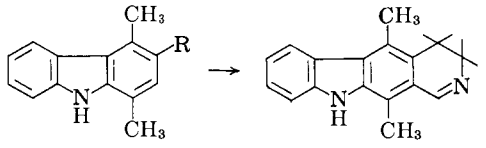
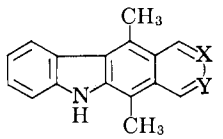
used for the synthesis of ellipticine[3] itself and for its demethyl derivative.[4] Reaction of 1 with nitromethane afforded the nitrovinyl carbazole **2**, which was reduced to the amine **3** with lithium aluminum hydride. Bischler–Napieralkski cyclization of the formamide **4** with polyphosphoric acid and catalytic dehydrogenation of the resultant dihydro compound **5** afforded isoellipticine **6**. It was inactive against leukemia L1210 transplanted in mice.



1, R=CHO
2, R=CH=CHNO$_2$
3, R=CH$_2$CH$_2$NH$_2$
4, R=CH$_2$CH$_2$NHCHO



5

6, X=CH, Y=N
7, X=N, Y=CH

Experimental Section[5]

1,4-Dimethyl-3-(2-nitrovinyl)carbazole (2).—1,4-Dimethylcarbazole-3-carboxaldehyde[2] heated with nitromethane and ammonium acetate[4] for 1 hr afforded 62–70% of **2**, recrystallized from butanol; mp 271–274°; λ_{max}^{EtOH} 241 mμ (ε 35,400), 248 (30,900), 288 (19,000), 322 (10,200), 415 (22,300). The infrared spectrum was free of any aldehyde C=O band at 6.07 μ and showed strong bands at 3.00 (NH), 6.3 (aryl), 7.6 (NO_2), 7.8, 8.0, 8.15 μ (unassigned) and medium bands at 10.2 and 10.5 μ (olefin).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.30; N, 10.5. Found: C, 72.3; H, 5.35; N, 10.7.

1,4-Dimethyl-3-(2-aminoethyl)carbazole (3) was obtained by $LiAlH_4$ reduction of **2** in tetrahydrofuran and purified by precipitation[4] from dilute acetic acid solution, mp 195–208° (80%); λ_{max}^{EtOH} 242 mμ (ε 47,700), 262 (21,300), 283 sh, 292 (14,400), 327 (3810), 341 (3860). The infrared spectrum was free of bands at 10.2 and 10.5 μ (olefin, as in **2**), and bands at 6.62 (medium) and 7.5 μ (strong) were not due to NO_2 impurity; weak–medium NH bands were observed at 3.00, 3.07, 3.2, 3.3 μ and other strong bands at 6.3 (aryl), 10.9, and 13.3 μ.

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.6; H, 7.61; N, 11.8. Found: C, 80.5; H, 7.68; N, 11.5.

A sample from another preparation, mp 160–185°, exhibited identical spectra and excellent analytical values also.

1,4-Dimethyl-3-(2-formamidoethyl)carbazole (4).—A suspension of 3.70 g (15.5 mmoles) of **3** in 125 ml of ethyl formate was heated in a sealed steel bomb at 100° for 2.5 hr. Evaporation of the contents *in vacuo* afforded 4.10 g (100%), mp 205–208°; as expected, strong bands at 3.05 (NH) and 6.05 μ (C=O) appeared in the infrared. A sample for analysis, mp 207–209°, was obtained by recrystallization from methanol–benzene, then from methanol–water, and dried for 3 days *in vacuo* at 80° to remove traces of solvent; nmr data (DMSO-d_6): singlets at δ 11.2 (carbazole NH, exchangeable) and at 2.71 and 2.43 ($ArCH_3$) multiplets at 6.9–8.2 (6 ArH plus NCHO) and at 2.2–3.5 (CH_2-CH_2NHCO-).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.81; N, 10.5. Found: C, 76.6; H, 6.78; N, 10.8.

