Synthesis of Potential Antineoplastic Agents. XXVII. (Reissert Compound Studies. XLIV.). The Ellipticine Reissert Compound as an Intermediate in the Syntheses of Ellipticine Analogs

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Ellipticine and a number of ellipticine analogs were converted to Reissert compounds. Alkylation of the 6-benzylellipticine Reissert compound gave a series of 1-substituted-6-benzylellipticines. 1-Cyanoellipticine, obtained through the Reissert compound, was hydrolyzed to ellipticine-1-carboxamide hydrochloride which was active against P388 lymphocytic leukemia. Other aspects of the chemistry of the ellipticine Reissert compound are presented.

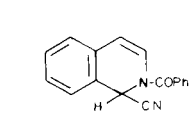
J. Heterocyclic Chem., **19**, 1275 (1982).

After the discovery of anti-tumor activity in ellipticine (**1**) and related compounds (1), interest developed in the synthesis of ellipticine analogs (2). The reported formation of an ellipticine Reissert compound (**2**) (3) opens the possibility of the synthesis, using Reissert compound chemistry (4), of a variety of 1-substituted ellipticine analogs as potential antineoplastic agents.

Reaction of ellipticine (**1**) with benzoyl chloride and trimethylsilyl cyanide afforded the Reissert compound, 2-benzoyl-1-cyano-1,2-dihydroellipticine (**2**), in 87% yield. The Reissert compounds **3-8** were all prepared by a similar treatment of the appropriate ellipticine with benzoyl chloride and trimethylsilyl cyanide. Interestingly, unlike 3,4-dihydro-β-carboline (5), neither ellipticine (**1**) nor 9-methoxyellipticine (**9**) underwent benzoylation at the 6-position to afford the 6-benzoyl Reissert compounds. The aminopropyl ellipticine (**10**), however, yielded the benzamidopropyl Reissert compound (**6**) under similar conditions. Also the reactions did not require the use of a catalyst; the same product in about the same yield was obtained whether anhydrous aluminum chloride was used as a catalyst or not. The formation of the ellipticine Reissert compound (**2**) from ellipticine (**1**) may be compared with the formation of the isoquinoline Reissert compound (**11**) from isoquinoline; it may also be contrasted with the failure to obtain a Reissert compound from γ-carboline (5), a three-ring analog of ellipticine.

The benzenesulfonyl analog (**12**) of the ellipticine Reissert compound (**2**) and the 4-chlorobutanoyl Reissert compound **13** were obtained by reacting ellipticine (**1**) or **14** respectively with the appropriate chloride and trimethylsilyl cyanide. The formation of these compounds parallels similar observations with quinoline, (6,7) isoquinoline, (6,7), 3,4-dihydro-β-carboline, (5) and phthalazine (8). Other Reissert compounds are listed in Table I.

Reaction of the ellipticine Reissert compound (**2**) with benzyl bromide and sodium hydride in anhydrous dimethylformamide gave a product which was an inseparable mixture of several components. This observation contrasts the facile dialkylation of the 3,4-dihydro-β-carboline Reissert compound under similar conditions (5). It was decided to investigate the use of a 6-protected ellipticine Reissert compound in the place of the ellipticine Reissert compound (**2**). Any of the several 6-substituted ellipticine Reissert compounds (**3-7**) that were already synthesized would have served this purpose, however, their



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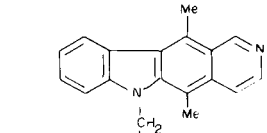

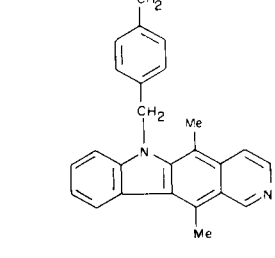

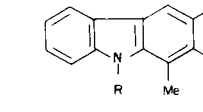

19, R = CH_2Ph

50, R = H

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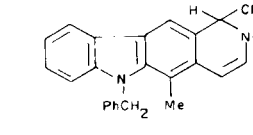

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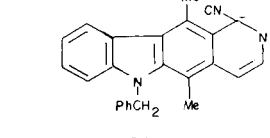

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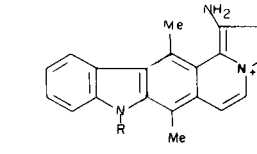

