*]carbazole (8,9-Methylenedioxyellipticine, 5c). A solution of 9c (7.0 g, 13.3 mmol) in dioxane (600 ml) containing 85 ml of 6 N HCl was stirred at room temperature overnight. The resulting precipitate was filtered and washed well with THF, and then was dispersed in a mixture of THF (500 ml) and 1 N NaOH solution (150 ml) and shaken until all solids dissolved. The layers were separated and the organic layer was washed with brine (twice); then it was dried (Na₂SO₄) and concentrated to give 2.8 g (74%) of the yellow 8,9-methylenedioxyellipticine 5c. Crystallization from ethanol furnished 2.5 g of pure material: mp 323° dec (vacuum); NMR (DMSO) δ 11.13 (s, 1 H, NH), 9.55 (br s, 1 H, C-1 H), 8.43 (br s, 1 H, C-3 H), 7.85 (hr s, 1 H, C-4 H), 7.80 (s, 1 H, C-10 H), 7.03 (s, 1 H, C-7 H), 6.07 (s, 2 H, -OCH₂O-), 3.10 (s, 3 H, CH₃), and 2.69 (s, 3 H, CH₃); uv (EtOH) 213 nm (ε 23,700), 230 (23,950) 249 (16,700), 272 inf (39,700), 282 (44,200), 316 (60,200), 243 (7700), and 395 (4200). Anal. (C₁₈H₁₄N₂O₂) C, H, N.

8,9-Dimethoxy-5,11-dimethyl-6H-pyrido[4,3-*b*]carbazole (8,9-Dimethoxyellipticine, 5d). A solution of 9d (1.3 g, 2.4 mmol) in dioxane (50 ml) and 6 N HCl (25 ml) was stirred at room temperature overnight. The precipitate that had formed was collected by filtration, washed with dioxane, and then suspended in H₂O (300 ml). The suspension was made basic using 1 N NaOH and after stirring at room temperature for 15 min, the solid was collected and dried to give 360 mg (49%) of 8,9-dimethoxyellipticine 5d, mp 315–319°. Recrystallization from MeOH gave analytically pure material: mp 322–324°; NMR (DMSO) δ 11.09 (s, 1 H, NH), 9.25 (s, 1 H, C-1 H), 7.95 (q, 2 H, C-3 H and C-4 H), 7.15 (s, 1 H, C-10 H), 6.66 (s, 1 H, C-7 H), 3.84 (s, 3 H, OCH₃), 3.80 (s, 3 H, OCH₃), 2.73 (s, 3 H, -CH₃), and 2.46 (s, 3 H, -CH₃); uv (EtOH) 211 nm (ε 20,500), 229 (24,500), 248 (16,250), 271 inf (33,000), 283 (43,600), 300 inf (46,000), 309 (61,500), 340 (6200), and 390 (3500). Anal. (C₁₉H₁₈N₂O₂) C, H, N.

1,2-Dihydro-2-tosyl-8,9-methylenedioxy-5,11-dimethyl-6H-pyrido[4,3-*b*]carbazole (10a). A solution of 9c (6.0 g, 11.4 mmol) in dioxane (210 ml) and 6 N HCl (85 ml) was stirred at 25–30° for 15 min, and then it was cooled in ice. The precipitate that had formed was collected by filtration and washed with a minimum amount of cold THF and then with water. The solids were

