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A Novel Reaction of Substituted Purines and Pyrimidines[1]

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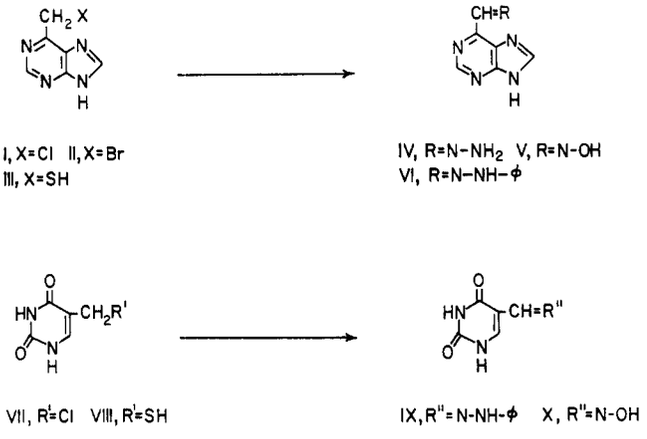
We have found that derivatives of aldehydes are obtained when halogeno- and mercaptomethylpurines or -methyluracils (substituted in the 6 or 5 positions, respectively) are allowed to react with hydrazine, hydroxylamine, or phenylhydrazine. When analytically pure 6-chloromethylpurine[2] (I) was refluxed for 4 hr with a fivefold excess of 10% hydrazine in ethanol, the known purine-6-carboxaldehyde hydrazone[3] (IV) was formed in 94% yield, with evolution of ammonia (Scheme I). A similar transformation resulted with

SCHEME I



6-bromomethyl-[2] (II) and 6-mercaptomethylpurine[4] (III). The reaction between the substituted methylpurine derivative (I, II, III) and the hydrazine solution starts after 20 min of refluxing, and is usually complete in 3 to 4 hr; prolonged treatment alters neither the reaction product nor its yield. Since equimolecular amounts of 6-chloromethylpurine and hydrazine provided only a 28% yield of IV, it appears that an excess of hydrazine is essential for the completion of the reaction. Solutions of hydrazine sulfate, buffered at pH 7, gave very poor yields of the hydrazone (IV). As previously observed,[5] an excess (20 equiv or more) and prolonged treatment (10–15 hr) with concentrated hydrazine (64–95%) in water or ethanol reduces hydrazone IV to 6-methylpurine, but, at the lower hydrazine concentration mentioned above, there is little conversion of IV to 6-methylpurine. Reaction of 6-chloromethylpurine (I) with hydroxylamine or with phenylhydrazine provided purine-6-carboxaldehyde oxime (V) or phenylhydrazone (VI) in 37 and 62% yield, respectively. With thiosemicarbazide and 6-chloromethylpurine (I), a solution showing the characteristic ultraviolet spectrum of the known[3] thiosemicarbazone obtained. Purine-6-carbinol,[6] 6-methylpurine 1-N-oxide[7] and alkyl or alkylaryl S-substituted mercaptomethylpurines did not react either with hydrazine or phenylhydrazine.

In an extension of this reaction to pyrimidine derivatives, we have converted 5-chloro- (VII) and 5-mercaptomethyluracil[8] (VIII) into the known[9] 5-uracilcarboxaldehyde phenylhydrazone (IX) in 39 and 47% yield, respectively, by reaction with phenylhydrazine. 5-Mercaptomethyluracil and ethanolic hydroxylamine gave an almost quantitative yield of the corresponding oxime (X). Similar treatment of either the chloro- or the mercaptomethyluracil derivatives with hydrazine and thiosemicarbazide failed to yield the corresponding aldehydo derivatives. The hydrazone could not be synthesized from 5-uracilcarboxaldehyde upon reaction with hydrazine; attempts to prepare the hydrazone by reaction of the thiosemicarbazone (prepared from 5-uracilcarboxaldehyde[9]) with hydrazine also failed. Such transformations have been achieved in excellent yield using purine-6-carboxaldehyde thiosemicarbazones.[6]

This conversion of a substituted methylpurine or pyrimidine with hydrazine, hydroxylamine, and phenylhydrazine resembles the reported reaction of phenacyl bromides with hydrazine.[10] It is known that substituted benzyl chlorides upon treatment with hydrazine are not converted into aldehyde derivatives.[11]

Attempts to transform 6-chloromethylpurine, 6-aminomethylpurine,[12] or 5-chloromethyluracil into the corresponding aldehydes with hexamethylenetetramine, according to the Sommelet method,[13] failed. Similar negative results have been reported with several heterocyclic derivatives.[14]

The reaction between the methylpurine derivatives and hydrazine may involve the steps shown in Scheme II. Compound XI, the initial reaction product of 6-