47, R = H

48, R = CH_2Ph

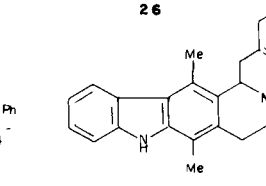

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Table I

Ellipticine Reissert Compounds

Compound	Mp, °C (a)	Yield, %	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Benzoyl-1-cyano-1,2-dihydroellipticine (**2**)	299-302	87	$C_{25}H_{19}N_3O$	79.55	5.07	11.14	79.45	5.19	10.85
2-Benzoyl-1-cyano-6-(2-propenyl)-1,2-dihydroellipticine (**3**)	164-166	70	$C_{28}H_{23}N_3O$	80.55	5.55	10.07	80.46	5.48	9.95
2-Benzoyl-1-cyano-6-(5-hexenyl)-1,2-dihydroellipticine (**4**)	164-165	81	$C_{31}H_{29}N_3O$	81.01	6.36	9.14	80.81	6.41	9.01
2-Benzoyl-6-(2-benzoyloxyethyl)-1-cyano-1,2-dihydroellipticine (**5**)	140-142	72	$C_{34}H_{27}N_3O_3$	77.69	5.18	7.99	77.58	5.27	7.79
6-(3-Benzamidopropyl)-2-benzoyl-1-cyano-9-methoxy-1,2-dihydroellipticine (**6**)	152-161	84	$C_{36}H_{32}N_4O_3$	76.03	5.67	9.85	75.92	5.68	9.78
2-Benzoyl-1-cyano-9-methoxy-6-(3-(*N*)-phthalimidopropyl)-1,2-dihydroellipticine (**7**)	174-175 (b)	92	$C_{37}H_{30}N_4O_4$	74.72	5.09	9.42	74.64	5.37	9.26
2-Benzoyl-1-cyano-9-methoxy-1,2-dihydroellipticine (**8**)	241-242 (c)	95	$C_{26}H_{21}N_3O_2$	76.65	5.20	10.31	76.46	5.28	10.23
2-Benzoyl-6-benzyl-1-cyano-1,2-dihydroellipticine (**21**)	170-172	83	$C_{32}H_{25}N_3O$	82.20	5.39	8.99	82.39	5.39	9.09
2-Benzoyl-6-benzyl-1-cyano-11-desmethyl-1,2-dihydroellipticine (**22**)	183-186	67	$C_{31}H_{23}N_3O$	82.09	5.11	9.27	81.69	5.13	9.26
2-(4-Chlorobutanoyl)-1-cyano-9-methoxy-6-(3-(*N*)-phthalimidopropyl)-1,2-dihydroellipticine (**13**)	119-126	72	$C_{34}H_{31}ClN_4O_4$	68.62	5.25	9.42	68.62	5.24	9.40
6-Benzyl-2-(4-chlorobutanoyl)-1-cyano-1,2-dihydroellipticine (**23**)	dec > 153	78	$C_{29}H_{26}ClN_3O \cdot 0.1CH_2Cl_2$ (d)	73.34	5.54	8.82	73.25	5.57	8.73
6-Benzyl-2-carboethoxy-1-cyano-1,2-dihydroellipticine (**25**)	173-174	63	$C_{28}H_{25}N_3O_2$	77.22	5.79	9.65	77.26	5.64	9.55

(a) Recrystallized from ethanol-dichloromethane unless otherwise noted. (b) Recrystallized from ethanol-chloroform. (c) Recrystallized from methanol-chloroform. (d) Calcd. for Cl: 8.93. Found: 8.52.

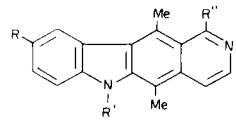
Table II

Spectral Properties of Compounds Listed in Table I

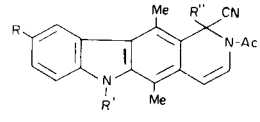
Compound	
2	ir: 3390, 2950, 1670, 1640, 1600, 1350, 1285 cm^{-1}; ms: m/e (%) 351.1463 (14.01, $C_{24}H_{19}N_2O$, $[M\text{-}CN]^+$), 350.1430 (51.62, $C_{24}H_{18}N_2O$, $[M\text{-}HCN]^+$), 246.1149 (68.38, $C_{17}H_{14}N_2$, $[M\text{-}PhCOCN]^+$), 245.1075 (24.28, $C_{17}H_{13}N_2$, $[M\text{-}PhCOCN\text{-}H]^+$), 231.0917 (11.50, $C_{16}H_{11}N_2$, $[M\text{-}PhCOCN\text{-}Me]^+$), 105.0339 (100, C_7H_5O), 77.0389 (20.18, C_6H_5)
3	ir: 3100-3050, 1670, 1640, 1460, 1365, 1285 cm^{-1}
4	ir: 3075, 2950, 1670, 1640, 1600, 1580, 1460, 1280, 920 cm^{-1}
5	ir: 3075, 2975, 1710, 1670, 1635, 1600, 1460, 1280 cm^{-1}
6	ir: 3300, 2950, 1670, 1630, 1490, 1235, 710 cm^{-1}
7	ir: 3000-2975, 1710, 1670, 1640, 1590, 1060, 1040 cm^{-1}; ms: m/e (%) 463.1900 (13.11, $C_{29}H_{25}N_3O_3$, $[M\text{-}PhCOCN]^+$), 289.1333 (5.13, $C_{19}H_{17}N_2O$), 275.1190 (2.23, $C_{18}H_{15}N_2O$), 188.0713 (1.64, $C_{11}H_{10}NO_2$), 160.0405 (0.87, $C_9H_6NO_2$), 131.0370 (79.44, PhCOCN), 105.0342 (100, C_7H_5O), 77.0395 (61.59, C_6H_5)
8	ir: 3450, 2980, 1670, 1640, 1610, 1510, 1360, 1290 cm^{-1}
21	ir: 3075, 3050, 2985, 1670, 1630, 1455 cm^{-1}
22	ir: 3050, 1640, 1620, 1450, 1350, 880 cm^{-1}
13	ir: 2950, 1760, 1700, 1670, 1630, 1225, 1040, 730 cm^{-1}
23	ir: 2950, 1670, 1630, 1050, 730 cm^{-1}
25	ir: 2975, 1710, 1630, 1285, 1020, 740 cm^{-1}

