[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthesis of 2-Methyl-4-amino-6-substituted Aminopyrimidines[1]

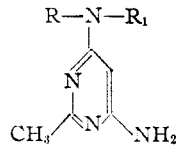
BY ALLISON MAGGIOLO, ARTHUR P. PHILLIPS AND GEORGE H. HITCHINGS

In connection with other studies it was desired to prepare a series of 2-methyl-4-amino-6-substituted aminopyrimidines.

The preparation of the intermediate for this series, 2-methyl-4-amino-6-hydroxypyrimidine (IV), has given diverse results in other laboratories. Földi, *et al.*,[2] using Traube's procedure[3a,3b] and several modifications in which the proportions of acetamide hydrochloride I, cyanoacetic ester II, and sodium ethoxide were varied, obtained chiefly a by-product, identified by Todd, *et al.*,[4,5] as ethyl-β-amino-α-cyanocrotonate III. The pyrimidine was obtained, however, when II was converted to the iminoether hydrochloride before condensation with I. On the other hand, Todd, *et al.*,[4,5] imply that Traube's procedure is satisfactory but do not provide experimental details or yields. As shown above the pyrimidine IV is obtained in 80% yield, with only traces of by-product III, by employing 4 molecular proportions of sodium methoxide in methanol as a condensing agent.

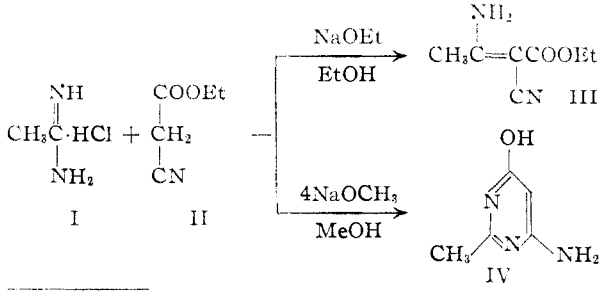
TABLE I

2-METHYL-4-AMINO-6-SUBSTITUTED AMINOPYRIMIDINES

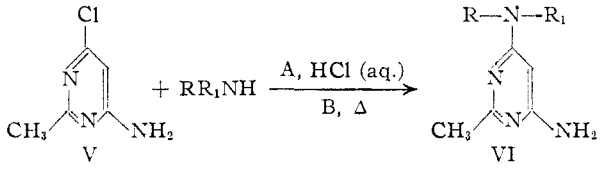


R	R_1	Procedure	Yield, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_2CH_2OH	B	70[a]	175–176	$C_7H_{12}ON_4$	33.3	33.1				
	$—CH_2CH_2OCH_2—CH_2—$	A	50								
		B	100[b]	209–210	$C_9H_{14}ON_4$			55.6	55.9	7.3	7.1
	$—CH_2(CH_2)_3—CH_2—$	B	100[c]	206–207	$C_{10}H_{16}N_4$			62.5	62.7	8.4	8.2
H	C_6H_5	A	83[d]	192–193	$C_{11}H_{12}N_4$	28.0	28.4				
H	p-C_6H_4OH	A	60[e]	252–253	$C_{11}H_{12}ON_4$	25.9	25.8	61.1	61.4	5.6	5.7
H	p-$C_6H_4OCH_3$	A	88[f]	251–252	$C_{12}H_{14}ON_4$	24.4	24.4				
H	p-C_6H_4Cl	A	90[f]	190–191	$C_{11}H_{11}N_4Cl$	24.9	24.8				
H	2-Resorcinol·HCl	A	80[f]	294–295	$C_{11}H_{14}O_2N_4Cl$	20.8	20.7	49.2	49.7	4.8	4.8
H	2-Methoxy-4-chlorophenyl·HCl	A	90[f]	281–282	$C_{13}H_{14}ON_4Cl_2$	18.7	18.5	47.9	48.1	4.7	4.6
H	p-$C_6H_4COOH·H_2O$	A	83[g]	314–315	$C_{12}H_{14}O_3N_4$	21.4	21.4				
H	5-Uracil	A	75[e]	>310	$C_6H_{10}O_2N_6$	35.9	36.3	46.1	46.4	4.3	4.0
H	p-$C_6H_4SO_2NH_2$	A	70[e]	272–273	$C_{11}H_{12}O_2N_6S$	25.1	24.4	47.3	47.6	4.7	4.8
H	2-Thiazolyl-N-phenyl-p-sulfonamido·H_2O	A	65[g]	245–247	$C_{14}H_{16}O_3N_6S_2$	22.1	22.0	44.2	44.6	4.2	4.2
H	2-Pyridyl-N-phenyl-p-sulfonamido·HCl	A	45[h]	285–286	$C_{16}H_{17}O_2N_6SCl$	21.4	21.1	48.9	49.1	4.4	4.5
H	2-Pyrimidyl-N-phenyl-p-sulfonamido	A	50[g]	238–239	$C_{15}H_{15}O_2N_7S$	23.8	24.0				
H	4-(4-Chlorophenoxy)-phenyl	A	80[f]	197–198	$C_{17}H_{15}ON_4Cl$	17.2	17.5				