Table II. Ellipticine Esters



No.	R	R'	Crystn solvent	Yield, %	Formula	Mol wt	Analyses	Mp, °C
13a	H	CH ₃	THF-EtOAc	86	C ₁₉ H ₁₆ N ₂ O ₂	304.4	H, N	303-304 (vacuum)
13b	CH ₃	CH ₃	CH ₂ Cl ₂ -EtOAc	70	C ₂₀ H ₁₈ N ₂ O ₂	318.4	C, H, N	198-199
13c	H	C ₆ H ₅	MeOH	88	C ₂₄ H ₁₈ N ₂ O ₂	366.4	C, H, N	294-296 (vacuum)
13d	H	CH ₃ CH ₂	THF-EtOAc	80	C ₂₀ H ₁₈ N ₂ O ₂	318.4	C, H, N	280-281 (vacuum)
13e	H	(CH ₃) ₂ CH	THF-EtOAc	89	C ₂₁ H ₂₀ N ₂ O ₂	332.4	C, H, N	304-305 (vacuum)
13f	H	CH ₃ (CH ₂) ₄	THF-EtOAc	80	C ₂₃ H ₂₄ N ₂ O ₂	360.5	C, H, N	235-236 (vacuum)
13g	CH ₃	CH ₃ (CH ₂) ₄	EtOAc	67	C ₂₄ H ₂₆ N ₂ O ₂	374.5	C, H, N	151-152
13h	H	CH ₃ (CH ₂) ₁₀	CH ₂ Cl ₂ -MeOH	74	C ₂₉ H ₃₆ N ₂ O ₂	444.6	C, H, N	189-190.5
13i	H	CH ₃ (CH ₂) ₁₆	CH ₂ Cl ₂ -MeOH	63	C ₃₅ H ₄₈ N ₂ O ₂	528.8	C, H, N	183-185
13j	H	1-Adamantyl	MeOH	34	C ₂₈ H ₂₈ N ₂ O ₂	424.5	H, N	350

extracted with THF and evaporation of the dried extract furnished 2.0 g of 10a. Recrystallization from ethanol furnished the pure compound: mp 209-210°; NMR (DMSO) δ 6.81 (d, 1 H, C-4 H), 6.25 (s, 1 H, C-3 H), 4.57 (s, 2 H, C-1 H₂), 2.57 (s, 3 H, -CH₃), 2.35 (s, 3 H, -CH₃), and 2.30 (s, 3 H, -CH₃); uv (EtOH) 226 nm (ϵ 24,800), 248 (32,300), 258 (32,600), 340 (25,000) 252 (24,800), and 370 (20,700). Anal. (C₂₅H₂₂N₂O₄S) C, H, N, S.

9-Methoxy-5,6,11-trimethyl-6H-pyrido[4,3-b]carbazole (11a). A solution of 5b (10.0 g, 36.2 mmol) in dry DMF (120 ml) was treated with 2.18 g of NaH (50% oil dispersion, 47.5 mmol) and stirred for 5 min. MeI (5.1 g, 36.0 mmol) in DMF (70 ml) was added rapidly and the mixture was stirred overnight at room temperature. The solution was poured into 1 l. of H₂O and extracted with CHCl₃ (6 \times 400 ml). The dried (Na₂SO₄) CHCl₃ extract was passed through a short column of Woelm basic alumina (120 g, grade III) and then was evaporated in vacuo. Crystallization of the residue from EtOAc afforded 6.8 g of 11a, mp 153-154° [lit.¹ 158° (vacuum)].

6-Acetoxy-9-methoxy-5,11-dimethyl-6H-pyrido[4,3-b]carbazole (11b). A solution of 5b (4.0 g, 14.5 mmol) in dry THF (125 ml) was treated with NaH (1.37 g, 50% dispersion in oil) and the mixture was stirred at room temperature for 1 hr. Acetyl chloride (4.5 ml) was added and the reaction was heated at reflux overnight. The mixture was cooled and poured into saturated NaHCO₃ solution and extracted with CHCl₃. The CHCl₃ layer was shaken with 1 N HCl (50 ml) and the acidic extract was separated, made basic with NaHCO₃, and reextracted using CHCl₃. The dried (Na₂SO₄) organic layer yielded 1.2 g of the *N*-acetyl derivative 11b contaminated with a trace of starting material 5b. Extensive purification via repeated crystallizations from MeOH and then C₆H₆ were required to obtain pure 11b: mp 159-160°; NMR (DMSO) δ 2.48 (s, 3 H, CH₃CO); ir (CHCl₃) 1700 cm⁻¹. Anal. (C₂₀H₁₈N₂O₂) C, H, N.