availability was limited. Attention was, therefore, directed towards the synthesis of a 6-substituted ellipticine with a 6-substituent that would be easily removed, if so desired, under mild conditions. The benzyl group was found to be easily attached by reacting (the sodium salt of) ellipticine with benzyl bromide to afford 6-benzylellipticine (**18**). 6-Benzyl-11-desmethylellipticine (**19**) was prepared similarly. 6-Benzylellipticine (**18**) thus synthesized proved to be a convenient starting material in the synthesis of several ellipticine derivatives. It was anticipated that the 6-benzyl group could easily be removed, if so desired, by hydrogenolysis. It is of interest to note here that the use of α,α'-dibromo-*p*-xylene in the place of benzyl bromide in the above alkylation procedure led to the novel dimeric ellipticine, **20**.

As was the case with ellipticine and its other derivatives, reaction of 6-benzylellipticine (**18**) with benzoyl chloride and trimethylsilyl cyanide afforded the Reissert compound, 2-benzoyl-6-benzyl-1-cyano-1,2-dihydroellipticine (**21**). The Reissert compound **22**, the 4-chlorobutanoyl Reissert compound **23**, the benzenesulfonyl Reissert compound analog **24** and the carboethoxy Reissert compound analog **25** were all prepared by the use of appropriate acid chloride with **18**.



Compound No.	R	R'	R''
1	H	H	H
9	Methoxyl	H	H
10	Methoxyl	3-Amino-1-propyl	H
14	Methoxyl	3-Phthalimido-1-propyl	H
15	H	Allyl	H
16	H	5-Hexen-1-yl	H
17	H	2-Benzyloxyeth-1-yl	H
18	H	Benzyl	H
34	H	Benzyl	Cyano
35	H	5-Hexen-1-yl	Cyano
36	H	Benzyl	Benzyl
37	H	Benzyl	Ethyl
38	H	Benzyl	Methyl
39	H	Benzyl	3-Trifluoromethyl-benzyl
40	H	Benzyl	*p*-Bromobenzyl
41	H	Benzyl	1-Propen-1-yl
43	H	H	Cyano
44	H	H	Carboxamido
45	H	Benzyl	Carboxamido
46	H	H	Carboxamido, hydrochloride
49	Methoxyl	3-Amino-1-propyl	H, dihydrochloride



Compound No.	R	R'	R''	Ac
2	H	H	H	Benzoyl
3	H	Allyl	H	Benzoyl
4	H	5-Hexen-1-yl	H	Benzoyl
5	H	2-Benzoyloxyethyl	H	Benzoyl
6	Methoxyl	3-Benzoylamido-propyl	H	Benzoyl
7	Methoxyl	3-Phthalimido-propyl	H	Benzoyl
8	Methoxyl	H	H	Benzoyl
12	H	H	H	Benzenesulfonyl
13	Methoxyl	3-Phthalimido-propyl	H	4-Chlorobutanoyl
21	H	Benzyl	H	Benzoyl
23	H	Benzyl	H	4-Chlorobutanoyl
24	H	Benzyl	H	Benzenesulfonyl
25	H	Benzyl	H	Ethoxycarbonyl
27	H	Benzyl	Benzyl	Benzoyl
28	H	Benzyl	Ethyl	Benzoyl
29	H	Benzyl	Methyl	Benzoyl
30	H	Benzyl	3-Trifluoro-methylbenzyl	Benzoyl
31	H	Benzyl	*p*-Bromobenzyl	Benzoyl
32	H	Benzyl	*p*-Benzyloxy-benzyl	Benzoyl
33	H	Benzyl	Allyl	Benzoyl

