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OXIDATION OF 3,5-DISUBSTITUTED 6-METHYL-1,2,4-TRIAZINES

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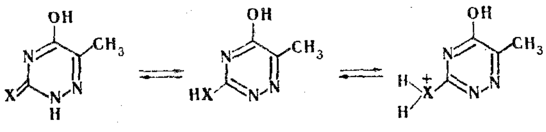
UDC 547.873:542.943

The corresponding substituted 1,2,4-triazine-6-carboxylic acids were obtained by oxidation of 3,5-disubstituted 6-methyl-1,2,4-triazines with hydrogen peroxide in an acidic medium. It is shown that the nature of the substituents does not affect the course of the process.

1,2,4-Triazine derivatives are finding ever increasing application as pesticides [1,2]. Carboxy-containing 1,2,4-triazines, which are the triazine analogs of nicotinic acid, which plays an important role in the metabolism of plants [3], are of interest from the point of view of their biological activity.

A general method for the production of aryl carboxylic acids is oxidation of the corresponding methyl derivatives [4]. However, their production by this method is difficult in the case of methyl-substituted 1,2,4-triazines. The oxidation of 3,5-diaryl-6-methyl-1,2,4-triazines with potassium permanganate in alkaline solution leads to the production of 3,5-diaryl-6-hydroxy-1,2,4-triazines, evidently as a consequence of decarboxylation of the probable intermediate, viz., the 3,5-diaryl-1,2,4-triazine-6-carboxylic acid.

We have carried out the oxidation of 3,5-dihydroxy-6-methyl-1,2,4-triazine (Ia), 3-thio-5-hydroxy-6-methyl-1,2,4-triazine (Ib), and 3-amino-5-hydroxy-6-methyl-1,2,4-triazine hydrochloride (Ic) with hydrogen peroxide in hydrochloric acid. The oxidation proceeds smoothly at 40-50°C. The reaction products were identified from the IR spectroscopic data and their elementary compositions. 3,5-Disubstituted-1,2,4-triazine-6-carboxylic acids were obtained in all cases. It should be noted that the character of the substituents in the 3 position does not have an appreciable effect on either the rate of oxidation or the yield of product. In view of the ability of hydroxy, mercapto, and amino groups to undergo oxidation even under relatively mild conditions, their inertness under the experimental conditions deserves discussion. A possible reason for the stability of the indicated groups may be their primary existence in tautomeric forms II (keto, thioxo, or imino), which are more resistant to oxidation than the III forms:



II III IV

X = O, S, NH

Chernigov Branch, Kiev Polytechnic Institute, Chernigov 250027. All-Union Scientific-Research Institute of Chemical Agents for the Protection of Plants, Moscow 109088. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1271-1273, September, 1982. Original article submitted August 4, 1981; revision submitted November 5, 1981.

0009-3122/82/1809-0985$07.50

A different possible explanation consists in the assumption of protonation of the substituting group to give onium ion IV, which is more stable with the oxidation conditions than starting III. It is apparent that in the case of oxidation of Ic the protection of the NH_2 group is due primarily to the formation of an ammonium salt. It is more difficult to determine the reasons for stability in the case of Ia,b in view of the lower basicity of the corresponding groups. It is possible that hydrochloric acid suppresses the dissociation of these groups, which leads to the formation of readily oxidizable anions $R{-}XH \rightleftharpoons H^+ + R{-}X^-$ and thereby increases the stability of the —SH and —OH groups.

To determine the reasons for the stability of the mercapto group under the adopted experimental conditions we carried out the oxidation of triazine Ib with hydrogen peroxide in a neutral medium. Oxidation takes place with warming up of the reaction mixture, and the pH of the medium decreases to two to three during the process. The principal products under these conditions are as follows: 5-hydroxy-1,2,4-triazine-6-carboxylic acid (V), 3-thio-5-hydroxy-1,2,4-triazine-6-carboxylic acid (VI), and elementary sulfur. The absorption band with ν = 1200 cm^{-1} in the IR spectrum of VI corresponds to the vibrations of the C=S group, which is absent in the spectrum of acid V. Parallel reactions involving the desulfuration of the triazine [6] and the formation of acid VI, which is an oxidation catalyst, since it increases the hydrogen ion concentration (the pK_a of acid VI is 3.5, while the pK_a of starting Ib is eight) and accelerates the reaction $H_2O_2 + 2H^+ + 2e \rightarrow 2H_2O$, evidently occur in the first stage of the process. In the second stage of the process the function of the resulting acid is most likely not just acceleration of oxidation but also consists in suppression of the dissociation of the sulfhydryl groups and thereby in increasing their stability in the oxidative medium.