9-Methoxy-6-(2-diethylaminoethyl)-5,11-dimethyl-6H-pyrido[4,3-b]carbazole (11c). Sodium hydride (50% oil dispersion, 1.6 g, 33.3 mmol) was washed with pentane and then suspended in dry DMF (100 ml). 9-Methoxyellipticine 5b (5.6 g, 20.3 mmol) was added and the mixture was stirred at room temperature for 30 min. A 3.2 M solution of diethylaminoethyl chloride in toluene (9.4 ml, 30 mmol) was added and the reaction was allowed to proceed at room temperature for 16 hr. The solvent was removed in vacuo and the residue was partitioned between H₂O (50 ml) and CH₂Cl₂ (100 ml). The aqueous layer was washed with CH₂Cl₂ (twice) and the combined organic layers were dried (MgSO₄) and evaporated to give 6.5 g of a dark red oil. A solution of the residue in Et₂O was decolorized (charcoal) and concentrated until crystallization occurred, giving 4.3 g of 11c, mp 96-98°. Additional crystallizations from Et₂O gave the analytical sample: mp 101-102°; NMR (CDCl₃) δ 4.42 (t, 2 H, -CH₂N), 2.71 [m, 2 H, -CH₂N(C₂H₅)₂], 2.58 [q, 4 H, 2(-NCH₂CH₃)], and 1.01 [t, 6 H, 2(CH₃CH₂-)]. Anal. (C₂₄H₂₉N₃O) C, H, N.

Dihydrochloride of 11c. The free base was crystallized from an excess of methanolic HCl to give the dihydrochloride salt 11d, mp

285-286° dec (vacuum). Anal. (C₂₄H₂₉N₃O·2HCl·1.5H₂O) C, H, N, Cl.

9-Hydroxy-5,11-dimethyl-6H-pyrido[4,3-b]carbazole (12a). 9-Methoxyellipticine 5b (30 g, 0.108 mol) was mixed with pyridine hydrochloride (500 g) and heated with gentle stirring at 200-210° for 40 min. The reaction mixture was cooled and diluted with brine (3 l.), and the resulting precipitate was filtered and washed with brine. The solids were then dissolved in hot H₂O (1.2 l.), and after cooling the filtered solution was poured into 5% aqueous NaHCO₃ (1 l.). The crude 9-hydroxyellipticine that precipitated was filtered, then dried (27.5 g), and dissolved in THF (4 l.) using a Soxhlet extractor. After the solution was concentrated to ~1.5 l. and cooled, 23 g of 9-hydroxyellipticine, mp 306-309°, was recovered by filtration. Crystallization from MeOH gave analytically pure material: mp 324-325° (vacuum) (The wide difference in melting point may be due to polymorphism. This was the only time that this melting point had been observed. Most purified samples melted in the range 307-310°); NMR (DMSO) δ 10.98 (s, 1 H, NH), 9.61 (s, 1 H, C-1 H), 8.46 (d, 1 H, C-4 H), 7.86 (d, 1 H, C-3 H), 7.82 (d, 1 H, C-10 H), 7.45 (d, 1 H, C-7 H), 7.08 (d of d, 1 H, C-8 H), 3.24 (s, 3 H, CH₃), and 2.75 (s, 3 H, CH₃); uv (EtOH) 212 nm (ϵ 24,900), 246 (24,900), 278 (42,400), 295 (52,500), 339 (5800), 355 (3000), and 410/2 (3000). Anal. (C₁₇H₁₄N₂O·0.25H₂O) C, H, N, H₂O.

9-Hydroxy-5,6,11-trimethyl-6H-pyrido[4,3-b]carbazole (12b). A mixture of 11a (6.5 g, 22.4 mmol) in 120 g of pyridine hydrochloride was heated at 210° for 1.5 hr. The reaction mixture was worked up as in the previous example to give 6.0 g of crude product. The dried solids were extracted (Soxhlet) into MeOH (1 l.) and the extract on cooling yielded 5.2 g of 12b, mp 336-337° (vacuum). Crystallization from DMF gave the pure sample: mp 337-338° (vacuum); NMR, too insoluble; uv (EtOH) 211 nm (ϵ 24,000), 249 (23,000), 277 (32,000), 300 (42,500), 342 (5800), 360 (4950), and 410 (3540). Anal. (C₁₈H₁₆N₂O) C, H, N.

