New Compounds

Some Pyrido[2,3-*d*]thiazole Systems

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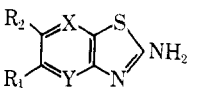
In recent studies of the biological activity of pyridine[1] and thiazole[2] systems, a combination of these two systems leading to pyridothiazoles has been found to show appreciable antiparasitic activity when tested against *Plasmodium lophurae* in ducklings.[3] In order to increase this activity and to investigate the effect of 6 substitution on the conversion of 2-aminopyridine in acid medium to the corresponding pyridothiazole, it was thought desirable to synthesize a number of unsubstituted and 5-substituted pyrido[2,3-*d*]thiazole systems. The results are summarized in Table I.

Unsubstituted 5- and 6-substituted 2-aminopyrido[2,3-*d*]thiazoles were prepared under similar reaction conditions from 2-aminopyridine, 2,6-diaminopyridine, 6-amino-2-picoline, 2-hydroxy-6-aminopyridine,[6] and 2-methoxy-5-aminopyridine. In a typical experiment, 2-methoxy-5-aminopyridine (20 g, 0.16 mole) was added with efficient mechanical agitation to a mixture of potassium thiocyanate (80 g) and glacial acetic acid (400 ml) while keeping the temperature below −25°. Bromine (10 ml) in glacial acetic acid (20 ml) was added at such a rate that the temperature never exceeded −25°. This temperature was maintained for additional 3 hr. Stirring was continued for 15 hr at room temperature. The mixture was filtered leaving an orange residue. The filtrate was partially neutralized with Na_2CO_3 to give crude 2-amino-6-methoxypyrido[2,3-*d*]thiazole (15 g) which was collected by filtration. The orange residue was extracted with boiling acetone. The acetone extract was concentrated *in vacuo* leaving the acetic acid salt which was neutralized with dilute NaOH to give 13 g more of the desired product. The combined product was purified by recrystallization from $CHCl_3$ (Norit) to give yellow needles of **2-amino-6-methoxypyrido[2,3-*d*]thiazole.**

These compounds undergo a facile base-catalyzed hydrolysis to the corresponding *o*-mercaptoaminopyridine.

TABLE I

DERIVATIVES OF PYRIDO[2,3-*d*]THIAZOLES



					Yield,		% C		% H		% N		% S	
R_1	R_2	X	Y	Mp, °C	%	Formula	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
H	OCH_3	N	C	201–202	83	$C_7H_7N_3OS$	46.41	46.41	3.87	3.85	23.21	23.30	17.68	17.81
H	H	C	N	118–119	7	$C_6H_5N_3S$	47.66	47.61	3.33	3.23	27.79	27.80	21.21	21.15
CH_3	H	C	N	185–186	3	$C_7H_7N_3S$	50.91	50.83	4.24	4.42	25.42	25.45	19.40	19.30
NH_2	H	C	N	140–141	32[a]	$C_6H_6N_4S$	43.37	43.18	3.62	3.79	33.74	33.71	19.34	19.21
OH	H	C	N	>310	55	$C_6H_5N_3OS$	45.12	42.92	3.00	3.10	25.15	25.19	19.16	19.26

[a] See ref 3b.

By a careful consideration of the implication of the acid medium in which these reactions were run as well as the yields of products, the order in which 6 substitution in 2-aminopyridine enhances the conversion to the corresponding pyridothiazole is $CH_3 < H < NH_3^+ < OH_2^+$.

Experimental Section

2-Methoxy-5-acetamidopyridine.—2-Chloro-5-nitropyridine[4] was prepared from 2-aminopyridine and converted to 2-methoxy-5-nitropyridine,[5] 30.8 g (0.2 mole) of which was added in small portions during 30 min to a stirred solution of $SnCl_2 \cdot 2H_2O$ (200 g) in concentrated HCl (400 ml). The reduction was exothermic (temperature 90°). Stirring was continued for 24 hr. Evaporation of the HCl *in vacuo* left a solution which, after neutralization with 40% KOH, cooling, and extraction with six portions of ether (100 ml) gave **2-methoxy-5-aminopyridine** (22 g, 89%) as a brown oil. Treatment with acetyl chloride gave dull, creamy platelets of 2-methoxy-5-acetamidopyridine; after two crystallizations from ethanol, mp 154–155°. The infrared spectrum shows a strong amide I band at 5.95 μ.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.95; H, 5.91; N, 17.01.

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(3) (a) J. Bernstein, B. Stearns, M. Dexter, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 1147 (1947); (b) J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *ibid.*, **69**, 1151 (1947).

(4) M. A. Phillips, *J. Chem. Soc.*, 9 (1941).

(5) W. T. Caldwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942).

(6) O. A. Stede and A. I. Titow, *Ber.*, **69**, 1884 (1936).

Synthesis of the Isoellipticine, 5,11-Dimethyl-10H-pyrido[3,4-*b*]carbazole[1]

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Interest in the biological properties and especially antitumor activity of the alkaloid ellipticine (**7**) prompted the synthesis of the isomer **6**, from the known aldehyde[2] **1** by a sequence recently

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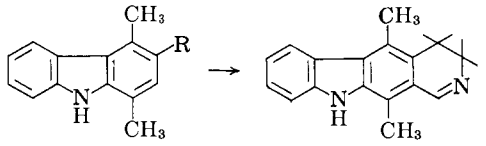
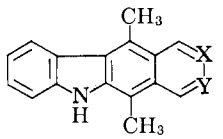
(2) P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 3482 (1962).

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); $\lambda_{max}^{0.01\,M\,HCl\text{ in }90\%\text{ EtOH}}$ 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); $\lambda_{max}^{0.01\,M\,HCl\text{ in }92\%\text{ EtOH}}$ 232 mμ (ε 26,300), 264 (17,500), 299 (62,700), 333 (8680); $\lambda_{max}^{0.1\,M\text{ aq HCl}}$ 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.

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(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).