RESEARCH ON BENZODIAZINES

VIII. Covalent Hydration and Splitting of Quinazoline Compounds*

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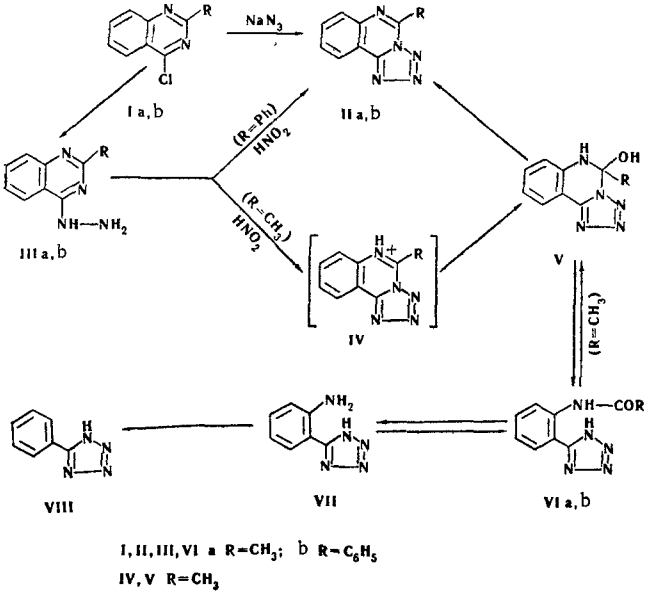
2-Methyl-4-hydrazinoquinazoline is shown to give on diazotization a covalent hydration product, 5,5-dihydro-5-methyl-5-hydroxytetrazolo[1,5-c]quinazoline (V). 2-phenyl-4-hydrazinoquinazoline gives the nonhydrated 5-phenyltetrazolo [1,5-c]-quinazoline (IIb). Hydrolysis of the hydrated 5-methyl derivative V is shown to result in opening of the pyrimidine ring and formation of 5-(2'-aminophenyl)tetrazole, while hydrolysis of the 5-phenyl derivative IIb is found to give, via the azide, 2-phenylquinazoline. Possible reasons for the different behavior on hydrolysis are considered.

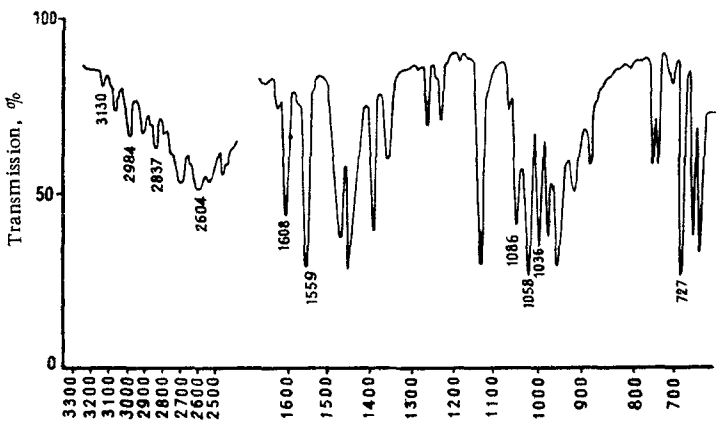
It was previously reported [1] that reaction of 2-R-4-chloroquinazolines **Ia, b** with sodium azide gives 5-R-tetrazolo[1,5-c]quinazolines **IIa, b** (see equations). **Tetrazole IIb** can also be obtained from the corresponding hydrazine **IIIb** by diazotization in hydrochloric acid. Subjecting hydrazine **IIIa** to this reaction led to isolation of a substance mp 197°–198°, whose structure was not determined [2]. Analysis and IR spectrum correspond to a hydrate of tetrazoloquinazoline **IIa**. From this compound the water is split off only on heating above the melting point, when the tetrazole **IIa** is formed [2]. No rehydration of this tetrazole, e.g. on crystallizing from aqueous ethanol, was observed. But the hydrate mp 197°–198° (decomp.) was formed when it was allowed to stand in cold in weak acid for 7 days.