3,4-Dihydro-5,11-dimethyl-10H-pyrido[3,4-*b*]carbazole (5).—A mixture of 9.70 g (36.4 mmoles) of **4** and 159 g of polyphosphoric acid (82–84%, Matheson Co.) was heated and the melt was stirred at 170° for 2 hr. The dark syrup was hydrolyzed with 400 ml of water with stirring, first at 0° and then at 80–90°. The product partially dissolved as a phosphate salt. The mixture was cooled and basified (pH 12) with 230 ml of concentrated NH_4OH. A golden precipitate of **5** mixed with ammonium phosphate formed, along with the gums already present. The mixture was stirred for several hours while the gummy portion gradually became solid. Water (100 ml) was added, and the solids were collected on a filter, triturated with 50-ml portions of dilute base and of water, and dried. The product weighed 8.0 g, mp 208–228°, and was recrystallized from $CHCl_3$–CCl_4 to yield 5.7 g, mp 232–249° dec; elemental analysis and comparison of ultraviolet extinctions with that of an analytical sample indicated that 15% by weight of chlorinated solvent was present,[6] even after drying overnight *in vacuo* at 60, so that the actual yield was 4.8 g (53%). Further drying at 100° for 4 days afforded a solvent-free sample for analysis, melting point unchanged; λ_{max}^{EtOH} 213 mμ (ε 18,900), 259 (46,600), 282 (12,800), 323 (25,500), 365 (5000); $\lambda_{max}^{0.01M\,HCl\ in\ 90\%\ EtOH}$ 215 mμ (ε 20,700), 250 (26,900), 284 (15,200), 368 (27,000). Strong infrared bands were at 3.18 and 3.23 (NH), 6.15 (aryl), 7.51, 9.7, 13.6 μ broad (unassigned); strong bands were at 12.7, 12.9, and 13.4 μ when $CHCl_3$ or CCl_4 were present but were weak in the dried sample.

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.2; H, 6.50; N, 11.3. Found: C, 82.0; H, 6.65; N, 11.3.

5,11-Dimethyl-10H-pyrido[3,4-*b*]carbazole (6, Isoellipticine).—A suspension of 6.5 g (19 mmoles, plus 27 wt % of solvent, by ultraviolet) of **5** and 6 g of Pd black in 800 ml of decalin was stirred and refluxed for 2 hr, chilled, and filtered. The solids from the filter were extracted, in a slurry, with five portions of hot methanol to dissolve the product, and the filtered extracts were concentrated. The residual product was dissolved in 50 ml of hot 3 *M* acetic acid, the solution was clarified by adding charcoal and filtering, and the red-orange filtrate was stirred and basified (pH 11–12) with concentrated NH_4OH. The resultant yellow precipitate, collected and washed, weighed 4.7 g, mp 255–285° dec. Recrystallization from methanol afforded 3.6 g (77%), dried *in vacuo* for 16 hr at 60°, mp 270–286° dec; λ_{max}^{EtOH} 231 mμ (ε 26,100), 273 sh, 282 (76,800), 303 sh, 318 (8060), 331 (4780); $\lambda_{max}^{0.01M\,HCl\ in\ 92\%\ EtOH}$ 232 mμ (ε 26,300), 264 (17,500), 299 (62,700), 333 (8680); $\lambda_{max}^{0.1\,M\ aq\ HCl}$ 235 mμ (ε 21,900), 263 (18,700), 291 (48,700), 330 (6750); strong infrared bands were at 3.20 and 3.27 (NH), 6.20 and 6.26 (aryl), 7.09, 7.22, 7.57, 7.62, 7.82, 8.11, 9.78, 9.85, 13.5 μ broad (unassigned).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.9; H, 5.73; N, 11.4. Found: C, 82.6; H, 5.86; N, 11.3.

Acknowledgment.—The authors are indebted to Mr. O. P. Crews and staff for preparation of intermediates and to Dr. Peter Lim and staff for the spectra.

(3) T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Indian J. Chem.*, **1**, 247 (1963).

(4) C. W. Mosher, O. P. Crews, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **9**, 237 (1966); 5-methyl-6H-pyrido[4,3-*b*]carbazole is a demethyl derivative of both ellipticine and olivacine.

(5) Melting points were observed on a Fisher-Johns hot stage and are corrected. Infrared spectra were determined in Nujol mull; only strong bands or those significant for their assignment to functional groups are reported. Ultraviolet spectra were determined with a Cary Model 11 recording spectrophotometer. The nmr spectrum of **4** was determined in DMSO-d_6 solution with $(CH_3)_4Si$ as external reference using a Varian A-60 spectrometer. In processing the products, concentration of solutions was done *in vacuo*.

(6) Other samples recrystallized from methanol or reprecipitated from base showed similar affinity for fractional moles of methanol or water, respectively.

Substituted 1,2,3,4-Tetrahydro-β-carbolines. II

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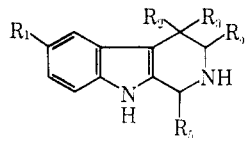
As part of a search for compounds which possess general physiological activity we have prepared a series of substituted 1,2,3,4-tetrahydro-β-carbolines (Table I). The compounds were prepared by reaction of acetaldehyde, benzaldehyde, or 3,4,5-trimethoxybenzaldehyde with the following tryptamines, according to the general method of Von Strandtmann, *et al.*:[1]

(1) M. Von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Med. Chem.*, **7**, 141 (1964).

