INVESTIGATIONS IN THE BENZODIAZINE SERIES

XI. Covalent Hydration in a Number of Tetrazolo[1, 5c]Quinazoline Derivatives*

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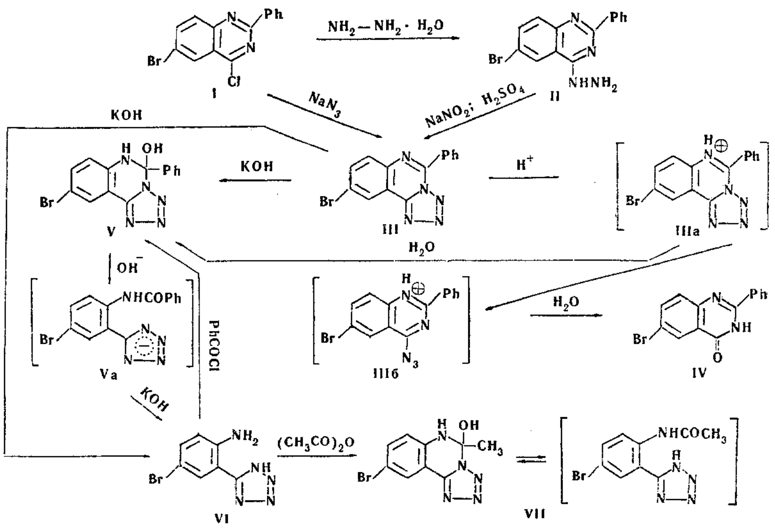
5-Phenyl-9-bromotetrazolo[1, 5c]quinazoline (I) was synthesized. It was shown that I is covalently hydrated at the $N_{(6)}=C_{(5)}$ bond. The structure of the covalent hydrate (V) was confirmed by cleavage to 5-(2'-amino-5'-bromophenyl)tetrazole. The probable mechanisms of the covalent hydration and cleavage are examined. V was converted to the 5-methyl derivative (VII).

The phenomenon of covalent hydration of the N═C bond has recently been attracting more and more attention (see the review in [2]). It was previously shown [3–5] that tetrazolo[1, 5c]quinazoline and its 5-methyl derivative are smoothly covalently hydrated at the $N_{(6)}=C_{(5)}$ bond, while the 5-phenyl derivative does not undergo hydration. Analyzing the probable reasons for this, we have proposed [6] that the electron-accepting groups in the benzo nucleus of tetrazolo[1, 5c]quinazoline may compensate for the electron-donating effect of the phenyl group in the 5 position. In fact, it was shown that 5-phenyl-9-carboxytetrazolo[1, 5c] is capable of covalent hydration [6]. In extending this investigation we thought it would be interesting to verify whether covalent hydration occurs in 5-phenyltetrazolo[1, 5c]quinazoline derivatives containing other electron-accepting substituents in the benzo nucleus, particularly halogen atoms. The greater availability of these compounds made it possible to study their properties in greater detail.

Reaction of 2-phenyl-4-chloro-6-bromoquinazoline (I) (obtained from the corresponding quinazoline and $POCl_3$ by the method in [7]) with sodium azide yielded 5-phenyl-9-bromotetrazolo[1, 5c]quinazoline (III) (see reaction scheme). The absence of an azide band (2000–2200 cm^{-1}) in the IR spectrum of the crystalline substance confirms the tetrazole structure of this compound. A product containing one water molecule than the starting tetrazole was isolated by refluxing III in hydrochloric acid. The compound, obtained in 75% yield, did not split off water during drying in vacuo over P_2O_5 at 100° C and was soluble in ammonium hydroxide; this indicates the covalent addition of a water molecule.



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*For part X, see [1].

Considering the results of previous investigations, one can conclude that covalent hydration proceeds at the $N_{(6)}=C_{(5)}$ bond, and that the compound formed has the 5,6-dihydro-5-phenyl-5-hydroxy-9-bromotetrazolo[1,5c]quinazoline (V) structure (the presence of a tautomeric form with an open pyrimidine ring, namely, 5-(2'-benzoylamino-5'-bromophenyl)tetrazole, cannot be excluded; a separate study is devoted to the question of tautomerization of the covalent hydrates). 2-Phenyl-6-bromoquinazolone-4 (IV) was obtained in low yield (6%) together with V by refluxing III in hydrochloric acid.

A compound of composition $C_7H_6BrN_5$ with amphoteric properties was isolated by refluxing V in aqueous alkali. Two intense absorptions at 3469 and 3357 cm^{-1}, which can be assigned to amino group valence vibrations, were present in the IR spectrum of this substance; in addition, there is a series of weak bands characteristic for the acidic NH group of a tetrazole [8] over a broad range (3130–2460 cm^{-1}). The analytical data and the IR spectrum enable one to conclude that the compound is 5-(2'-amino-5'-bromophenyl) tetrazole (VI). The formation of this compound confirms that covalent hydration of III occurs at the $N_{(6)}=C_{(5)}$ bond. Amine VI can also be obtained by refluxing III in aqueous alkali. The structure of VI was confirmed by the fact that it again gives V on reaction with benzoyl chloride, while acetylation with acetic anhydride gives a product of composition $C_9H_8BrN_5O$, which corresponds to 5-methyl-5-hydroxy-9-bromo-5,6-dihydrotetrazolo[1,5c] quinazoline (VII), i.e., the covalent hydrate of 5-methyl-9-5-methyl-9-bromotetrazolo[1,5c]quinazoline. Thus, the phenyl derivative was coverted to the methyl derivative.