As observed in the isoquinoline, (4) quinoline, (4) phthalazine, (8) and 3,4-dihydro-β-carboline (5) series, the Reissert anion (**26**) was conveniently generated by the action of sodium hydride on **21** in anhydrous dimethylformamide. The anion thus generated readily underwent a nucleophilic displacement reaction with benzyl bromide to afford **27**. The anion **26** also reacted with other halides such as ethyl iodide, methyl iodide, *m*-trifluoromethylbenzyl chloride, *p*-bromobenzyl bromide, *p*-benzyloxybenzyl chloride and allyl bromide to yield **28-33**. Most of these alkylation products, however, were contaminated with a fluorescent yellow compound identified as 1-cyano-6-benzylellipticine (**34**) based on its elemental composition and spectral characteristics. Confirmation of this structure was had by its unambiguous synthesis from the benzenesulfonyl analog **24**. 1-cyano-6-benzylellipticine (**34**) was the only product when **26** was reacted with 3,4-dimethoxybenzyl chloride, 3,4-dimethoxybenzyl bromide, 3,4-methylenedioxybenzyl chloride and 1,3-dibromopropane. The reaction of **4** with α,α'-dibromo-*p*-xylene and sodium hydride similarly afforded 1-cyano-6-(5-hexenyl)ellipticine **35** instead of the expected product. The cyanoellipticines **34** and **35** presumably arise from air-oxidation of the appropriate Reissert anions. A few examples of such oxidation in other series are reported in the literature (4,9,10). In harmony with this assumption, the formation of 1-cyano-6-benzylellipticine was suppressed when the reaction of **26** with ethyl iodide was carried out under an atmosphere of argon.

Treatment of **27** with refluxing ethanolic potassium hydroxide yielded 1,6-dibenzylellipticine (**36**). 1-Ethyl-6-benzylellipticine (**37**), 1-methyl-6-benzylellipticine (**38**), 1-(3-trifluoromethylbenzyl)-6-benzylellipticine (**39**), 1-(4-bromobenzyl)-6-benzylellipticine (**40**) and 1-(1-propenyl)-6-benzylellipticine (**41**) were all obtained by a similar treatment. The base-catalyzed isomerization of the double bond accompanying the hydrolysis of **33** to **41** is to be expected as it leads to a conjugated system. A precedent to such an isomerization exists in the isoquinoline series, (11).

In an attempt to remove the 6-benzyl group by hydrogenolysis, 1-(*p*-bromobenzyl)-6-benzylellipticine (**40**) was subjected to hydrogenation in the presence of palladium-carbon catalyst. Although the compound underwent debenzylation, with retention of the bromine, the required conditions for hydrogenolysis caused concurrent reduction of the D-ring leading to the tetrahydroellipticine **42**. The mass spectrum of **42** showed peaks at m/e 339 (1.27%), 249 (100%) and 247 (10.28%) which are attributable to [M-Br], [M-$CH_2C_6H_4Br$], and [M-$CH_2C_6H_4Br$-H_2].

Treatment of the benzenesulfonyl Reissert compounds **12** and **24** with sodium hydride in anhydrous dimethylformamide yielded 1-cyanoellipticine (**43**) and 1-cyano-6-benzylellipticine (**34**), respectively. The cyanoellipticines were found to be easily hydrolyzed by ethanolic potassium hydroxide to the corresponding 1-carboxamides, **44** and

45. Ellipticine-1-carboxamide hydrochloride (**46**) was prepared by treating **44** with concentrated hydrochloric acid in ethanol.

The fluoroborate salts of the ellipticine and 6-benzylellipticine Reissert compounds, **47** and **48**, were prepared by treating an acetic acid solution of **2** or **21** with fluoroboric acid. This is analogous to the formation of the fluoroborate of the 3,4-dihydro-β-carboline Reissert compound, (5).

Compounds **2, 18, 34, 36, 43**, and **45** were all inactive (maximum T/C ranged from 95-102%) when screened, through the auspices of the Division of Cancer Treatment, National Cancer Institute, against P388 lymphocytic leukemia. Ellipticine has a T/C of 190% at 100 mg/Kg in this system. The hydrochloride of ellipticine-1-carboxamide (**46**) was active with a T/C of 134% at 400 mg/Kg.

EXPERIMENTAL

General.

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrometer as potassium bromide pellets. Proton magnetic resonance spectra were determined with a Hitachi Perkin-Elmer Model R-24B instrument using tetramethylsilane as an internal standard. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska (supported under the N. S. F. Regional Instrumentation Facilities Program). Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan. 60-200 Mesh silica gel (J. T. Baker) was used for all column chromatographic separations unless otherwise noted. Thin layer chromatographic comparisons were done on Eastman-Kodak silica gel chromagrams with fluorescent indicator (No. 13181).

Ellipticine (**1**) and Substituted Ellipticines (**9, 10, 14-17, 49, 50**).

Ellipticine (**1**), 6-(2-propenyl)ellipticine (**15**), 6-(5-hexenyl)ellipticine (**16**), 6-(2-benzoyloxyethyl)ellipticine (**17**), 6-(3-aminopropyl)-9-methoxyellipticine dihydrochloride (**49**) and 6-(3-(*N*)-phthalimidopropyl)-9-methoxyellipticine (**14**) were kindly furnished by the National Cancer Institute, 9-methoxyellipticine (**9**) was generously donated by Hoffmann-La Roche, Inc. and 11-desmethylellipticine (**50**) was graciously provided by Dr. René Carlson of the Royal Institute of Technology, Stockholm, Sweden. A mixture of 0.6 g (1.48 mmoles) of 6-(3-aminopropyl)-9-methoxyellipticine dihydrochloride (**49**) and 0.27 g (5.63 mmoles) of sodium hydride (50% in oil) was stirred in 20 ml of anhydrous dimethylformamide for 30 minutes. The contents were then poured onto about 300 g of crushed ice, filtered and dried to get 0.49 g (100%) of **10**.

