trometrically at 625 mμ with a Baush and Lomb Spectronic 20 spectrophotometer in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at 0 absorbance. For each assay, appropriate controls were performed and reproducible results of the minimum inhibitory concentrations of compounds were obtained on repeating the assay 12 times.

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Ellipticine Derivatives

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Several acyloxy and alkyl derivatives of ellipticine have been prepared. In addition, a modified synthesis leading to the hitherto unobtainable 8,9-dimethoxy- and 8,9-methylenedioxyellipticines is described. Some of the derivatives described herein exhibit antitumor activity. However, none of the compounds showed activity superior to that of the naturally occurring pyridocarbazoles, ellipticine and 9-methoxyellipticine.

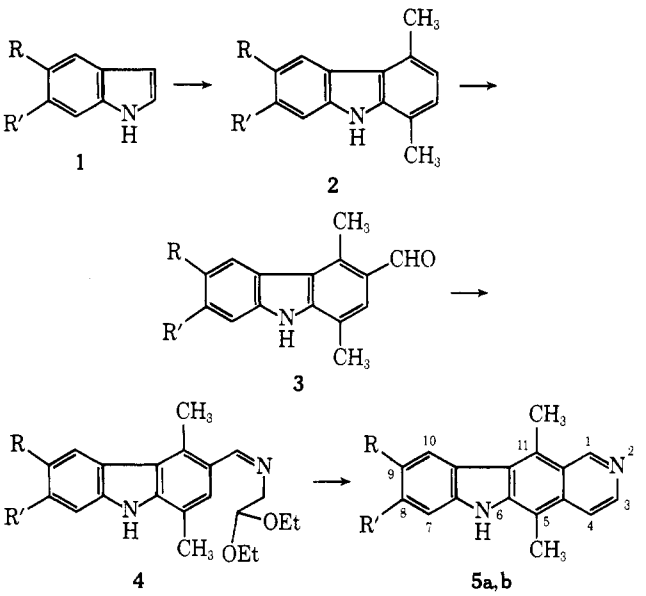
The disclosure of potentially useful tumor inhibitory[1-4] properties of the pyridocarbazole alkaloids, ellipticine **5a** and 9-methoxyellipticine **5b**, has prompted considerable interest in the compounds. These alkaloids are widely distributed in the genera *Aspidosperma*[5] and *Orchrosia*[6] and several syntheses have been elaborated in attempts to make ellipticine[1,7-10] and, more particularly, related substances[1,2,10-14] available for evaluation as chemotherapeutic agents. In the search for compounds which might exhibit similar or hopefully superior antitumor properties, it has been generally established that skeletal modifications of ellipticine diminish its antitumor effect.[11-14] Accordingly, this report describes the preparation of compounds that are peripheral modifications of the parent molecule.

Thus far, the most versatile and efficient method for the syntheses of ellipticine and its analogs has been that as shown in Scheme I developed by the Australian workers.[1] However, the rather severe conditions required to cyclize the azomethine **4** precluded the preparation of several potentially useful analogs, e.g., **5c**[14] and **5d**. It was therefore desirable to find a method that would effect the transformation **4** into **5** under milder conditions.

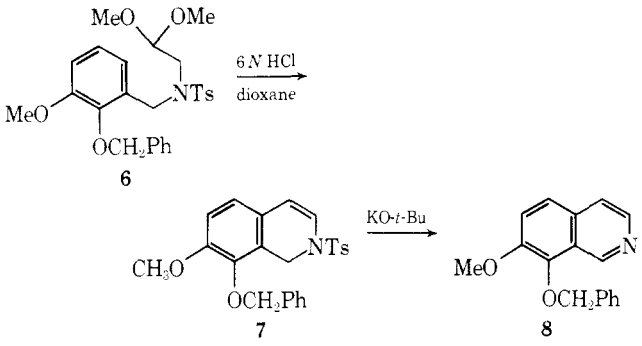
Jackson and Stewart[15] reported a new isoquinoline synthesis that involved cyclization of the *N*-tosyl derivative **6** using HCl in dioxane to give the *N*-tosyldihydroisoquinoline **7** and subsequent conversion of **7** to the isoquinoline **8** on treatment with KO-*t*-Bu. Modification of the existing ellipticine synthesis by the successful incorporation of this method has enabled the preparation of hitherto unattainable analogs.