These observations allowed it to be postulated that the molecule of water in the hydrate is bond constitutionally. Taking into account the results of other authors regarding so-called covalent hydration of some heteroaromatic nitrogen compounds, [3], hydration could be assumed to take place at the $N_6{=}C_5$ azomethine bond, and that the hydrate is 5,6-dihydro-5-methyl-5-hydroxytetrazolo[1,5-c]quinazoline (**V**). Further studies of the properties of the hydrate confirmed that structure. Thus brief boiling in 2 N hydrochloric acid gave compound $C_7H_7N_5$, mp 140°–144°, with amphoteric properties. The IR spectrum of this compound shows amino group valence vibrations bands (3400, 3317 cm^{-1}), and in addition over the wide interval 3100–2650 cm^{-1} there is a series of weak bands characteristic of the tetrazole acid NH group [4]. The tetrazole ring shows the 1086, 1064, 1040 cm^{-1} characteristic triplet of bands. From these results it can be inferred that heating in acid solution led to opening of the pyrimidine ring, and that the then initially formed 5 (2'acetylaminophenyl)tetrazole (VIa) was hydrolyzed to a compound mp 140°–144°, which was 5-(2'aminophenyl)tetrazole (VII). To prove the structure of VII it was deaminated



when 5-phenyltetrazole (**VIII**) mp 209°–210° was obtained.

*For Part VII see [1].



IR spectrum of 5-phenyltetrazole (VIII).

It gave an undepressed mixed melting point with an authentic specimen obtained as described in [5]. Over the range 3100–690 cm^{-1} the IR spectra of the two specimens were quite identical.

Acetylation of amine VII might have been expected to give the intermediate acetyl derivative VIa. Experiment showed that when amine VII was dissolved in acetic anhydride, acetylation takes place even in the cold, and the cyclic hydroxy compound V was isolated. Obviously isomerization of the open intermediate product (acetylamine VIa) to a ring compound takes place very easily in acid solution. It might have been expected that the ring could easily be opened. Actually ring opening with compound V takes place even on dissolving in pyridine. The IR spectrum of this solution lacks the hydroxyl band in the interval 3600–3100 cm^{-1}, but in place of it is a sharp band of amide group carbonyl (1697 cm^{-1}), showing that the substance is present as the open form in pyridine solution.

In the light of these results it was of interest to consider possible causes of the difference between the behaviors of the phenyl and methyl derivatives. As was stated above, the hydrazine IIb (with a phenyl radical) gives, on diazotization in hydrochloric acid, the nonhydrated tetrazoloquinazoline IIb.* Hydration at the $N_6{=}C_5$ bond is connected with strong electron-accepting effect of the fused tetrazole ring, giving rise to a considerable δ^+ charge at atom C_5. This effect agrees with the effect of protonization of the $\overset{+}{H}N_6$ nitrogen atom on C_5 (diazotization proceeds in mineral acid solution).

Evidently in the case of compound IIb the π electron cloud in the phenyl is, under the action of the strongly electron-accepting tetrazole group drawn towards the quinazoline ring, thus to some extent compensating for the δ^+ charge at C_5. Because of that there is no hydration at $N_6{=}C_5$. It is also impossible to overlook the fact that the bulky phenyl group can give rise to steric hindrance to nucleophidic attack at the $N_6{=}C_5$ bond. In accord with this the benzoyl derivative VIb formed on benzoylating the amine is, unlike the acetyl derivative VIa, incapable of isomerizing to the hydrate quinazoline ring even on heating.

EXPERIMENTAL**

Compounds IIa, b, and V were prepared as described in [2].

IR spectra of compound IIa, cm^{-1}: 3095 very strong, 3030 very strong, 2940 very strong, (CH benzene ring); 1937 strong, 1563 weak, 1526 weak, 1477 strong. (C=C, C=N); 1240 medium, (CH_3); 1286 medium, 1257 weak, 1217 weak, 1170 weak, 1135 weak, 1106 weak, 1086 strong, 1021 medium (tetrazole); 976 strong, 856 strong, 777 strong, (tetrazole); 717 medium, 689 weak.

IR spectra of compound V, cm^{-1}: 3585 strong (OH); 3316 medium, 3195 weak. (NH); 3060 medium, (CH benzene ring); 2995 weak, 2890 weak. 2850 weak, 2790 weak. (CH_3); 1682 medium, 1667 medium, (NH); 1623 strong, 1597 strong, 1552 strong. (C=N); 1491 weak, (CH_3); 1417 weak, 1317 very strong, 1270 medium, 1247 weak, 1155 medium, 1116 weak, 1095 weak, 1077 medium, 1066 strong, 1059 medium, (tetrazole); 992 strong, 837 weak, 756 very strong (tetrazole); 697 weak.