6-Benzylellipticine (**18**).

To a stirred suspension of 0.6 g (12.5 mmoles) of sodium hydride (50% in oil) in 10 ml of anhydrous dimethylformamide was added 2.0 g (8.1 mmoles) of ellipticine (**1**) over a period of 5 minutes. Then, 1.8 g (10.5 mmoles) of benzyl bromide was introduced, the contents diluted with 30 ml of anhydrous ether, stirred for an additional 3 hours and poured onto ice-water slurry to obtain 2.15 g (79%) of **18**, mp 237-239° (from dichloromethane-ethanol), reported (12) mp 239-240°; ir: 3075, 3045, 1600, 1480, 1360 cm^{-1}.

Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.23. Found: C, 85.51; H, 5.94; N, 8.21.

6-Benzyl-11-desmethylellipticine (**19**).

Following the procedure described for the preparation of **18**, 0.3 g (1.3 mmoles) of 11-desmethylellipticine (**50**), 0.1 g (2.1 mmoles) of sodium hydride and 0.27 g (1.6 mmoles) of benzyl bromide gave 0.43 g of a crude compound which was chromatographed on a column of silica gel and eluted with chloroform to obtain 0.19 g (45%) of **19**, mp 197-198° (from ethanol); ir: 3050, 1600, 1465, 1220 cm^{-1}.

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.79; H, 5.57; N, 8.83.

α,α′-Bis[6-ellipticinyl]-*p*-xylene (**20**).

A mixture of 0.7 g (2.9 mmoles) of ellipticine (**1**), 0.17 g (3.5 mmoles) of sodium hydride (50% in oil) and 0.38 g (1.4 mmoles) of α,α′-dibromo-*p*-xylene in 12 ml of anhydrous dimethylformamide was stirred for 3 hours and poured onto ice to obtain 0.45 g (52%) of **20**, mp >313° (from dichloromethane-ethanol); ir: 3050, 1590, 1470, 1230, 820, 750 cm^{-1}.

Anal. Calcd. for $C_{42}H_{34}N_4$: C, 84.82; H, 5.76; N, 9.42. Found: C, 84.31; H, 5.73; N, 9.29.

Preparation of Reissert Compounds Listed in Table I.

Compounds **2, 6, 7**, and **22**.

A mixture of the appropriate ellipticine (1 equivalent), trimethylsilyl cyanide (2.5 equivalents) and benzoyl chloride (2.5 equivalents) was stirred for 24 hours in anhydrous dichloromethane. The solvent was then removed *in vacuo*, ethanol added, the product filtered and crystallized. (See Table II for spectral properties.)

Compounds **8, 13, 21**, and **23**.

A mixture of the appropriate ellipticine (1 equivalent), trimethylsilyl cyanide (2.5 equivalents) and the appropriate acid chloride (2.5 equivalents) was stirred for 24-48 hours in anhydrous dichloromethane. The dichloromethane solution was washed with water, 5% hydrochloric acid, water, 10% sodium hydroxide, and water and the dried solvent removed to afford after trituration with ethanol the title compounds. (See Table II for spectral properties.)

Compounds **3-5**, and **25**.

A mixture of the appropriate ellipticine (1 equivalent), trimethylsilyl cyanide (2.5 equivalents) and the appropriate acid chloride (2.5 equivalents) was stirred and worked up as above. The crude reaction product so obtained was chromatographed on a column of silica gel and eluted with dichloromethane. Evaporation of the eluate afforded analytically pure sample. (See Table II for spectral characteristics.)

6-Benzyl-1-cyanoellipticine (**34**).

Benzenesulfonyl chloride (1.58 g, 8.9 mmoles) was added to a well stirred mixture of 1.5 g (4.5 mmoles) of 6-benzylellipticine (**18**) and 0.9 g (9.1 mmoles) of trimethylsilyl cyanide in 50 ml of anhydrous dichloromethane. The contents were stirred for 24 hours and worked up as described above to obtain 1.70 g of crude **24**.

The above crude benzenesulfonyl analog (**24**) (1.0 g) and 0.14 g (2.8 mmoles) of sodium hydride (50% in oil) were stirred together for 2 hours in 4 ml of anhydrous dimethylformamide and 20 ml of anhydrous ether. The contents were poured onto about 400 g of crushed ice, the solid filtered and dried to obtain 0.71 g (99%) of **34**, mp 237-239° (from ethanol-chloroform); ir: 3050, 2950, 2250, 1585 cm^{-1}.

Anal. Calcd. for $C_{25}H_{19}N_3$: C, 83.07; H, 5.30; N, 11.63. Found: C, 83.18; H, 5.28; N, 11.49.

1-Cyanoellipticine (**43**).

