STUDIES IN THE BENZODIAZINE SERIES

IX. Covalent Hydration And Cleavage of Tetrazolo[1, 5-c]quinazoline*

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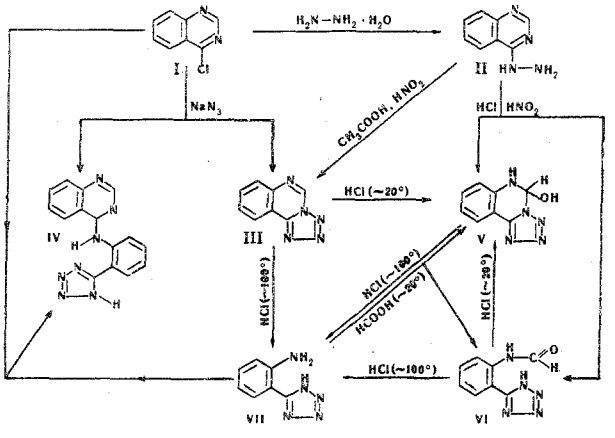
It has been shown that when there is no substituent in position 5 of a tetrazolo[1, 5-c]quinazoline covalent hydration at the $N_{(6)}=C_{(5)}$ bond and cleavage of the pyrimidine ring with the formation of 5-(2'-aminophenyl)-tetrazole take place more readily than in the case of the 5-methyl derivative. The 5-phenyl derivative of tetrazolo[1, 5-c]quinazoline does not undergo hydration. The mechanism of the hydration of the compounds mentioned is discussed.

In a preceding communication [1] it was shown that in a weakly acid medium 5-methyltetrazolo[1, 5-c]quinazoline, unlike 5-phenyl- and 5-(γ-pyridyl)-tetrazolo[1, 5-c]quinazolines, gives a product covalently hydrated at the $N_{(6)} = C_{(5)}$ bond and that the acid hydrolysis of 5-methyltetrazolo[1, 5-c]-quinazoline and its covalent hydrate leads to the opening of the pyrimidine ring with the formation of 5-(2'-aminophenyl)tetrazole. Under the same hydrolysis conditions, 5-phenyl- and 5-(γ-pyridyl)-tetrazolo[1, 5-c]quinazolines do not hydrate but hydrolyze at the tetrazole ring forming the corresponding 2-substituted 4-quinazolones [2].

Starting from these observations it might be expected that in the case of a tetrazolo[1, 5-c]quinazoline having no substituent in position 5 covalent hydration and, subsequently, cleavage of the pyrimidine ring would take place even more readily than in the 5-methyl derivative.



The tetrazolo[1, 5-c]quinazoline III required to test this hypothesis was obtained as described by Sidni et al. [3] by diazotizing 4-hydrazinoquinazoline (II) in 50% acetic acid (see scheme). The resulting product III, did in fact hydrate very readily. After only a few hours in 2 N hydrochloric acid, tetrazolo[1, 5-c]quinazoline (III) was converted into a substance which, from the results of elementary analysis and the IR spectra, was the covalently hydrated product V. When it was heated with 2 N hydrochloric acid, this hydrate was smoothly converted into 5-(2'-aminophenyl)tetrazole (VII).

Tetrazolo[1, 5-c]quinazoline is also formed by adding an aqueous solution of sodium azide to an alcoholic solution of 4-chloroquinazoline (I) in molar proportions. If, however, the reaction is carried out with a two-fold excess of the chloride I, 1-C-tetrazoly-2-(4'-quinazolylamino)benzene (IV) is obtained. The formation of this product suggests that under these conditions of carrying out the experiment the covalent hydrate V originally formed rapidly undergoes ring opening and, evidently, through the stage of the formation of the formyl compound VI, gives 5-(2'-aminophenyl)tetrazole VII, which reacts immediately with the 4-chloroquinazoline that has not yet reacted with the sodium azide. The structure of compound IV was confirmed by its synthesis through the reaction of 4-chloroquinazoline with 5-(2'aminophenyl)tetrazole. This gave a reaction product having an IR spectrum identical with that of substance IV. The production of compound IV shows the instability of the pyrimidine ring in the hydrated compound V formed as an intermediate. Its instability is also characterized by the fact that in an attempt to effect dehydration by heating the substance above the melting point as can be done in the case of the hydrate of the 5-methyl derivative) resinification takes place.

When 4-hydrazinoquinazoline (II) was diazotized in hydrochloric acid, instead of the expected tetrazolo[1, 5-c]quinazoline we isolated two products which could be separated by crystallization from water. The first of them, plates with mp 173–174° C, was obtained in very low yield (in some experiments it could not be obtained at all). From the results of elementary analysis and the IR spectra, the product was the desired covalently hydrated substance V. The other product, needles, had mp 145°–147° C (decomp.) after drying over P_2O_5. The IR spectrum had a well defined band at 1707 cm^{-1} corresponding to a carbonyl group and bands characteristic for the tetrazole ring. When it was heated in hydrochloric acid, this compound formed 5-(2'-aminophenyl)- tetrazole (VII). These facts and also the results of elementary analysis enable this compound to be regarded provisionally as the formyl

*For communication VIII, see [1].

derivative VI. However, this substance requires further investigation in order to establish its structure. The fact that in hydrochloric acid it forms a covalent hydrate can be explained on the assumption that in this medium protonation takes place at $N_{(6)}$ of the ring, in consequence of which the $\delta+$ change on $C_{(5)}$ increases and the nucleophilic attack of the hydroxyl on the carbon atom is facilitated. If the formyl derivative is treated with 2 N hydrochloric acid in the cold, it is converted completely into the covalent hydrate V after only a few minutes.