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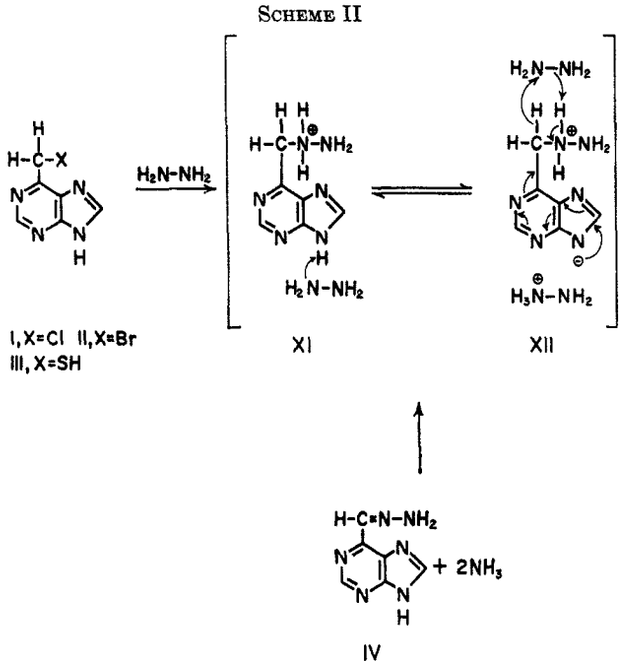
TABLE I

REACTION OF HYDRAZINE, HYDROXYLAMINE, AND PHENYLHYDRAZINE WITH 6-METHYLPURINE AND 5-METHYLURACIL DERIVATIVES

Base	Reagent	Mol ratio of reagent/ 1 mole of base	Reflux time, hr	Product	Yield, %
6-Chloromethylpurine (I)	Hydrazine[a]	5–10	1–4	Hydrazone (IV)	94
6-Chloromethylpurine (I)	Hydrazine (10%)	1	4	Hydrazone (IV)	28
6-Bromomethylpurine (II)	Hydrazine[a]	5–10	4	Hydrazone (IV)	85
6-Mercaptomethylpurine (III)	Hydrazine[a]	5–10	4	Hydrazone (IV)	24
6-Chloromethylpurine (I)	Hydroxylamine[b]	4–10	1	Oxime (V)	37
6-Chloromethylpurine (I)	Phenylhydrazine	3	6	Phenylhydrazone (VI)	62
5-Chloromethyluracil (VII)	Phenylhydrazine	5	6	Phenylhydrazone (IX)	39
5-Mercaptomethyluracil (VIII)	Phenylhydrazine	3	5	Phenylhydrazone (IX)	47
5-Chloromethyluracil (VII)	Hydroxylamine[b]	20	6	Oxime (X)	98

[a] No variation in the yields was observed by using different concentrations of the hydrazine solution; its range was 10–95%. [b] A 1 *M* solution in ethanol (*cf.* ref 12).

SCHEME II



chloromethylpurine with hydrazine, undergoes ionization in the basic reaction medium giving XII. One molecule of hydrazine would be reduced to give the hydrazone (IV) with evolution of 2 moles of ammonia.[15]

Experimental Section

The purine or uracil derivative was refluxed with the corresponding solution of reagent in ethanol (see Table I for conditions and product yields). After cooling, the resulting precipitate was collected by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue was suspended in water, filtered, washed with ethanol, and combined with the first precipitate. The reaction products were in all cases found to be identical with the previously described purine-6-carboxaldehyde[3] and 5-uracilcarboxaldehyde derivatives,[9] by mixture melting point, ultraviolet spectra at different values of pH, and paper chromatography in the following solvent systems: water saturated with *n*-butyl alcohol (1:1, v/v); *n*-butyl alcohol saturated with water (same proportions) with or without 1% ammonia and in *n*-butanol (77%), formic acid (10%), and water (13%) (v/v). The ammonia which evolved from the reaction of 6-chloromethylpurine and hydrazine was drawn up in a stream of dry nitrogen which was passed through the reaction mixture and through a cooled trap (to condense any hydrazine which could accompany the nitrogen) into a 5% aqueous solution of boric acid and determined by titration with standard HCl. The recovery of ammonia was between 80 and 95% of the expected value.

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(15) We are indebted to Dr. S. Cohen, for valuable discussion concerning the proposed mechanism.

The Reaction Product from Aspartic and Maleic Acids in Aqueous Ammoniacal Solution[1]

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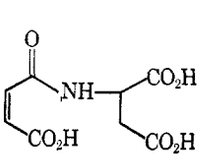
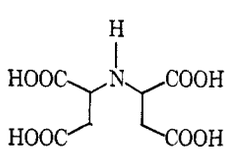
The reaction of aspartic acid with maleic anhydride has been investigated by several workers seeking the elusive N-maleoylaspartic acid (1) as an intermediate in polypeptide synthesis; thus far the product has not been made.[2] The reaction of fumaric acid with aqueous ammonia produces chiefly DL-aspartic acid and a small amount of iminodisuccinic acid,[8] $C_8H_{11}NO_8$ (2).



$C_8H_9NO_7$

1



$C_8H_{11}NO_8$

2

(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

(2) Although many N-maleoylamino acids have been prepared by shaking an aqueous solution of the amino acid with a benzene solution of maleic anhydride,[3-5] and by reaction of amino acids with maleic anhydride dry[6] or in acetic acid solution,[7] N-maleoylaspartic acid (1) has not yet been made.

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