Tetrahedron Letters No. 9, pp 693 - 694, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS AND CONVERSION OF 5-AMINO-4-PYRIMIDINECARBOXYLIC ACIDS INTO 4-HYDROXYPYRIMIDINES VIA THEIR DIAZONIUM SALTS

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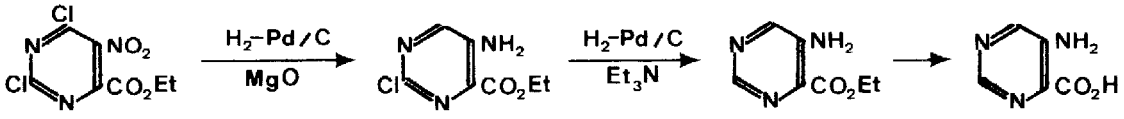
(Received in UK 15 January 1976; accepted for publication 23 January 1976)

Having in mind the generation of 4,5-didehydropyrimidines, according to Friedman and Logullo's procedure[1], we have studied the synthesis of some 5-amino-4-pyrimidinecarboxylic acids. Along with their preparation, we report the results of the diazotization of these compounds in concentrated sulfuric acid.

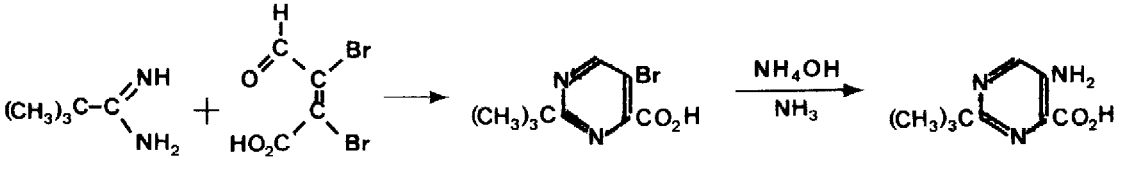
Synthesis.

Very few 5-amino-4-pyrimidinecarboxylic acids are known[2]. The parent compound has now been prepared as shown in the following scheme :



Catalytic hydrogenation of ethyl 2,6-dichloro-5-nitro-4-pyrimidinecarboxylate[3], in anhydrous dioxane, gave predominantly ethyl 5-amino-2-chloro-4-pyrimidinecarboxylate (m.p. 155°)[4], along with minor amounts of ethyl 5-amino-4-pyrimidinecarboxylate and its 2,6-dichloro derivative. Separation was carried out by column chromatography on silica gel. Subsequent dehalogenation, in ethanol, yielded ethyl 5-amino-4-pyrimidinecarboxylate (m.p. 148°). Treatment with aqueous sodium hydroxide finally gave 5-amino-4-pyrimidinecarboxylic acid (m.p. 256-258°, dec.) in high yield.

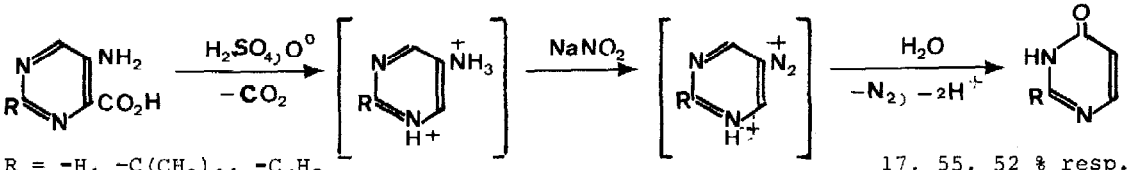
A second 5-amino-4-pyrimidinecarboxylic acid was synthesized by a scheme developed from the earlier work of Kunckell and Zumbusch[5].



Pivalamidine (3 equivalents) and mucobromic acid were condensed in ethanol to give 5-bromo-2-t-butyl-4-pyrimidinecarboxylic acid (m.p. 140°). Subsequent ammonolysis, at 70°, converted the bromo compound to 5-amino-2-t-butyl-4-pyrimidinecarboxylic acid (m.p. 105-107°).

Diazotization.

5-Amino-4-pyrimidinecarboxylic acid and the corresponding 2-t-butyl and 2-phenyl[5] derivatives were diazotized in concentrated sulfuric acid. Pouring the reaction mixtures onto ice caused the instantaneous evolution of gas. 4-Hydroxypyrimidines were isolated and identified by their spectral data and by comparison with authentic samples[6,7,8].



R = -H, $-C(CH_3)_3$, $-C_6H_5$ 17, 55, 52 % resp.

The decarboxylation has been checked when R = t-butyl (53 % yield). The diazotization of the corresponding 5-aminopyrimidines[9,10,12] led to the same 4-hydroxypyrimidines, although in lower yields. The formation of these compounds may be rationalized on the assumption that the hydrolysis of the diazonium salts proceeds by an abnormal addition-elimination mechanism[13].

In experiments carried out with 5-amino-2-t-butylpyrimidine, 2-t-butyl-5-hydroxypyrimidine could not be detected in spite of a careful search[14]; on the other hand, decomposition occurred to a large extent.

Our findings are not consistent with some conclusions reported in the literature. Whittaker[9] stated that 5-aminopyrimidine did not give a diazonium salt with nitrous acid or nitrosylsulfuric acid. However, in one experiment, he collected a volume of gas corresponding to a 77 % conversion of the amino group into nitrogen. Boarland and McOmie[15] reached the same conclusion. They failed to isolate 5-hydroxypyrimidine from the reaction mixture. Fanta and Hedman[12] attempted the diazotization of 5-amino-2-phenylpyrimidine in a variety of conditions and never observed the formation of a coupling product with β-naphthol.

References and footnotes

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(14) In a blank experiment, 2-t-butyl-5-hydroxypyrimidine could be recovered in high yield from a concentrated sulfuric acid solution. We are grateful to Dr. R. Nasielski-Hinkens for a sample of this compound.
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