The experimental results permit one to present probable mechanisms for covalent hydration and cleavage in the following manner (see scheme). III in acidic medium is protonated at $N_{(6)}$ to give IIIa. Two competitive processes then occur: nucleophilic attack of a water molecule at $C_{(5)}$ to form V, and opening of the tetrazole ring to give IIIb followed by hydrolytic cleavage of the azide group to form IV. The first reaction path predominates. The covalent hydrate is stable in acidic medium but removal of a proton from the hydroxyl group occurs in alkali, and the pyrimidine ring opens. Anion Va is hydrolyzed to amine VI. Covalent hydration of III also occurs in alkaline medium. In this case, the strongly nucleophilic hydroxyl ion attacks $C_{(5)}$ and the covalent hydrate, which subsequently immediately is cleaved via the scheme V → Va → VI, is formed as an intermediate. Thus, it is shown that covalent hydration is possible when an electron-accepting bromine atom is present on the benzo nucleus of 5-phenyltetrazolo[1,5c]quinazoline due to the increase in the δ^+ charge on $C_{(5)}$.

EXPERIMENTAL

2-Phenyl-4-hydrazino-6-bromoquinazoline (II). 2-Phenyl-4-chloro-6-bromoquinazoline (I) (0.01 mole) was refluxed in 50 ml of benzene with 0.05 mole of hydrazine hydrate for 1 hr. II, mp 226–228° C (decomp., from alcohol), precipitated as colorless crystals on cooling. Yield 90%. Found, %: C 53.51; H 3.00; N 17.88. Calculated for $C_{14}H_{11}BrN_4$, %: C 53.35; H 3.52; N 17.78.

5-Phenyl-9-bromotetrazolo[1,5c]quinazoline (III). A) A solution of 0.01 mole of sodium azide in 2 ml of water was added to 0.01 mole of I in 100 ml of boiling alcohol and the mixture was refluxed for 1 hr. After cooling, the resulting precipitate was filtered to give colorless needles, mp 160–161° C. Yield 95%. Found, %: C 51.25; H 2.54; N 21.38. Calculated for $C_{14}H_8BrN_5$, %: C 51.56; H 2.47; N 21.47.

B) II (0.01 mole) was dissolved in 50 ml of conc HCl, 50 ml of water was added, and an aqueous solution of 0.01 mole of $NaNO_2$ was poured into the mixture at 80° C. The mixture was cooled and the resulting precipitate was filtered. The reaction product did not depress the melting point of the product obtained from the chloride.

Hydration of 5-phenyl-9-bromotetrazolo[1,5c]quinazoline (III). III (0.01 mole) in 150 ml of HCl (1 : 1) was refluxed for 3 hr. The precipitate was filtered, and the acidic mother liquor was neutralized with ammonium hydroxide to precipitate colorless needles of 2-phenyl-6-bromoquinazolone-4 (IV), mp 303–305° C (from isopropyl alcohol). Yield 6%. Found, %: C 56.20; H 3.24; N 9.17. Calculated for $C_{14}H_9BrN_2O$, %: C 55.84; H 3.01; N 9.30. The precipitate on the filter after removal of the acidic mother liquor was dissolved in ammonium hydroxide, carbon was added, the mixture was filtered, and V was precipitated as colorless needles, mp 251–252° C (decomp., from isopropyl alcohol), with HCl. Yield 75%. Found, %: C 48.72; H 3.05; N 20.46. Calculated for $C_{14}H_{10}BrN_5O$, %: C 48.85; H 2.93; N 20.35.

Hydrolysis of V. V (0.005 mole) was refluxed in 70 ml of 10% aqueous KOH for 4 hr. The reaction mixture was neutralized with acetic acid, and colorless needles of 5-(2'-amino-5'-bromophenyl)tetrazole (VI), mp 205–206° C (from water), precipitated on cooling. Yield 50%. Found, %: C 35.57; H 2.68; Br 33.43; N 28.98. Calculated for $C_7H_6BrN_5$, %: C 35.24; H 2.52; Br 33.29; N 29.17.

Benzoylation of VI. VI (0.001 mole) was dissolved in 5 ml of dry pyridine and 0.001 mole of benzoyl chloride was added. The mixture was kept at room temperature for 30 min and then poured into dil HCl. The resulting oil was treated with acetone and the precipitate formed was crystallized from isopropyl alcohol. The product did not depress the melting point of V, obtained in the hydration of III.

Acetylation of VI. VI (0.005 mole) was dissolved in 12 ml of acetic anhydride and the solution was refluxed for 20 min. The precipitate of VII obtained on cooling was filtered and recrystallized from aqueous isopropyl alcohol to give colorless crystals, mp 205–206° C. Yield 70%. Found, %: C 38.51; H 3.08; N 24.43. Calculated for $C_9H_8BrN_5O$, %: C 38.32; H 2.86; N 24.83.

Cleavage of III. III (0.005 mole) was refluxed in 40 ml of 10% KOH for 5 hr. Carbon was added, the mixture was filtered, and the filtrate was neutralized with acetic acid. The precipitate was recrystallized from water. The product did not depress the melting point of VI obtained in the hydrolysis of V.

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