The title compound was prepared by following the procedure described for the preparation of 6-benzyl-1-cyanoellipticine (**34**). Thus, the reaction of 1.0 g (4.1 mmoles) of ellipticine (**1**) with 1.0 g (10.0 mmoles) of trimethylsilyl cyanide and 1.8 g (10.0 mmoles) of benzenesulfonyl chloride gave 1.35 g of crude **12**, which upon treatment with sodium hydride afforded 1-cyanoellipticine (**43**) in 94% yield, mp >330° (from 1-butanol-dimethylformamide); ir: 3175, 2275, 1620, 1590, 1280 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.53; H, 4.91; N, 15.44.

1,6-Dibenzylellipticine (**36**).

To a stirred solution of 1.42 g (3.0 mmoles) of **21** and 0.93 g (3.6 mmoles) of benzyl bromide in 12 ml of anhydrous dimethylformamide was added 0.25 g (5.1 mmoles) of sodium hydride (50% in oil). The mixture was stirred for 3.5 hours and then poured onto ice. Filtration afforded 2-benzoyl-1-cyano-1,6-dibenzyl-1,2-dihydroellipticine (**27**) which was directly hydrolyzed by refluxing for 7 hours with 5.9 g of potassium hydroxide in 7 ml of water and 10 ml of 95% ethanol. Most of the solvent was then removed *in vacuo* and the contents poured onto ice to obtain 0.94 g (72%) of **36**, mp 208-211° (from chloroform-ethanol); ir: 3050, 1590, 1370 cm^{-1}.

Anal. Calcd. for $C_{31}H_{26}N_2$: C, 87.29; H, 6.14; N, 6.57. Found: C, 86.93; H, 6.10; N, 6.45.

2-Benzoyl-6-benzyl-1-cyano-1-ethyl-1,2-dihydroellipticine (**28**) and 6-Benzyl-1-ethylellipticine (**37**).

A mixture of 0.25 g (0.53 mmole) of **21**, 1 ml of ethyl iodide and 0.08 g (1.67 mmoles) of sodium hydride (50% in oil) was stirred for 3 hours in 3 ml of anhydrous dimethylformamide under an atmosphere of argon. The contents were then poured onto ice, the solid filtered, dried and chromatographed on a column of silica gel. Elution with chloroform afforded 0.08 g (30%) of 2-benzoyl-6-benzyl-1-cyano-1-ethyl-1,2-dihydroellipticine (**28**), mp 191-194° (from dichloromethane-ethanol); ir: 2925, 1640, 1450, 1340, 1275 cm^{-1}.

Anal. Calcd. for $C_{34}H_{29}N_3O$: C, 82.39; H, 5.90; N, 8.48. Found: C, 81.94; H, 6.12; N, 8.40.

A mixture of 0.034 g (0.069 mmole) of **28** and 0.2 g of potassium hydroxide in 0.5 ml of water and 1 ml of ethanol was refluxed for 2 hours, cooled and the solid filtered to obtain 0.016 g (64%) of 6-benzyl-1-ethylellipticine (**37**), mp 169-172° (from dichloromethane-ethanol); ir: 2970, 1580, 1470, 1450, 1360 cm^{-1}.

Anal. Calcd. for $C_{26}H_{24}N_2$: C, 85.68; H, 6.64; N, 7.69. Found: C, 85.26; H, 6.67; N, 7.63.

6-Benzyl-1-methylellipticine (**38**).

The title compound was prepared by a procedure similar to that described for the synthesis of 1,6-dibenzylellipticine (**36**). Thus, 0.8 g (1.7 mmoles) of **21**, 0.5 ml of methyl iodide and 0.16 g (3.4 mmoles) of sodium hydride (50% in oil) gave **29**, which was directly hydrolyzed by refluxing with ethanolic potassium hydroxide to obtain 0.26 g (43%) of **38**, mp 210-211° (from chloroform-ethanol); ir: 3060, 1600, 1480, 1370 cm^{-1}.

Anal. Calcd. for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.48; H, 6.21; N, 7.84.

6-Benzyl-1-(1-propenyl)ellipticine (**41**).

By following the procedure described for the preparation of **35**, 1.0 g (2.1 mmoles) of **21**, 0.5 g (4.1 mmoles) of 3-bromopropene and 0.2 g (4.2 mmoles) of sodium hydride (50% in oil) gave a very crude compound which was chromatographed on a column of silica gel and eluted with dichloromethane to obtain 0.54 g of **33**. The intermediate **33** on hydrolysis yielded 0.31 g (39%) of **41**, mp 177-180° (from dichloromethane-ethanol); ir: 3050, 2925, 1585, 1480, 1365, 1000, 760 cm^{-1}; pmr (deuteriochloroform-dimethylsulfoxide-d_6): δ 8.20 (m, 2H), 7.15 (m, 9H), 5.70 (s, 2H), 3.26 (broad singlet, 5H), 2.73 (s, 3H), 2.05 (d, 3H, J = 6 Hz).

Anal. Calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44. Found: C, 86.12; H, 6.34; N, 7.36.