Thus 5,6-methylenedioxyindole **1c** was condensed with hexane-2,5-dione to give the corresponding carbazole **2c** which was formylated and then allowed to react with aminoacetal to give the Schiff base **4c**.[14] Reduction of **4c** with sodium borohydride in methanol furnished the amine **9a** which when allowed to react with tosyl chloride afforded the corresponding *N*-tosyl derivative **9c**. Treatment of **9c**

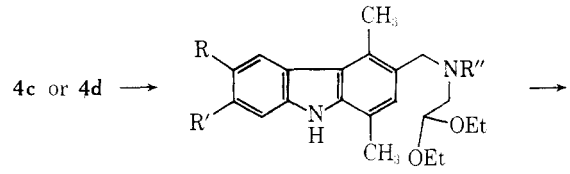
Scheme I



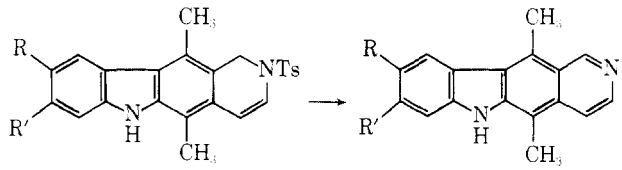
	R	R'
a	H	H
b	OCH_3	H
c	OCH_2O	
d	OCH_3	OCH_3



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 expectations[15] 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*-toluenesulfinic 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 reported[16] recently that *N*-tosyl derivatives related to **6** can be converted directly to the corresponding isoquinolines using similar acidic conditions.