TABLE I
YIELDS, PHYSICAL CONSTANTS, AND ANALYTICAL RESULTS OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINES



R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3O	H	H	H	CH_3	60	154–155	$C_{13}H_{16}N_2O$	72.2	7.46	13.0	72.4	7.48	13.2
CH_3O	H	H	H	C_6H_5	51	295–297 dec	$C_{18}H_{19}N_2O \cdot HCl$	68.7	6.08	8.90	69.0	6.13	9.06
CH_3O	H	H	CH_3	CH_3	48	211–213	$C_{14}H_{18}N_2O$	73.0	7.88	12.2	72.6	7.83	12.3
CH_3O	H	H	CH_3	C_6H_5	45[a]	281–284 dec	$C_{19}H_{21}N_2O \cdot HCl$	69.1	6.44	8.52	69.1	6.47	8.80
CH_3O	H	H	CH_3	$(CH_3O)_3C_6H_2$	33[a]	273–277 dec	$C_{22}H_{26}N_2O \cdot HCl \cdot 0.5H_2O$	61.7	6.59	6.55	61.3	6.78	6.70
CH_3S	H	H	H	CH_3	20	185–188	$C_{13}H_{16}N_2S$	67.2	6.94	12.1	67.4	6.81	11.8
CH_3S	H	H	H	C_6H_5	17[a]	268–273	$C_{18}H_{19}N_2S \cdot HCl$	65.3	5.79	8.47	64.8	5.80	8.58
CH_3S	H	H	CH_3	CH_3	36	235–240	$C_{14}H_{18}N_2S$	68.3	7.36	11.4	68.0	7.27	11.6
CH_3S	H	H	CH_3	C_6H_5	30	250–263 dec	$C_{19}H_{20}N_2S \cdot HCl$	66.2	6.14	8.12	66.6	6.12	8.02
CH_3S	H	H	CH_3	$(CH_3O)_3C_6H_2$	35	273–278 dec	$C_{22}H_{26}N_2O_3S \cdot HCl \cdot H_2O$	58.3	6.45	6.18	58.1	6.53	6.15
H	H	H	CH_3	CH_3	56	188–189	$C_{13}H_{16}N_2$	78.0	8.05	14.0	77.8	7.91	14.2
H	H	H	CH_3	C_6H_5	52	287–290 dec	$C_{18}H_{19}N_2 \cdot HCl$	72.4	6.41	9.38	72.2	6.18	9.18
H	H	H	CH_3	$(CH_3O)_3C_6H_2$	16	255–258 dec	$C_{22}H_{26}N_2O_3 \cdot HCl \cdot H_2O$	62.0	6.69	6.89	62.0	6.65	7.06
F	H	H	CH_3	CH_3	42	179–181	$C_{13}H_{15}FN_2$	71.5	6.93	12.8	71.7	6.96	12.8
F	H	H	CH_3	C_6H_5	15[a]	297–300 dec	$C_{18}H_{18}FN_2 \cdot HCl$	68.2	5.73	8.84	68.2	5.89	9.02
F	H	H	CH_3	$(CH_3O)_3C_6H_2$	56[a]	273–277 dec	$C_{22}H_{25}N_2O_3F \cdot HCl \cdot H_2O$	59.1	6.17	6.59	59.1	6.16	6.71
F	CH_3	H	H	C_6H_5	16[a]	296–300	$C_{18}H_{17}FN_2 \cdot HCl$	68.2	5.73	8.84	67.9	5.99	8.76
F	CH_3	H	H	$(CH_3O)_3C_6H_2$	38[a]	253–257	$C_{22}H_{25}N_2O_3F \cdot HCl$	62.0	5.95	6.89	61.7	6.33	7.13
F	CH_3	CH_3	H	CH_3	37	153–157	$C_{14}H_{17}FN_2$	72.4	7.38	12.1	72.1	7.63	12.2

[a] Hydrochloride isolated from 6 *N* HCl.

5-methoxy-, 5-methoxy-α-methyl-,[2] 5-methylthio-,[3] 5-methylthio-α-methyl-,[3] α-methyl-, 5-fluoro-α-methyl-, 5-fluoro-β-methyl-,[3] and 5-fluoro-β,β-dimethyltryptamine.[4]

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(3) J. K. Horner, J. I. DeGraw, and W. A. Skinner, *Can. J. Chem.*, **44**, 307 (1966).

(4) J. I. DeGraw and W. A. Skinner, *ibid.*, in press.