Esters of 9-Hydroxyellipticines 13a-j. These esters (see Table II) were prepared essentially by the procedure described below for 9-dodecanoyloxyellipticine 13h.

Lauroyl chloride (1.65 g, 7.5 mmol) was added to a stirred suspension of 12a (1.3 g, 5.0 mmol) and Na₂CO₃ (5.0 g in Me₂CO, 75 ml). After 2 hr (the initial reddish purple color had changed to a pale yellow within 90 min), H₂O was added slowly to a final volume of ~600 ml. The precipitate was collected by filtration and was washed with hot H₂O. (In the case of 13b and 13g, the precipitate was oily so the acetone was removed in vacuo and the product isolated by extraction into CHCl₃.) The dried solid was crystallized from CH₂Cl₂-MeOH to give 1.63 g (74%) of yellow crystalline ester, mp 188-190°. The analytically pure material melted in the range 189-190.5°; NMR (DMSO) δ 1.26 (br s, 20 H, 10CH₂) and 0.85 (t, 3 H, CH₃CH₂-); uv (EtOH) 205 nm (ϵ 18,100), 218 (17,800), 240 infl (20,300), 249 (23,000), 277 (48,000), 289 (63,200), 298 (60,700), 317 (3980), 332 (5780), 348 (3210), 370 infl (2500), 387 (3600), and 405 (3620). Anal. (C₂₉H₃₆N₂O₂) C, H, N.

(±)-1,2-Dihydro-2-acetyl-9-methoxy-5,11-dimethyl-6H-

pyrido[4,3-*b*]carbazol-1-ylacetic Acid (16a) and Its Methyl Ester (16b). 9-Methoxyellipticine **5b** (1.0 g, 3.62 mmol) in a mixture of Ac₂O (100 ml) and pyridine (100 ml) was left at room temperature for 4 days during which time a solid precipitated. The reaction mixture was divided in two portions, "A" and "B", which were both evaporated to dryness in vacuo.

"A" was dissolved in THF and 1 *N* NaOH (5 ml) was added. The organic solvent was removed in vacuo to give a clear aqueous solution, which was diluted with water and washed three times with CH₂Cl₂. The aqueous layer was acidified and dried to give 0.4 g of the acid **16a**. Recrystallization from DMF-H₂O furnished the pure material: mp 221° dec (vacuum); NMR (DMSO) δ 6.91 (d, 1 H, C-4 H), 6.55 (m, 1 H, C-1 H), 6.37 (d, 1 H, C-3 H), 2.54 (m, 2 H, -CH₂CO₂H), and 2.14 (s, 3 H, CH₃CO); uv [EtOH-DMSO (50:1)] 268 nm (ε 30,000), 292 sh (118,000), 303 (113,000), 335 (29,400), 360 inf (11,500), and 375 sh (7800). Anal. (C₂₂H₂₂N₂O₄) C, H, N.

"B" was dissolved in MeOH (10 ml) and after being heated for 10 min the solution was evaporated in vacuo. The residue was dissolved in CHCl₃ and the extract was washed in turn with aqueous NaHCO₃, 0.5 *N* HCl solution, and water. The dried (Na₂SO₃) CHCl₃ layer was evaporated and the residue was crystallized from CH₂Cl₂-MeOH to yield 190 mg of the methyl ester **16b**: mp 286° dec (vacuum); NMR (DMSO) δ 3.89 (s, 3 H, OCH₃), 3.56 (s, 3 H, OCH₃), and 2.18 (s, 3 H, CH₃CO); uv (EtOH) 220 nm (ε 24,700) 256 sh (26,300), 267 (28,550), 334 (27,850), and 377 sh (7200). Anal. (C₂₃H₂₄N₂O₄) C, H, N.