9a. R,R′ = OCH_2O; R″ = H
b. R = OCH_3; R′ = OCH_3; R″ = H
c. R,R′ = OCH_2O; R″ = Ts
d. R = OCH_3; R′ = OCH_3; R″ = Ts

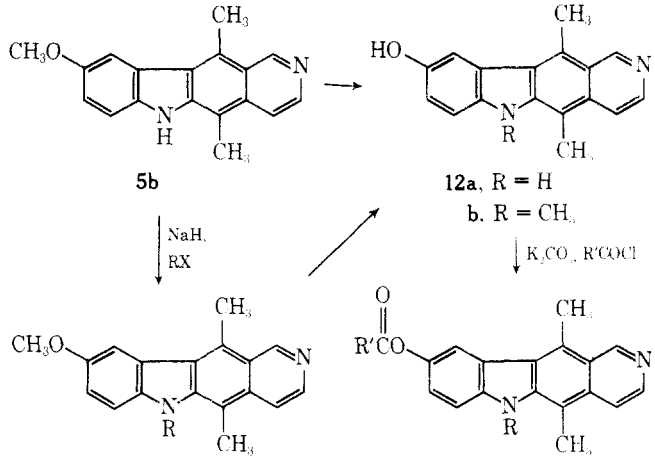


10a, R,R′ = OCH_2O
b, R = OCH_3; R′ = OCH_3

5c, R,R′ = OCH_2O
d. R = OCH_3; R′ = OCH_3

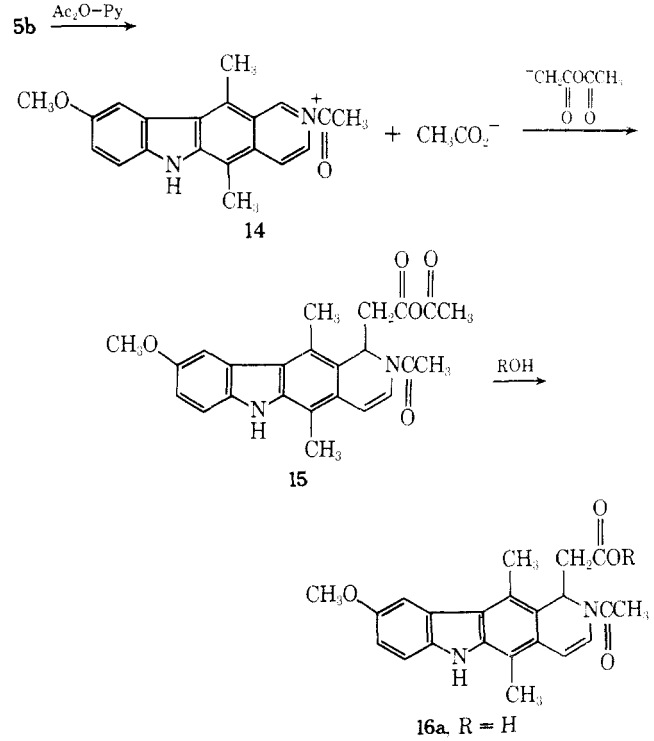
Several acyl derivatives of ellipticine were prepared using 9-methoxyellipticine **5b** or 9-methoxy-6-methylellipticine **11a** as starting materials. Demethylation of **5b** or **11a** with pyridine hydrochloride furnished the corresponding 9-hydroxyellipticine **12a** or its *N*-methyl analog **12b,** respectively. Treatment of **12** with the appropriate acyl halide in the presence of Na_2CO_3 or K_2CO_3 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.

Parenthetically, treatment of 9-methoxyellipticine **5b** under mild acetylating conditions, i.e., Ac_2O 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-



13a, R = H; R′ = CH_3
b, R = CH_3; R′ = CH_3
c, R = H; R′ = C_6H_5
d, R = H; R′ = CH_3CH_2
e, R = H; R′ = $(CH_3)_2CH$
f, R = H; R′ = $CH_3(CH_2)_4$
g, R = CH_3; R′ = $CH_3(CH_2)_4$
h, R = H; R′ = $CH_3(CH_2)_{10}$
i, R = H; R′ = $CH_3(CH_2)_{16}$
j, R = H; R′ = 1-adamantyl

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 reported[17] as an artifact during an acetylation reaction using Ac_2O and pyridine. The authors showed that the formation of the *N*-acetyl compound was due to the reaction of Ac_2O with pyridine presumably by a mechanism similar to that postulated for the formation of **16a.**



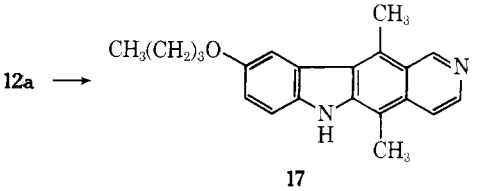
Several O- and N-alkylated analogs of ellipticine were also prepared. 9-*n*-Butoxyellipticine **17** was obtained by

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	8/8	4.24				40 ip	7/8	1.85
11b	80 ip	8/8	2.80				80 ip	6/8	2.42
	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

[a]For test methodologies, see E. Grunberg, H. N. Prince, E. Titsworth, G. Beskid, and M. D. Tendler, *Chemotherapia*, 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). [b]ip = intraperitoneally; po = orally.

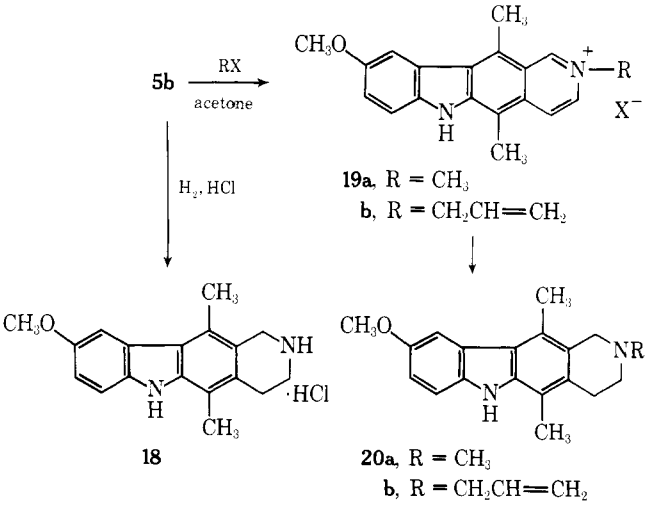
the reaction of **12a** with 1-butanol in the presence of the dineopentyl acetal of DMF.[18] Treatment of **5b** with sodium hydride in a suitable aprotic solvent (THF or DMF) followed by the addition of the appropriate alkyl halide led to the 6-alkylated ellipticines **11a** and **11c**.