2-Benzoyl-6-benzyl-1-(*p*-benzyloxybenzyl)-1-cyano-1,2-dihydroellipticine (**32**).

A mixture of 0.85 g (1.9 mmoles) of **21**, 0.58 g (2.5 mmoles) of *p*-benzyloxybenzyl chloride and 0.2 g (4.2 mmoles) of sodium hydride (50% in oil) was stirred for 3 hours in 10 ml of anhydrous dimethylformamide and poured into ice to obtain 0.72 g of a crude compound. The crude compound was chromatographed on a column of silica gel and eluted with dichloromethane to obtain 0.14 g (11%) of **32**, mp 177-179° (from dichloromethane-ethanol); ir: 3050, 1645, 1600, 1510, 1335, 1280, 1030, 740 cm^{-1}.

Anal. Calcd. for $C_{46}H_{37}N_3O_2$: C, 83.23; H, 5.62; N, 6.33. Found: C, 83.27; H, 5.64; N, 6.27.

Further elution of the column with dichloromethane afforded 0.17 g (25%) of 6-benzyl-1-cyanoellipticine (**34**) identical in all respects with an authentic sample.

2-Benzoyl-6-benzyl-1-cyano-1-(*m*-trifluoromethylbenzyl)-1,2-dihydroellipticine (**30**).

A mixture of 1.62 g (3.46 mmoles) of **21**, 1.6 ml of *m*-trifluoromethylbenzyl chloride and 0.34 g (7.1 mmoles) of sodium hydride (50% in oil) was stirred for 3 hours in 10 ml of anhydrous dimethylformamide and poured onto ice to obtain 0.72 g (33%) of the title compound, mp 209-211° (from dichloromethane-ethanol).

Anal. Calcd. for $C_{40}H_{30}F_3N_3O$: C, 76.78; H, 4.83; N, 6.72. Found: C, 76.47; H, 4.97; N, 6.66.

6-Benzyl-1-(*m*-trifluoromethylbenzyl)ellipticine (**39**).

The intermediate **30** was converted into **39** in 93% yield by following the procedure for the synthesis of **37** from **28**, mp 169-172° (from dichloromethane-ethanol); ir: 3050, 2950, 1580, 1480, 1460, 1340, 1130 cm^{-1}.

Anal. Calcd. for $C_{32}H_{25}F_3N_2$: C, 77.71; H, 5.10; N, 5.67. Found: C, 77.54; H, 5.05; N, 5.63.

6-Benzyl-1-(*p*-bromobenzyl)ellipticine (**40**).

The title compound was obtained from **21** *via* **31** in 38% yield by following the procedure described for the preparation of 1,6-dibenzylellipticine (**36**), mp 194-197° (from dichloromethane-ethanol); ir: 3050, 2940, 1580, 1200, 1020, 870 cm^{-1}.

Anal. Calcd. for $C_{31}H_{25}BrN_2$: C, 73.66; H, 4.99; N, 5.54. Found: C, 73.78; H, 4.94; N, 5.50.

Other Alkylation Reactions of the 6-Benzylellipticine Reissert Compound (**21**).

Reaction of 2-Benzoyl-6-benzyl-1-cyano-1,2-dihydroellipticine (**21**) with 3,4-dimethoxybenzyl chloride, 3,4-dimethoxybenzyl bromide, 3,4-methylenedioxybenzyl chloride, 1,3-dibromopropane, isatin and *N*-methylisatin did not yield the anticipated products. The product in each case was identified to be either 6-benzyl-1-cyanoellipticine (**34**) or a mixture of **34** and 6-benzylellipticine (**18**).

In a typical procedure, 1.0 g (2.2 mmoles) of **21** was reacted with 1.13 g (6.6 mmoles) of 3,4-methylenedioxybenzyl chloride and 0.21 g (4.4 mmoles) of sodium hydride (50% in oil) to obtain, after column chromatography (silica gel, chloroform), 0.58 g (73%) of 6-benzyl-1-cyanoellipticine (**34**).

Reaction of **4** with α,α'-Dibromo-*p*-xylene. Formation of 1-Cyano-6-(5-hexenyl)ellipticine (**35**).

Sodium hydride (50% in oil) (0.1 g, 2.0 mmoles) was added to a well-stirred mixture of 0.4 g (0.87 mmole) of 2-benzoyl-1-cyano-6-(5-hexenyl)-1,2-dihydroellipticine (**4**) and 0.12 g (0.43 mmole) of α,α'-dibromo-*p*-xylene in 5 ml of anhydrous dimethylformamide. Stirring was continued for 3 hours after which the contents were poured onto ice to obtain 0.4 g of crude solid. The crude solid was chromatographed on a column of silica gel and eluted with chloroform to get 0.22 g (72%) of **35**, mp 137-139° (from dichloromethane-ethanol); ir: 2950, 2900, 1570, 1465, 1370, 920, 760 cm^{-1}.

Anal. Calcd. for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.74; H, 6.58; N, 11.74.