9-*n*-Butoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (17). A mixture of 9-hydroxyellipticine **12a** (2.0 g, 7.62 mmol), *N,N*-dimethylformamide dioneopentyl acetal (2 ml), and 1-butanol (40 ml) was heated at reflux for 48 hr. The solvent was removed in vacuo and the residue was dissolved in EtOAc (700 ml). The solution was decolorized (charcoal) and concentrated to ~200 ml to give 1.1 g of **17**, mp 248-249° (vacuum). An additional 0.1 g, mp 241-244°, was recovered from the mother liquors. Recrystallization from EtOAc furnished the analytical sample: mp 249-250° (vacuum); NMR (DMSO) δ 3.97 (t, 2 H, -CH₂O-), 1.70 (m, 4 H, -CH₂CH₂-), and 1.03 (t, 3 H, CH₃CH₂-). Anal. (C₂₁H₂₂N₂O) C, H, N; C: calcd, 79.21; found, 79.78.

1,2,3,4-Tetrahydro-9-methoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole Hydrochloride (18). To a solution of **5b** (2.5 g, 9.05 mmol) in MeOH was added 0.65 *N* methanolic HCl (14.5 ml, 9.4 mmol). The mixture was hydrogenated overnight using 0.5 g of Pt₂O as catalyst. The reaction had stopped after 575 ml (23°, 760 mm) of H₂ had been absorbed. The solution was filtered through Celite and evaporated to give 2.7 g of crude material. Recrystallization of the material from MeOH-EtOAc and then from MeOH furnished 1.91 g of **18**: mp 323-324°; NMR (DMSO) δ 4.30 (s, 2 H, C-1 H₂) and 3.20 (br m, 4 H, C-3 H₂ and C-4 H₂); uv (EtOH) 233 nm sh (ε 22,500), 238 (33,800), 248 (30,900), 258 (25,100), 269 (17,400), 292 sh (9900), 302 (16,000), 327 sh (2150), 343 (3600), and 357 (3700). Anal. (C₁₈H₂₀N₂O·HCl) Cl: calcd, 11.19; found, 10.66.

1,2,3,4-Tetrahydro-9-methoxy-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazole (20a). **5b** (2.0 g) was converted via the methiodide **19a** according to the method of Loder¹⁹ to give 1.5 g of **20a**, mp 189-190°. Recrystallization from CH₂Cl₂-MeOH furnished the pure material, mp 191-193° (vacuum) (reported¹⁹ 193°).

1,2,3,4-Tetrahydro-9-methoxy-2-allyl-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (20b). Allyl bromide (50 ml) was added to a solution of **5b** (2.0 g, 7.24 mmol) in Me₂CO (3 l). After 1 hr,

the crystalline precipitate that had formed was filtered and washed with acetone to give 2.5 g of the quaternary salt **19b**. The salt was dispersed in MeOH (1 l) containing H₂O (25 ml) and NaBH₄ (1.3 g) was added in portions over 5 min. After 75 min, the pale yellow solution was concentrated to ~100 ml and H₂O (400 ml) was added. The resulting solid was filtered and washed with water to give, after drying, 1.7 g of the crude product. Three recrystallizations from CH₂Cl₂-CH₃OH furnished 1.08 g of **20b** as pale yellow needles: mp 169-172° (vacuum); NMR (CDCl₃) δ 5.98 (m, 1 H, -CH=CH₂), 5.25 (m, 2 H, -CH=CH₂), 3.76 (s, 2 H, C-1 H₂), 3.28 (d, 2 H, NCH₂CH=), and 2.86 (m, 4 H, C-3 H₂ and C-4 H₂); uv (EtOH) 238 nm (ε 36,900), 249 (34,700), 258 (24,700), 269 (15,400), 292 sh (12,000), 303 (21,050), 342 (4100), and 356 (4250). Anal. (C₂₁H₂₄N₂O) C, H, N.

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