17

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 Me_4Si. 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 BF_3 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 Et_2O (500 ml). The resulting solution was washed with 0.5 *N* NaOH solution and with H_2O (2 × 100 ml) and the aqueous layers were backwashed with Et_2O (2 × 250 ml). Some solid material was removed and discarded, and the combined organic layers were dried (Na_2SO_4) and evaporated. Crystallization of the residue from benzene gave 17.2 g of the carbazole, mp 157–158° (reported[14] 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 BF_3 etherate (5 ml) was heated at reflux for 6 hr and worked up as in the previous example except that the dried (Na_2SO_4) Et_2O 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 C_6H_6: mp 179–180.5°; NMR ($CDCl_3$) δ 2.47 (s, 3 H, CH_3–), 2.66 (s, 3 H, CH_3–), 3.90 (s, 3 H, CH_3O–), and 4.0 (s, 3 H, CH_3O–). Anal. ($C_{16}H_{17}NO_2$) 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 $POCl_3$ (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 H_2O (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 $PhCH_3$ (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° (reported[14] 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 $POCl_3$ (11.2 g) in *o*-dichlorobenzene (60 ml). The product was isolated by concentration of the $PhCH_3$ extract to ~400 ml to give 8.6 g of crystalline **3d,** mp 252–256°. The analytically pure material obtained from MeOH–H_2O: mp 261.5–263°; NMR (DMSO) δ 10.27 (s, 1 H, –CHO). Anal. ($C_{17}H_{17}NO_3$) 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 $CHCl_3$ (~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 C_6H_6 furnished the analytically pure material: mp 150–151°; NMR ($CDCl_3$) δ 8.77 (s, 1 H, –CH=N–). Anal. ($C_{22}H_{26}N_2O_4$) 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 C_6H_6 afforded analytically pure material, mp 143–144°. Anal. ($C_{23}H_{30}N_2O_4$) C, H, N.

3-(2,2-Diethoxyethylaminomethyl)-6,7-methylenedioxy-1,4-dimethylcarbazole (9a). $NaBH_4$ (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 C_6H_6 and washed with H_2O 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 $CHCl_3$ (3 × 200 ml). The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give 18 g of the crude amine **9a.** Crystallization of the residue (C_6H_6–C_6H_{14}) afforded 10.2 g of material: mp 117–118°; NMR ($CDCl_3$) δ 3.94 (s, 2 H, $ArCH_2N$–) and 1.67 (s, 1 H, NH). Anal. ($C_{22}H_{28}N_2O_4$) 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 $NaBH_4$ 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. ($C_{23}H_{32}N_2O_4$) 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 H_2O (300 ml) containing Na_2CO_3 (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 H_2O (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. ($C_{29}H_{34}N_2O_6S$) C, H, N, S.

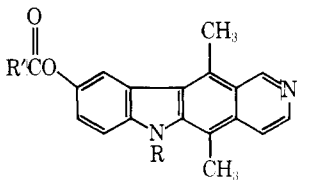
3-[*N*-Tosyl-(2,2-diethoxyethylaminomethyl)]-6,7-dimethoxy-1,4-dimethylcarbazole (9d). A mixture of 8.7 g (21.7 mmol) of the amine **9b,** Na_2CO_3 (2.8 g), THF (200 ml), and H_2O (100 ml) was treated as above with tosyl chloride (5.3 g, 27.8 mmol). A noncrystalline material separated from the reaction medium and after 2 hr, the mixture was diluted to ~1 l. with H_2O and extracted with EtOAc (3 × 500 ml). The extracts were washed in turn with 0.1 *N* HCl (150 ml), water (150 ml), $NaHCO_3$ solution, and water. Evaporation of the combined, dried (Na_2SO_4) 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. ($C_{30}H_{38}N_2O_6S$) C, H, N, S.

