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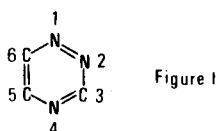
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The acid hydrolysis of 3-hydrazino-5,6-disubstituted-1,2,4-triazine, 3,5-dihydrazino-6-substituted-1,2,4-triazine, and 2-hydrazinopyrimidine derivatives was studied. It was found that the reaction proceeded through the formation of 3-keto and 3,5-diketo derivatives of the related 2,3-dihydro, 2,3,4,5-tetrahydro-1,2,4-triazines, and 2-keto derivatives of 1,2-dihydropyrimidines. It was concluded from these reactions that in 1,2,4-triazine derivatives the C-5 carbon is more reactive than the C-3 carbon toward nucleophiles. The reaction mechanism is discussed.

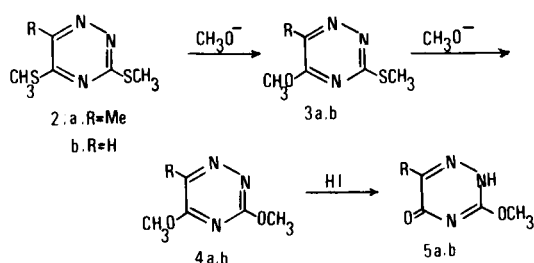
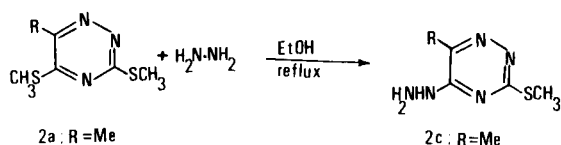
*J. Heterocyclic Chem.*, **16**, 817 (1979).

Arrangement of three nitrogen atoms in a six-membered nucleus in the form of **1** (Figure I) makes the C-3 and C-5 carbons very reactive, so that most nucleophiles attack these carbon atoms readily. This is understood from the fact that the contribution of the N-4 and N-2 nitrogen atoms for the C-5 carbon atoms are more than



that for the C-3 carbon atom. For example Libermann, *et al.* (2), have reported that the reaction of 3,5-dimethylmercapto-6-methyl-1,2,4-triazine (**1a**) yields 5-hydrazino-6-methyl-1,2,4-triazine (**2c**) (Scheme I).

Piskala (3) has reported that the reaction of compounds **2a,b** with other nucleophiles such as methoxide anion proceeds according to Scheme II.

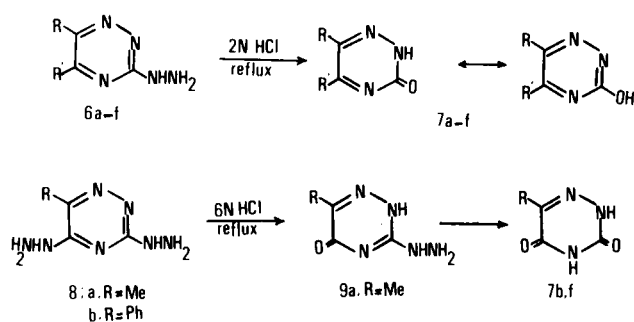


In this paper we wish to report another interesting reactivity of C-3 and C-5 substituted 1,2,4-triazines.

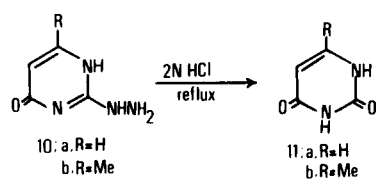
In the course of the synthesis of *p*-aminobenzene-sulfonyl hydrazide derivatives of 1,2,4-triazines with possible pharmacological activity, the classical Hinsberg synthetic method for the synthesis of sulfonamides was attempted. Namely, 3-hydrazino-5,6-disubstituted-1,2,4-triazines **6a-f** were allowed to react with *p*-acetamidobenzene-sulfonyl chloride, followed by acid hydrolysis. The reaction products were not the expected sulfonylhydrazide derivatives, but proved to be the 3-keto derivatives of 2,3-dihydro-1,2,3-triazines **7a-f**, and sulfanilic acid hydrazide. These results led us to investigate the acid hydrolysis of the starting 3-hydrazino-5,6-disubstituted-1,2,4-triazine derivatives **6a-f** under the same conditions. In this case, the products were also identical with those obtained in the former reaction (Scheme III). The characteristics of the reaction products are summarized in Table I.

In attempts to differentiate the reactivity of the C-3 and C-5 carbon atoms, the acid hydrolysis of 3,5-dihydrazino-6-substituted-1,2,4-triazines **8a,b** was studied. It was found that the reaction proceeded in two steps. In the first step, 3-hydrazino-6-substituted-1,2,4-triazin-5-(2*H*)one **9** derivatives were formed, which on continuation of the hydrolysis yielded the corresponding 3,5-(2*H*,4*H*)-dione derivatives **7a,f**. These results are consistent with the fact that as an electrophile, the C-5 carbon atom is more reactive than the C-3 carbon atom (Scheme III). The characteristics of the reaction products are summarized in Table II.

Acid hydrolysis of the substituted 2-hydrazinopyrimidines **10a,b**, utilizing the same reaction conditions, also yielded the related pyrimidin-2(1*H*)ones **11a,b** in moderate yields (Scheme IV). The characteristics of these reaction products are summarized in Table III.