[a] Recrystallized from ethyl acetate. [b] From methanol–ether. [c] From benzene–hexane. [d] From 50% ethanol. [e] From solution in dilute hydrochloric acid and reprecipitation with ammonia. [f] From ethanol. [g] From dilute potassium hydroxide and reprecipitation with dilute acid. [h] From methanol–ethyl acetate.



The reaction of amines with 2-methyl-4-amino-6-chloropyrimidine[2] V gave the desired pyrimidines VI as listed in Table I either in aqueous solution in acid by procedure A,[6] or by direct heating in the absence of solvent, procedure B.



It is of interest that amines in which the amino group is part of an amidine or guanidine-like system do not react with V *via* procedure A and give very poor yields, if any, by procedure B. Thus, no substituted pyrimidines were obtained by the attempted reactions of V with 2-aminopyridine, 2-

(1) This work was supported in part by a grant from the Charles F. Kettering Foundation to the Wellcome Research Laboratories.

(2) Földi, von Fodor, Demjén, Szekers and Holmos, *Ber.*, **75**, 755 (1942).

(3) (a) Traube, German Patent 135,371 (1902); (b) Traube, *Ann.*, **432**, 286 (1923).

(4) Kenner, Lythgoe, Todd and Topham, *J. Chem. Soc.*, 388 (1943).

(5) Hull, Lovel, Openshaw, Payman and Todd, *ibid.*, 357 (1946).

(6) Banks, THIS JOURNAL, **66**, 1127 (1944).

amino-4-*p*-bromphenylthiazole and 2-aminobenzimidazole.

Experimental

2-Methyl-4-amino-6-hydroxypyrimidine (IV).—Acetamidine hydrochloride (9.5 g., 0.10 mole) and cyanoacetic ester (11.4 g., 0.10 mole) in 20 ml. of methanol cooled in an ice-bath was added to 22.0 g. (0.40 mole) of sodium methoxide dissolved in 100 ml. of methanol. The mixture was refluxed for 2 hours, taken down to dryness under reduced pressure, and dissolved in 80 ml. of warm water. The cooled solution was filtered from a trace of precipitate[7] and diluted to twice its volume with water. Upon acidification to *p*H 5 with glacial acetic acid, a voluminous white powdery precipitate appeared, which was filtered off the next day. The solid was washed with water, dried at 110°, and weighed 10.1 g. (81%). It melted at 295–297° and gave a mixed melting point of 294.5–296.5° with a sample, m.p. 294–296°, prepared according to Földi's procedure.

2-Methyl-4-amino-6-*p*-chloroanilinopyrimidine. Procedure A.—A mixture of 7.2 g. (0.05 mole) of 2-methyl-4-amino-6-chloropyrimidine,[2] 6.4 g. (0.05 mole) of *p*-chloroaniline, 50 ml. of water and 4.2 ml. of concd. hydrochloric acid was heated just to boiling on a hot-plate for 1 hour. Upon cooling the crystalline hydrochloride of 2-methyl-4-amino-6-*p*-chloroanilinopyrimidine precipitated. The contents were made basic with 5% ammonium hydroxide, and the resulting white crystalline solid was filtered off. After drying at 110° the yield was 10.5 g. (90%), m.p. 189–190°. Recrystallization from 50% ethanol raised the m.p. to 190–191°. *Anal.* Calcd. for $C_{11}H_{11}ClN_4$: N, 24.9. Found: N, 24.8.