8,9-Methylenedioxy-5,11-dimethyl-6*H*-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 it 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 (Na_2SO_4) 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 333° 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 (br 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, $-OCH_2O$–), 3.10 (s, 3 H, CH_3), and 2.69 (s, 3 H, CH_3); uv (EtOH) 213 nm (ε 23,700), 230 (23,950) 249 (16,700), 272 infl (39,700), 282 (44,200), 316 (60,200), 243 (7700), and 395 (4200). Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

8,9-Dimethoxy-5,11-dimethyl-6*H*-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 H_2O (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, OCH_3), 3.80 (s, 3 H, OCH_3), 2.73 (s, 3 H, $-CH_3$), and 2.46 (s, 3 H, $-CH_3$); uv (EtOH) 211 nm (ε 20,500), 229 (24,500), 248 (16,250), 271 infl (33,000), 283 (43,600), 300 infl (46,000), 309 (61,500), 340 (6200), and 390 (3500). Anal. ($C_{19}H_{18}N_2O_2$) C, H, N.

1,2-Dihydro-2-tosyl-8,9-methylenedioxy-5,11-dimethyl-6*H*-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	$C_{19}H_{16}N_2O_2$	304.4	H, N	303–304 (vacuum)
13b	CH_3	CH_3	CH_2Cl_2–EtOAc	70	$C_{20}H_{18}N_2O_2$	318.4	C, H, N	198–199
13c	H	C_6H_5	MeOH	88	$C_{24}H_{18}N_2O_2$	366.4	C, H, N	294–296 (vacuum)
13d	H	CH_3CH_2	THF–EtOAc	80	$C_{20}H_{18}N_2O_2$	318.4	C, H, N	280–281 (vacuum)
13e	H	$(CH_3)_2CH$	THF–EtOAc	89	$C_{21}H_{20}N_2O_2$	332.4	C, H, N	304–305 (vacuum)
13f	H	$CH_3(CH_2)_4$	THF–EtOAc	80	$C_{23}H_{24}N_2O_2$	360.5	C, H, N	235–236 (vacuum)
13g	CH_3	$CH_3(CH_2)_4$	EtOAc	67	$C_{24}H_{26}N_2O_2$	374.5	C, H, N	151–152
13h	H	$CH_3(CH_2)_{10}$	CH_2Cl_2–MeOH	74	$C_{29}H_{36}N_2O_2$	444.6	C, H, N	189–190.5
13i	H	$CH_3(CH_2)_{16}$	CH_2Cl_2–MeOH	63	$C_{35}H_{48}N_2O_2$	528.8	C, H, N	183–185
13j	H	1-Adamantyl	MeOH	34	$C_{28}H_{28}N_2O_2$	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 H_2), 2.57 (s, 3 H, $-CH_3$), 2.35 (s, 3 H, $-CH_3$), and 2.30 (s, 3 H, $-CH_3$); uv (EtOH) 226 nm (ε 24,800), 248 (32,300), 258 (32,600), 340 (25,000) 252 (24,800), and 370 (20,700). Anal. ($C_{25}H_{22}N_2O_4S$) C, H, N, S.

9-Methoxy-5,6,11-trimethyl-6*H*-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 H_2O and extracted with $CHCl_3$ (6 × 400 ml). The dried (Na_2SO_4) $CHCl_3$ 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-6*H*-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 $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ layer was shaken with 1 *N* HCl (50 ml) and the acidic extract was separated, made basic with $NaHCO_3$, and reextracted using $CHCl_3$. The dried (Na_2SO_4) 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 C_6H_6 were required to obtain pure **11b:** mp 159–160°; NMR (DMSO) δ 2.48 (s, 3 H, CH_3CO); ir ($CHCl_3$) 1700 cm^{-1}. Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

9-Methoxy-6-(2-diethylaminoethyl)-5,11-dimethyl-6*H*-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 H_2O (50 ml) and CH_2Cl_2 (100 ml). The aqueous layer was washed with CH_2Cl_2 (twice) and the combined organic layers were dried ($MgSO_4$) and evaporated to give 6.5 g of a dark red oil. A solution of the residue in Et_2O was decolorized (charcoal) and concentrated until crystallization occurred, giving 4.3 g of **11c,** mp 96–98°. Additional crystallizations from Et_2O gave the analytical sample: mp 101–102°; NMR ($CDCl_3$) δ 4.42 (t, 2 H, $-CH_2N$), 2.71 [m, 2 H, $-CH_2N(C_2H_5)_2$], 2.58 [q, 4 H, $2(-NCH_2CH_3)$], and 1.01 [t, 6 H, $2(CH_3CH_2-)$]. Anal. ($C_{24}H_{29}N_3O$) 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. ($C_{24}H_{29}N_3O \cdot 2HCl \cdot 1.5H_2O$) C, H, N, Cl.