The question as to why decarboxylation of resulting acid VI does not take place to an appreciable extent under the adopted experimental conditions is noteworthy. One of the reasons is undoubtedly the fact that the degree of oxidation in the case of oxidation with hydrogen peroxide is more easily controlled by the reagent ratio (the excess amount of hydrogen peroxide as against the stoichiometric quantity is no more than 10%). In the case of oxidation with potassium permanganate in an alkaline medium [5] this is difficult, since further oxidation of the resulting 1,2,4-triazine-6-carboxylic acid by the products of reduction of the permanganate is possible even when the stoichiometric amount of potassium permanganate is introduced. A more weighty reason is evidently the fact that under these conditions triazine-6-carboxylic acid will be present in the form of the carboxylate ion, whereas the concentration of carboxylate ions is extremely low in the oxidation with hydrogen peroxide in hydrochloric acid. The mechanism of decarboxylation under the influence of oxidizing agents has not been studied to any great extent. It is completely likely that it is similar in its principal features to the mechanism of the Kolbs electrolysis [7]. Thus the role of the acidic medium in the oxidation with hydrogen peroxide consists in accleration of the process, protection of the substituting groups from oxidation, and suppression of decarboxylation.

The formation of an N-oxide at the heteroatom is possible in the case of oxidation with hydrogen peroxide in an acidic medium [8],but the IR spectroscopic data (the absence of the absorption band at ~700-800 cm^{-1} that is characteristic for N-oxides) indicate that this reaction does not occur under our experimental conditions.

EXPERIEMNTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-29 spectrometer. The ionization constants of the acids were determined by potentiometry with an MB-85 precision pH meter (German Democratic Republic) at 20°C and a concentration of 10^{-3} mole/liter in water.

3,5-Dihydroxy-1,2,4-triazine-6-carboxylic Acid (IVa). A 21-ml sample of a 10% solution of hydrogen peroxide was added dropwise to a suspension of 2.54 g (0.02 mole) of methyltriazine Ia in 50 ml of a 2 N HCl solution, and the mixture was stirred at 40-50°C for ~30 min. It was then filtered, and the filtrate was evaporated. The residue was washed with hot ethanol to give a white substance that was quite soluble in water but insoluble in most organic solvents. The yield was 2.35 g (75%). The product had mp 300°C and pK_a 3.3. IR spectrum: 3300 (OH), 1650 (C=O), 1110, 1040, 990, and 855 cm^{-1} (triazine ring vibrations). Found: C 30.2, H 1.8, N 26.9%. Calculated: C 30.6, H 1.9, N 26.8%.

3-Thio-5-hydroxy-1,2,4-triazine-6-carboxylic Acid (VIb). This compound was obtained by a method similar to that used to prepare acid VIa. The bright yellow substance was quite soluble in water but insoluble in most organic solvents. The yield was 2.26 g (65%). The product had mp 149-150°C and pK_a 3.5. IR spectrum: 3300 (OH), 1650 (C=O), 1200 (C=S), 1110, 1040, 990, and 855 cm^{-1} (triazine ring vibrations). Found: C 27.6, H 1.1, N 24.4%. Calculated: C 27.9, H 1.2, N 24.2%.

3-Amino-5-hydroxy-1,2,4-triazine-6-carboxylic Acid Hydrochloride (VIc). This compound was obtained by a method similar to that used to prepare acid VIa. The pinkish substance was quite soluble in water but insoluble in most organic solvents and melted above 300°C. The yield was 2.76 g (70%). IR spectrum: 3170 (NH), 1650 (C=O), 1110, 1040, 995, and 855 cm^{-1} (triazine ring vibrations). Found: C 24.7, H 2.5, N 29.3%. Calculated: C 24.9, H 2.6, N 29.1%.

5-Hydroxy-1,2,4-triazine-6-carboxylic Acid (V). A 150-ml sample of 3% H_2O_2 was added with stirring to a suspension of 14.3 g (0.1 mole) of methyltriazine Ib in 100 ml of water, during which the mixture became warm and the acidity of the medium increased to pH 2-3. The mixture was stirred for 5 h, after which the sulfur was separated by filtration. The filtrate was evaporated, and the residue was refluxed in ethanol. The mixture was filtered, and the filtrate was cooled to precipitate 5.1 g (35%) of pale-yellow crystals with mp 139-141°C and pK_a 4.3. IR spectrum: 3300 (OH), 1650 (C=O), 1110, 1040, 990, and 850 cm^{-1} (triazine ring vibrations). Found: C 33.8, H 2.1, N 29.8%. Calculated: C 34.0, H 2.2, N 29.9%.

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