Hydration of 5-methyltetrazolo[1, 5-c]quinazoline (IIa). 0.1 g (0.0005 mole) Ia was suspended in 5 ml 2 N HCl, and left at room temperature for 7 days. The precipitate of hydrated product was filtered off and washed with water. Yield 0.1 g (90%). Crystallization from aqueous EtOH gave pale yellow crystals of compound V, mp 195°–196° (decomp.) undepressed mixed mp with the product obtained as described in [2]. The IR spectra of the two compounds were identical.

Hydrolysis of 5, 6-dihydro-5-methyl-5-hydroxytetrazolo[1, 5-c] quinazoline (V). 0.7 g (0.0034 mole) recrystallized hydroxy product V, mp 196°–197° was refluxed with 35 ml 2 N HCl for 15–20 min. After cooling the solution was carefully made alkaline with saturated Na_2CO_3 solution, when a colorless crystalline precipitate of tetrazole VII formed. Yield 0.45 g (82%), long needles (ex water). After drying at 60° over P_2O_5 it had mp 140°–144°. Found: C 52.39; H 4.54; N 43.54%, calculated for $C_7H_7N_5$: C 52.16; H 4.38; N 43.46%; The product crystallized from water as the monohydrate. Found: H_2O 9.64%, calculated for $C_7H_7N_5 \cdot H_2O$: H_2O 10.00%. Hydrochloride mp 233°–235°.

IR spectrum of compound VII, cm^{-1}: 3410 strong, (NH_2); 3320 strong (NH); 3210 weak, 3130 weak; 3070 weak, 3040 weak, 2990 weak, 2895 very weak 2860 weak. 2765 weak, 2640 weak (NH tetrazole); 1615 strong, 1493 strong, (C=N); 1466 medium, 1410 weak, 1327 medium, 1300 medium, 1254 medium, 1154 medium, 1105 weak, 1086 weak, 1063 weak, 1038 weak. (tetrazole); 993 strong, 958 weak, 856 medium, 835 medium, 776 weak, 758 strong. (tetrazole); 703 medium, 668 medium.

Deamination of VII. 0.32 g (0.002 mole) VII was dissolved in 0.7 ml conc. H_2SO_4. Aftering cooling to 0°, 2 ml EtOH was added, when the amine sulfate came down as minute crystals. The mixture was stirred, and a concentrated aqueous solution of 0.3 g $NaNO_2$ added, then the whole refluxed for 1 hr until evolution of nitrogen ceased. The solution was evaporated to dryness, and the residue crystalized from aqueous EtOH, yield 0.1 g (50%) VIII, long colorless needles, mp 209°–210°.

Acetylation of VII. 2 ml Ac_2O was added to 0.32 g (0.002 mole) VII, the solid gradually dissolved, and after some minutes the acetylated product came down. The solid was filtered off, washed with water, yield 0.3 g (75%), mp after recrystallizing from aqueous EtOH 196°–197° (decomp.), underpressed mixed mp with an authentic specimen [1].

Benzoylation of VII. 0.32 g (0.002 mole) VII was suspended in boiling benzene (about 10 ml). A solution of 0.3 ml benzoyl chloride was added to this suspension, and the whole refluxed for 1 hr. After cooling the precipitate of 5-(2'-benzoylamino) tetrazole (VIb) was filtered off and washed with water, yield 0.4 g (80%). After recrystallizing from aqueous EtOH it had mp 225°–226° (decomp.) Found: 63.33; H 4.19%, calculated for $C_{14}H_{11}N_5O$: C 63.39; H 4.15%.

IR spectrum: 3130 medium, 3065 strong, (NH); 2940 medium, 2790 medium, 2640 medium, 1665 medium, 1626 strong, (NHCO); 1600 medium, (phenyl); 1580 weak, 1548 strong, (C=N); 1446 strong, 1327 strong, 1270 medium, 1166 medium, 1154 medium, 1080 medium, 1060 strong, 1038 weak, (tetrazole); 907 medium, 890 weak, 791 weak, 767 medium, 705 strong, (phenyl).

The IR spectra were determined with a UR-10 instrument, using a vaseline mull (NaCl prism) or perfluorohydrocarbon one (LiF prisms). *

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*When R = β-pyridyl or α-furyl, the hydrazine behaves similarly.

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*The spectra were determined by N. I. Mudretsova and K. V. Aglitska.

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