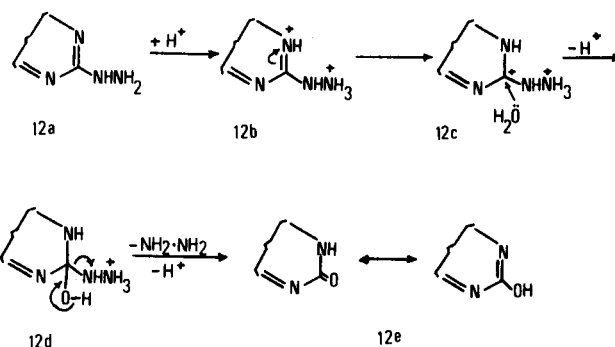


Scheme III



Scheme IV

In the case of the 2-hydrazino-1,2,4-thiadiazoles and phenylhydrazine the same reaction failed to give the desired products, and the starting hydrazino derivatives were recovered. In order to compare the reactivity of the hydrazino group with the amino group, the same type of reaction was tried with 3-amino-1,2,4-triazine and 2-aminopyrimidine derivatives. In this case the starting materials were also recovered unchanged. A simple mechanism for this reaction is thought to be as shown in Scheme V.



Scheme V

Table I (a)

Compound No.	R	R	M.p. of Product °C	M.p. of Reference °C	Yield %
7a	-H	-Ph	242	234 (3)	81
7b	-Me	= 0 (4H)	216	216 (4)	39
7c	-Ph	-Ph	218	218 (5)	42
7d	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	= 0 (4H)	297	298 (4)	47
7e	-Ph	= 0 (4H)	264	262 (6)	74
7f	-H	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	286		85

(a) Except for compound 7f, other compounds are known, and are identical with authentic samples.

Table II

Compound No.	R	M.p. of Product °C	M.p. of Reference °C	Yield %
7b	-Me	216	216 (4)	73
7e	-Ph	264	262 (6)	40

Table III

Compound No.	R	M.p. of Product °C	M.p. of Reference °C	Yield %
11a	-H	335	335 (7)	45
11b	-Me	320	over 300 (8)	28

Protonation of the hydrazino derivative **12a** affords the intermediate **12b**, which through transformation to **12c** and nucleophilic attack of water gives an unstable geminal hydrazinoalcohol **12d**. Ketone formation of the hydrazino alcohol followed by the elimination of the hydrazino group results in the formation of the keto-enol tautomer of **12e**.

#### EXPERIMENTAL

All melting points are uncorrected. Except for compound **7f** in Table I, all other compounds are known, and were found identical in every respect with the reference samples. The general method was applicable for all the compounds mentioned in Tables I and III. For the compounds mentioned in Table II the reaction conditions were slightly different from the general method. The experimental conditions for the formation of these compounds are described separately.

##### General method.

A mixture of the 3-hydrazino-5,6-disubstituted-1,2,4-triazine derivative **6a-f** or of the 2-hydrazinopyrimidine derivative **10a,b** (0.2 g.) and 2*N* hydrochloric acid (20 ml.) was refluxed for 2 hours. After cooling, the reaction medium was neutralized with 2*N* sodium hydroxide solution, and the precipitate was filtered off. Purification and recrystallization of the precipitate from the appropriate solvent gave the compounds listed in Tables I and III.

Acid Hydrolysis of 3,5-Dihydrazino-6-methyl-1,2,4-triazine (**8a**).

1) A mixture of compound **8a** (0.2 g.) in 6*N* hydrochloric acid (12 ml.) was refluxed for 4 hours, then cooled, and neutralized with 6*N* sodium hydroxide solution. The reaction mixture was condensed under reduced pressure, and the residual solid was extracted with anhydrous ether. The extract was dried over anhydrous sodium sulfate, and condensed to give a colorless solid, which was crystallized from ethanol to yield 0.05 g. (28%) of colorless prisms, m.p. 140-141°, undepressed on admixture with an authentic sample of 3-hydrazino-6-methyl-1,2,4-triazin-5(2*H*)-one **9a** (2). Other spectral data of the product were identical in every respect with the reference sample.

2)

A mixture of compound **8a** (0.1 g.) in 6*N* hydrochloric acid (12 ml.) was refluxed for 12 hours, then cooled, and neutralized with 6*N* sodium hydroxide solution. The mixture was condensed under reduced pressure and the residual solid was extracted with anhydrous ethyl acetate. The solvent was removed under reduced pressure, and the residue was purified by recrystallization from water to give colorless prisms, m.p. 216°. The physical and spectral data of this compound were identical with an authentic sample of 6-methyl-1,2,4-triazin-3,5(2*H*,4*H*)dione **7b** (4) (Table II).

Acid Hydrolysis of 3,5-Dihydrazino-6-phenyl-1,2,4-triazine (**8b**).

A mixture of compound **8b** (0.1 g.) and 6*N* hydrochloric acid (20 ml.) was refluxed for 36 hours, then cooled, and neutralized with 6*N* sodium hydroxide solution. The precipitate was filtered off, and purified by recrystallization from water to give prisms, m.p. 264°. The physical and spectral data of this compound were identical with an authentic sample of 6-phenyl-1,2,4-triazin-3,5(2*H*,4*H*)dione **7e** (6,9) (Table II).

#### REFERENCES AND NOTES

- (1) Author to whom correspondence should be directed.
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- (9) In this reaction the intermediate related to compound **9a**, though its formation was checked by tlc throughout the reaction, was not isolated.