Ellipticine-1-carboxamide (**44**) and Ellipticine-1-carboxamide Hydrochloride (**46**).

A mixture of 0.82 g (3.0 mmoles) of 1-cyanoellipticine (**43**) and 8.5 g (0.15 mmole) of potassium hydroxide in 4 ml of water and 17 ml of 95% ethanol was refluxed for 10 hours and cooled. Part of the ethanol was then removed *in vacuo*, the contents poured into cold water and the solid filtered to obtain 0.81 g (93%) of **44**, mp 295-298° (from 1-butanol); ir:

3400-3200, 1640, 1590, 1340, 1270 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.65; H, 5.28; N, 14.43.

Treatment of 0.52 g (1.9 mmoles) of **43** and 6.0 g (0.11 mmole) of potassium hydroxide as above gave a clear solution to which was added 22 ml of 6 *M* hydrochloric acid. The solid was filtered and dried to get 0.58 g (94%) of **46**, mp >330° (from ethanol-1-butanol); ir: 3150, 2725, 1680, 1600, 1420, 1260 cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; Cl, 10.88; N, 12.90. Found: C, 66.22; H, 5.16; Cl, 10.93; N, 12.67.

6-Benzylellipticine-1-carboxamide (**45**).

The title compound was obtained in 91% yield from 6-Benzyl-1-cyanoellipticine (**34**) by following a procedure identical to that described for the preparation of **44**, mp 288° (from ethanol-chloroform); ir: 3440, 3275, 3150, 1640, 1600, 1370, 1220 cm^{-1}.

Anal. Calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.08. Found: C, 78.87; H, 5.69; N, 10.99.

1-(*p*-Bromobenzyl)-1,2,3,4-tetrahydroellipticine (**42**).

A mixture of 0.24 g (0.47 mmole) of **40** and 0.1 g of 10% Pd/C in 100 ml of absolute ethanol was heated to 60° and the hot suspension was shaken with hydrogen at 60 psi for 12 hours. The contents were then filtered hot through a celite bed to remove the catalyst and the filtrate evaporated to get 0.12 g (62%) of the title compound, mp 248-252° (from ethylacetate-methanol); ir: 3490, 3330, 2975, 2900-2800, 1620, 1580, 1460, 1340 cm^{-1}; ms: m/e (%) 339.1861 (1.27, $C_{24}H_{23}N_2$, $[M\text{-}Br]^+$), 249.1377 (100, $C_{17}H_{17}N_2$, $[M\text{-}CH_2C_6H_4Br]^+$), 248.1295 (8.78, $C_{17}H_{16}N_2$), 247.1218 (10.28, $C_{17}H_{15}N_2$, $[M\text{-}CH_2C_6H_4Br\text{-}H_2]^+$), 246.1140 (9.03), 245.1071 (3.31), 234.1139 (2.22), 204.0820 (2.02), 117.0575 (1.15).

Anal. Calcd. for $C_{24}H_{23}BrN_2$: C, 68.73; H, 5.53; Br, 19.06; N, 6.68. Found: C, 68.63; H, 5.88; Br, 19.07; N, 6.99.

1-Amino-7,13-dimethyl-3-phenyl-8*H*-indolo[2,3-*g*]oxazolo[4,3-*a*]isoquinolinium Tetrafluoroborate (**47**).

To 0.5 g (1.32 mmoles) of **2** was added 50 ml of glacial acetic acid and the contents heated on a steam bath for 5 minutes. Fluoroboric acid (5 ml) was then added and the mixture heated for another 10 minutes. The contents were then cooled and the product filtered to yield 0.48 g (78%) of **47**, mp 321-323° (from ethanol); ir: 3375, 3300, 1640, 1600, 1420, 1250, 1100-1030, 800 cm^{-1}.

Anal. Calcd. for $C_{25}H_{20}BF_4N_3O\cdot H_2O$: C, 62.13; H, 4.59; B, 2.24; F, 15.73; N, 8.70. Found: C, 61.79; H, 4.59; B, 2.08; F, 15.50; N, 8.90.

1-Amino-8-benzyl-7,13-dimethyl-3-phenyl-8*H*-indolo[2,3-*g*]oxazolo[4,3-*a*]-isoquinolinium Tetrafluoroborate (**48**).

A mixture of 0.29 g (0.63 mmole) of **21** and 10 ml of glacial acetic acid was gently refluxed until a clear solution resulted. The solution was cooled in an ice-bath and 5 ml of fluoroboric acid was introduced. The yellow fluoroborate salt (**48**) was filtered, washed several times with anhydrous ether and dried to obtain 0.29 g (84%), mp 243-270° (from absolute ethanol); ir: 3250, 3125, 1630, 1590, 1570, 1400, 1210, 1100-1040, 800 cm^{-1}.

Anal. Calcd. for $C_{32}H_{26}BF_4N_3O$: C, 69.20; H, 4.72; N, 7.57. Found: C, 69.11; H, 4.77; N, 7.56.

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