New Compounds

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

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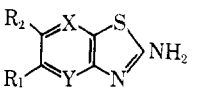
In recent studies of the biological activity of pyridine[1] and thiazole[2] systems, a combination of these two systems leading to pyridothiazoles has been found to show appreciable antiparasitic activity when tested against *Plasmodium lophurae* in ducklings.[3] In order to increase this activity and 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

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	$C_6H_5N_3OS$	43.12	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.

$CHCl_3$ (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.

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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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