We naturally made an attempt to obtain the covalent hydrate by an independent route involving the formylation of 5-(2'-aminophenyl)tetrazole, assuming that the formyl derivative formed would give the covalent hydrate by ring closure. In actual fact, the reaction of VII with formic acid even in the cold gave equal amounts of the covalent hydrate V and substance VI. When the reaction was carried out with formic acid (boiling solution), the main product was the covalent hydrate V.

Thus, hydration at the $N_{(6)}=C_{(5)}$ apparently takes place through the induction of a considerable $\delta+$ charge on $C_{(5)}$ under the influence of the strong electron-accepting tetrazole ring. The phenyl residue, by its electronic system, compensates the $\delta+$ charge on $C_{(5)}$ (conjugation effect) and, exhibiting electron-donating properties in this case, effectively annuls the electron-accepting influence of the tetrazole ring.

A methyl group in position 5, acting inductively only as a weak electron-donating group, is not capable of reducing the electron-accepting properties of the tetrazole ring to a sufficient extent. In consequence of this, covalent hydration of the $N_{(6)}=C_{(5)}$ bond takes place and then in an acid medium, as a result of the protonation of the nitrogen atom of the pyrimidine ring, the pyrimidine ring opens. However, in accordance with these considerations hydration at the $N_{(6)}=C_{(5)}$ bond and the subsequent cleavage take place even more readily when there is no substitutent.

EXPERIMENTAL

Tetrazolo[1, 5-c]quinazoline (III). a) A solution of 3.2 g (0.021 mole) of 4-hydrazinoquinazoline [4] in 60 ml of glacial acetic acid was treated with 60 ml of water, and then it was cooled to 5° C and, with stirring, a solution of 1.6 g of sodium nitrite in the minimum amount of water was added dropwise. A yellow precipitate of the tetrazole deposited. After an hour, the precipitate was filtered off and washed with water. Yield 2.7 g (78%). Yellow needles with mp 208–209° C (from benzene or isopropanol). According to the literature [3], mp 205° C.

b) A solution of 0.25 g (0.003 mole) of sodium azide in the minimum amount of water (~2 ml) was added to a solution of 0.5 g (0.003 mole) of 4-chloroquinazoline in a small amount of ethanol. When the solution had been boiled for a few minutes light yellow needles of the tetrazoloquinazoline separated out. After cooling, the precipitate was filtered off. Yield 0.4 g (75%), mp 207–209° C.

Hydration of tetrazolo[1, 5-c]quinazoline with 2 N hydrochloric acid. A mixture of 0.3 g (~0.002 mole) of tetrazolo[1, 5-c]quinazoline and 6 ml of 2 N hydrochloric acid was left to stand at room temperature for periods of time of from 3.5 to 25 hr, depending on the purity of the starting material. Crystallized and dried tetrazoloquinoline was hydrated in 24 hr and uncrystallized tetrazolo[1, 5-c]quinazoline in 3.5 hr. The precipitate was filtered off, washed with a small amount of water, and dried. Yield 0.25 g (80%). Mp after crystallization from water 173–174° C (decomp). The product was 5, 6-dihydro-5-hydroxytetrazolo[1, 5-c]quinazoline.

Hydrolysis of 5, 6-dihydro-5-hydroxytetrazolo[1, 5-c]quinazoline (V) with 2 N hydrochloric acid. A mixture of 0.2 g (~0.0011 mole) of 5, 6-dihydro-5-oxotetrazolo[1, 5-c]quinazoline was heated with 10 ml of 2 N hydrochloric acid until the solid matter had dissolved. After cooling, the solution was neutralized with saturated sodium carbonate solution and the precipitate was filtered off. Yield 0.15 g (88%). After crystallization from water and drying over P_2O_5, the product had mp 140–144° C. Found, %: C 52.27; H 4.30. Calculated for $C_7H_7N_5$, %: C 52.17; H 4.38. The substance was identified as 5-(2'-aminophenyl)-tetrazole (VII).

Formation of 1-C-tetrazolyl-2-(4'-quinazolylamino)benzene (IV) by the reaction of 4-chloroquinazoline with sodium azide. To 0.4 g (0.0024 mole) of 4-chloroquinazoline and 0.1 g (0.0014 mole) of sodium azide were added 5 ml of ethanol and 1 ml of water. Boiling led to the dissolution of the tetrazole formed initially, and after 15–20 min a light yellow product separated out. Yield 0.18 g (34%), mp > 320° C. The compound was soluble in 2 N NaOH. It crystallized from dimethylformamide. Found, %: C 62.10; H 4.02; N 34.26. Calculated for $C_{15}H_{12}N_7$, %: C 62.07; H 4.14; N 38.81.