Some Reactions with 4-Cyano-4-phenyltetrahydropyran

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4-Cyano-4-phenyltetrahydropyran[1] has been used as a starting point for the synthesis of compounds of possible pharmacological interest, including imines, ketones, and alcohols derived from an initial reaction with an appropriate Grignard reagent.[2] New compounds prepared are listed in Table I (on next page).

Experimental Section[3]

4-Aminomethyl-4-phenyltetrahydropyran. Method A.—4-Cyano-4-phenyltetrahydropyran[1] (10 g) in benzene (125 ml) was added to $LiAlH_4$ (3 g) in ether (125 ml) and refluxed for 3.5 hr. Standard procedures afforded the desired product.

N-(Morpholinoethyl)tetrahydro-4-phenylpyran-4-methylamine. Method B.—4-Acetamidomethyl-4-phenyltetrahydropyran (7.6 g) in dioxane (50 ml) was treated with morpholinoethyl chloride (5.4 g) in the presence of sodamide (1.4 g) using a method previously described.[4] Hydrolysis of the acetyl derivative was effected by refluxing with 6 *N* HCl for 2 hr.

4-Amino-4-phenyltetrahydropyran. Method C.—4-Phenyltetrahydropyran-4-carboxylic acid[1] (5 g) was stirred with benzene (80 ml) and concentrated H_2SO_4 (40 ml) at 50–55°. Sodium azide (1.8 g) was added in small portions over a period of 30 min. The temperature was maintained at 50–55° for a further 5 hr. The mixture stood at room temperature overnight, was diluted with an equal volume of ice, and basified with 10 *N* NaOH. The mixture was extracted with ether, and the extracts were dried ($MgSO_4$). Addition of ethereal HCl afforded a crude hydrochloride (1.3 g). Acidification of the alkaline solution and extraction with ether gave unchanged carboxylic acid (3.3 g). The combined base hydrochlorides from three experiments (6.0 g) were dissolved in water (25 ml); the solution was basified with 2 *N* NaOH and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled. A fraction (2.1 g) of bp 80–82° (20 mm) proved to be aniline while 4-amino-4-phenyltetrahydropyran was obtained as a pale yellow oil (1.0 g), bp 158–160 (20 mm).

N-(2-Diethylaminoethyl)tetrahydro-4-phenylpyran-4-carboxamide. Method D.—4-Phenyl-4-tetrahydropyranoyl chloride[1] (9.2 g) was suspended in benzene (100 ml) and N,N-diethylethylenediamine (7.2 g) was added dropwise with stirring. When the exothermic reaction had subsided, the mixture was refluxed for 2 hr and allowed to stand overnight. The cooled mixture was shaken with 2 *N* NaOH and the benzene layer was removed. The aqueous solution was extracted with ether; the combined organic phases were dried (KOH) and evaporated, and the residue was distilled *in vacuo*. The diethylaminoethyl compound crystallized on cooling.

Ketimines. Method E.—4-Cyano-4-phenyltetrahydropyran (10 g, 1 molar equiv) in dry tetrahydrofuran (THF) (10 ml) was added slowly to a refluxing solution of the appropriate Grignard reagent (3 molar equiv) in dry THF (100 ml). The mixture was refluxed for 5 hr. The imine was obtained by normal work-up procedures and was purified by distillation. $LiAlH_4$ failed to reduce these imines.

Tetrahydro-4-phenyl-4-pyranyl Ketones. Method F.—The appropriate imine (10 g) was refluxed with 2 *N* HCl (170 ml) for 5 hr. The cooled mixture was extracted with ether, and the ether was dried ($MgSO_4$) and evaporated. The ketone was obtained by distillation. Attempts to convert the ketones to amines by reductive amination failed, as did an attempt to reduce the oxime of ethyl tetrahydro-4-phenyl-4-pyranyl ketone with $LiAlH_4$.

Secondary Alcohols. Method G.—The appropriate ketone (0.055 mole) in THF (50 ml) was added to $LiAlH_4$ (0.065 mole) in ether (150 ml) and the mixture refluxed with stirring for 7 hr. The alcohol was obtained by conventional procedures.

Acknowledgments.—The authors are grateful to Dr. R. E. Bowman for his advice and encouragement and Mr. F. H. Oliver for the microanalyses.

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(2) A. Burger, L. B. Turnbull, and J. G. Dinwiddie, *J. Am. Chem. Soc.*, **72**, 5512 (1950).

(3) Melting points are corrected and were determined in a capillary tube. Boiling points are uncorrected.

(4) D. Hoekle, I. M. Lockhart, and M. Wright, *J. Chem. Soc.*, 1137 (1965).