2-Methyl-4-amino-6-piperidinopyrimidine. Procedure B.—A mixture of 12.7 g. (0.15 mole) of piperidine and 7.2 g. (0.05 mole) of 2-methyl-4-amino-6-chloropyrimidine was refluxed at 160° for 2 hours. The cooled contents were triturated with 100 ml. of water to give a gray-white crystalline residue, which was dissolved in dilute hydrochloric acid and was reprecipitated with 5% ammonia. Recrystallization from benzene–hexane gave 9.3 g. (100%) of white crystals; m.p. 206–207°. *Anal.* Calcd. for $C_{10}H_{16}N_4$: C, 62.5; H, 8.4. Found: C, 62.7; H, 8.2.

(7) Földi and Todd found ethyl β-amino-α-cyanocrotonate to be insoluble in water and aqueous base.

Acknowledgment.—We are indebted to Samuel W. Blackman and N. Martinez, Jr., for microanalyses and to Elizabeth Burgi for the preparation of intermediates.

Summary

A series of 2-methyl-4-amino-6-substituted aminopyrimidines have been prepared from the reaction of alkyl and arylamines with the corresponding chloropyrimidine.

Amino compounds in which the amino group is a portion of an amidine or guanidine system appeared to give no product with the chloropyrimidine under aqueous acid conditions.

A simple and improved procedure for the preparation of 2-methyl-4-amino-6-hydroxypyrimidine is described.

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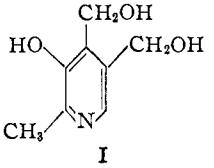
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Lithium Aluminum Hydride Reduction of Pyridine Carboxylic Esters: Synthesis of Vitamin B_6

BY REUBEN G. JONES AND EDMUND C. KORNFELD

One of the major problems in the synthesis of vitamin B_6 (I) has been the reduction of carboxyl groups to hydroxymethyl groups in the 4- and 5-positions of the pyridine ring. Generally, in the



I

synthesis of I, carboxyl groups have been converted *via* amides to nitriles and the nitriles reduced catalytically to aminomethyl side chains.[1] A further step, *viz.*, treatment with nitrous acid, is then necessary to convert the aminomethyl to hydroxymethyl groups.[1] It occurred to us that this awkward process might be avoided, and the desired hydroxymethyl functions at positions 4 and 5 might be obtained directly by reducing an appropriately substituted 4,5-pyridinedicarboxylic acid ester with lithium aluminum hydride. Previous work in this Laboratory has shown that esters of imidazole,[2] pyrazole,[3] pyrrole,[4] furan,[4] indole[4] and other heterocyclic carboxylic acids are smoothly reduced with lithium aluminum hydride to the corresponding hydroxymethyl compounds. On the other hand, esters of pyrazine carboxylic acid,[4] oxazole carboxylic acid[4] and certain others appear to undergo extensive decomposition when treated with lithium aluminum hydride. Furthermore, Hochstein[5] has reported that pyridine itself is attacked by lithium aluminum hydride.

A variety of pyridinecarboxylic acid esters has now been reduced with lithium aluminum hydride, and in most cases good to excellent yields of the corresponding hydroxymethyl compounds have been obtained. In no case was reduction of the pyridine ring observed. 3-Hydroxymethylpyridine[6] was obtained in 80% yield from ethyl nicotinate.[7] The reduction of diethyl 2-methyl-4,5-pyridinedicarboxylate[8] gave a satisfactory yield of 2-methyl-4,5-dihydroxymethylpyridine (II). Reduction of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate[9] gave a 50% yield of 2,6-dimethyl-3,4-dihydroxymethyl-

(1) See, for example, Szabo, U. S. Patent 2,410,531, Nov. 6, 1946; Mowatt, Pilgrim and Carlson, THIS JOURNAL, **65**, 954 (1943); Harris and Folkers, *ibid.*, **61**, 1245, 3307 (1939).

(2) Jones and McLaughlin, *ibid.*, **71**, 2444 (1949).

(3) Jones, *ibid.*, **71**, 3994 (1949).

(4) Unpublished studies by the authors.

(5) Hochstein, THIS JOURNAL, **71**, 305 (1949).

(6) Panizzon, *Helv. Chim. Acta*, **24E**, 24 (1941).

(7) Since this paper was submitted for publication a similar reduction has been reported in British Patent 631,078 [*C. A.*, **44**, 5397ᵃ (1950)].

(8) The intermediate 2-methyl-4,5-pyridinedicarboxylic acid used in this experiment was obtained by permanganate oxidation of 3-methylisoquinoline (see Experimental).

(9) Mumm and Hüneke, *Ber.*, **50**, 1573 (1917).