Synthesis of 1-C-tetrazolyl-2-(4'-quinazolylamino)benzene (IV). A solution of 0.1 g (0.0006 mole) of 5-(2'-aminophenyl)tetrazole and 0.1 g (~0.0006 mole) of 4-chloroquinazoline in 5 ml of ethanol was boiled. After some time, a yellow precipitate deposited. Yield 0.06 g (30%), mp> 320° C. The compound dissolved in 2 N NaOH, and crystallized from dimethylformamide. A comparison of the IR spectra of the two products showed their identity (the IR spectra were recorded on a IKS-14 instrument).

Action of nitrous acid on 4-hydrazinoquinazoline in 2 N hydrochloric acid. A solution of 0.4 g of sodium nitrite in water was slowly added to a solution of 1 g (~0.007 mole) of 4-hydrazinoquinazoline in 15 ml of 2 N hydrochloric acid cooled to 5° C. A yellow precipitate deposited which was filtered off after standing for an hour. Yield 0.9 g. The precipitate was crystallized twice from water with the addition of activated carbon. On slow cooling, two types of crystals deposited. Down to 50° C, a small yield (0.1 g) was obtained of the hydrated product V, 5, 6-dihydro-5-hydroxytetrazolo[1, 5-c]quinazoline. Mp 175–176° C (decomp.). Found, %: C 50.63; H 3.72; N 37.22. Calculated for $C_8H_7N_5O$, %: C 50.79; H 3.73; N 37.02.

When the solution was cooled to room temperature, long needles deposited. Yield 0.3 g. Mp after drying over P_2O_5, 145°–147° C. The IR spectrum of the undried substance had an absorption band in the 1709 cm^{-1} region which is characteristic for the vibrations of a carbonyl group. However, after the substance had been dried this band in the spectrum had shifted to 1669 cm^{-1}. Analysis for nitrogen did not give consistent results. The product is obviously 5-(2'-formylaminophenyl)tetrazole (VI). In some experiments, the covalent hydrate V could not be isolated since it was rapidly converted into substance VI and resinuous products under the experimental conditions.

Action of 2 N hydrochloric acid on 5-(2'-formylaminophenyl)tetrazole. With stirring, 2 ml of 2 N hydrochloric acid was added to 0.1 g (~0.0005 mole) of substance V. The long needles immediately changed into plates. After a few minutes the solid matter was filtered off and washed with water. Yield 0.008 g (80%). After crystallization from water the substance had mp 173–174° C (decomp.). Found, %: C 50.60; H 3.90. Calculated for $C_8H_7N_5$, %: C 50.79; H 3.73. The product was 5, 6-dihydro-5-oxotetrazolo[1, 5-c]quinazoline.

Hydrolysis of 5-(2'-formylaminophenyl)tetrazole with 2 N hydrochloric acid. A mixture of 0.2 g (~0.001 mole) of 5-(2'-formylaminophenyl)tetrazole and 7 ml of 2 N hydrochloric acid was heated until the solid matter had dissolved. After cooling, the solution was neutralized with saturated sodium carbonate solution. The precipitate that deposited was filtered off. Yield 0.14 g (82%). After crystallization from water and drying over P_2O_5, the product was identified as 5-(2'aminophenyl)tetrazole. Mp 140–144° C. Found, %: C 51.72; H 4.37. Calculated for $C_7H_7N_5$, %: C 52.17; H 4.38.

Formylation of 5-(2'aminophenyl)tetrazole. a) In the cold. A mixture of 0.5 g (~0.003 mole) of 5-(2'-aminophenyl)tetrazole (VII)

and 4 ml of commercial formic acid was allowed to stand at room temperature for 24 hr. The solution was evaporated to dryness in the air. Yield 0.5 g (86%). The residue was crystallized from water. Initially, on cooling to 50° C, plates separated out with mp 173°–174° C (decomp). Yield 0.2 g (34%). On complete cooling, needles deposited with mp 145–147° C (after drying over P_2O_5). Yield 0.2 g (34%).

The substance with mp 173–174° C was hydrated tetrazole tetrazolo[1,5-c]quinazoline (V). The substance with mp 145–147° C was 5-(2'-formylaminophenyl)tetrazole (VI).

b) On heating. A mixture of 0.3 g (~0.002 mole) of 5-2'-aminophenyl)tetrazole (VII) and 3 ml of formic acid (99%) was boiled for 1.5 hr. The solution was evaporated to dryness in the air. Yield 0.3 g. The residue was boiled with a small amount of water and filtered hot from the insoluble light yellow product IV (0.12 g). On cooling the solution deposited plates with mp 173–174° C (decomp.). Yield 0.12 g. Found, %: C 50.46; H 3.77. Calculated for $C_8H_7N_5O$, %: C 50.79; H 3.73. The product was V. When the aqueous mother liquor was evaporated, a small amount of residue remained which consisted of 5-(2'-formylaminophenyl)tetrazole (VI).

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