9-Hydroxy-5,11-dimethyl-6*H*-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 H_2O (1.2 l.), and after cooling the filtered solution was poured into 5% aqueous $NaHCO_3$ (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, CH_3), and 2.75 (s, 3 H, CH_3); 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. ($C_{17}H_{14}N_2O \cdot 0.25H_2O$) C, H, N, H_2O.

9-Hydroxy-5,6,11-trimethyl-6*H*-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. ($C_{18}H_{16}N_2O$) 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 Na_2CO_3 (5.0 g in Me_2CO, 75 ml). After 2 hr (the initial reddish purple color had changed to a pale yellow within 90 min), H_2O was added slowly to a final volume of ~600 ml. The precipitate was collected by filtration and was washed with hot H_2O. (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 $CHCl_3$.) The dried solid was crystallized from CH_2Cl_2–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, $10CH_2$) and 0.85 (t, 3 H, CH_3CH_2-); 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. ($C_{29}H_{36}N_2O_2$) C, H, N.

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

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 Ac_2O (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 CH_2Cl_2. The aqueous layer was acidified and dried to give 0.4 g of the acid **16a.** Recrystallization from DMF–H_2O 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, $-CH_2CO_2H$), and 2.14 (s, 3 H, CH_3CO); uv [EtOH–DMSO (50:1)] 268 nm (ε 30,000), 292 sh (118,000), 303 (113,000), 335 (29,400), 360 infl (11,500), and 375 sh (7800). Anal. ($C_{22}H_{22}N_2O_4$) 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 $CHCl_3$ and the extract was washed in turn with aqueous $NaHCO_3$, 0.5 *N* HCl solution, and water. The dried (Na_2SO_3) $CHCl_3$ layer was evaporated and the residue was crystallized from CH_2Cl_2–MeOH to yield 190 mg of the methyl ester **16b:** mp 286° dec (vacuum); NMR (DMSO) δ 3.89 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), and 2.18 (s, 3 H, CH_3CO); uv (EtOH) 220 nm (ε 24,700) 256 sh (26,300), 267 (28,550), 334 (27,850), and 377 sh (7200). Anal. ($C_{23}H_{24}N_2O_4$) 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 dineopentyl 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, $-CH_2O-$), 1.70 (m, 4 H, $-CH_2CH_2-$), and 1.03 (t, 3 H, CH_3CH_2-). Anal. ($C_{21}H_{22}N_2O$) 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 Pt_2O as catalyst. The reaction had stopped after 575 ml (23°, 760 mm) of H_2 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 H_2) and 3.20 (br m, 4 H, C-3 H_2 and C-4 H_2); 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. ($C_{18}H_{20}N_2O$·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 Loder[19] to give 1.5 g of **20a,** mp 189–190°. Recrystallization from CH_2Cl_2–MeOH furnished the pure material, mp 191–193° (vacuum) (reported[19] 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 Me_2CO (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 H_2O (25 ml) and $NaBH_4$ (1.3 g) was added in portions over 5 min. After 75 min, the pale yellow solution was concentrated to ~100 ml and H_2O (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 CH_2Cl_2–CH_3OH furnished 1.08 g of **20b** as pale yellow needles: mp 169–172° (vacuum); NMR ($CDCl_3$) δ 5.98 (m, 1 H, $-CH{=}CH_2$), 5.25 (m, 2 H, $-CH{=}CH_2$), 3.76 (s, 2 H, C-1 H_2), 3.28 (d, 2 H, $NCH_2CH{=}$), and 2.86 (m, 4 H, C-3 H_2 and C-4 H_2); 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. ($C_{21}H_{24}N_2O$) C, H, N.

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