STUDIES ON BENZODIAZINES

XV*. SYNTHESIS AND PROPERTIES OF SOME DERIVATIVES OF QUINAZOLINE AND OF TETRAZOLO[1,5-c]QUINAZOLINE WITH SUBSTITUENTS IN THE BENZENE NUCLEUS

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Derivatives of 5-phenyltetrazolo[1,5-c]quinazoline with substituents in the benzene nucleus – 7-methyl-5-phenyltetrazolo[1,5-c]-quinazoline and 9-methyl-5-phenyltetrazolo-[1,5-c]quinazoline – have been obtained for the first time. The oxidation of the 9-methyl derivative gave the corresponding carboxylic acid which, in contrast to the 5-phenyltetrazolo[1,5-c]quinazoline unsubstituted in the benzene nucleus, is covalently hydrated.

It has been reported previously [2, 3] that the covalent hydration of the pyrimidine ring at the $N_6{=}N_5$ bond that is characteristic for the tetrazolo[1,5-c]quinazolines does not come about if a phenyl residue is present in position 5 of the tetrazoloquinazoline. The hypothesis has been put forward that the π-electron cloud of the phenyl radical is repelled in the direction of the quinazoline ring under the influence of the strongly electron-accepting tetrazole grouping and compensates to some extent the δ^+ charge on the C-5 carbon atom, so that the nucleophilic attack of this position is hindered. It could be assumed that the magnitude of the δ^+ charge would also be affected by substituents in the benzene nucleus. In view of this, it appeared of interest to study the reactivity and covalent hydration of tetrazoloquinazolines with substituents in the benzene nucleus.

We set ourselves the task of first obtaining 5-phenyltetrazolo[1,5-c]quinazolines with a methyl group in the benzene nucleus in order then to oxidize the methyl group and obtain carboxy derivatives.

So far as we know, tetrazoloquinazolines with substituents in the benzene ring have not been reported in the literature. The starting materials for them – quinazolin-4-ones substituted in the benzene nucleus – are difficult to obtain. Only a few representatives of them are known [4, 5, 6].

In the synthesis of the planned compounds we used the method recently proposed by Blatter et al. [7, 8] for obtaining 2-phenylquinazoline-4-thiones from imidoyl isothiocyanates (II), obtained, in their turn, from the imidoyl chlorides (I) (see reaction scheme).

From IIa and b we obtained the 6- and 8-methyl derivatives of 2-phenylquinazoline-4-thione (IIIa and b). Under the action of hydrogen peroxide in an alkaline medium, they gave the corresponding quinazolinones (IVa and b). The subsequent reaction of these quinazolinones with phosphorus oxychloride in the presence of dimethylaniline gave the chlorides Va and b. To evaluate the influence of the methyl groups and the reactivity of the chlorine atom, polarograms of Va and b were recorded in dimethylformamide on a support of tetraethylammonium iodide. The polarograms have two waves (Table 1). The introduction of a methyl

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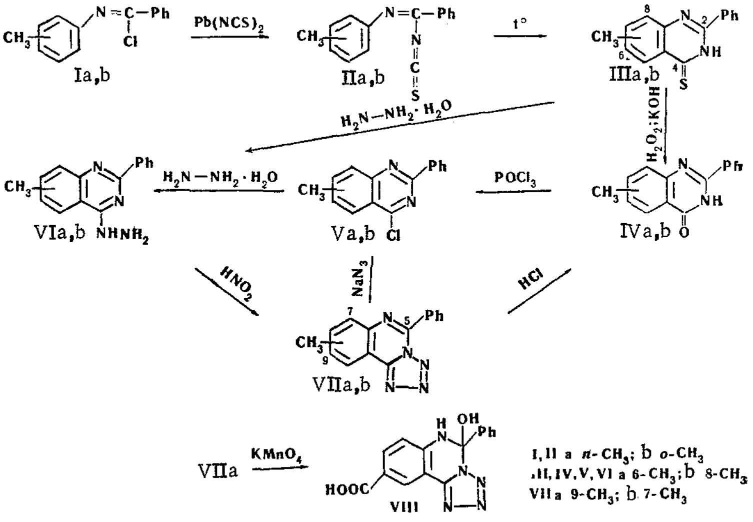
TABLE 1. Polarographic Half-Wave Potentials ($-E_{1/2}$) [support 0.1-M $(C_2H_5)NI$, concentration of depolarizer $5 \cdot 10^{-4}$ M, $-E_{1/2}$ relative to the bottom mercury electrode]

Compound	$E_{1/2}$, V	
	wave I	wave II
4-Chloro-2-phenylquinazoline	−0,93	−1,26
4-Chloro-6-methyl-2-phenylquinazoline	−1,01	−1,37
4-Chloro-8-methyl-2-phenylquinazoline	−1,02	−1,38

group leads to a shift of $E_{1/2}$ in the direction of negative potentials, which shows an electron-donating influence of the methyl groups and the capacity of the benzene nucleus for transmitting the influence of substituents to the pyrimidine part of the molecule.



Characteristic for Va and b (and also for the other 4-chloroquinazolines [2]) is the ready nucleophilic exchange of the chlorine: they react with hydrazine hydrate with gentle heating giving the hydrazines VIa and b (it is interesting that the latter can also be obtained by the reaction of IIIa and b with hydrazine hydrate). On reaction with nitrous acid, these compounds give the tetrazoloquinazolines VIIa and b. The identical compounds were obtained from Va and b by boiling them with sodium azide in ethanolic solution.

When the tetrazoloquinazolines VIIa and b were boiled in dilute hydrochloric acid [2], no covalently hydrated products were obtained and compounds Va and b, respectively, were obtained, as has been found in the case of the 5-phenyltetrazolo[1,5-c]quinazoline unsubstituted in the benzene nucleus [2]. The oxidation of VIIa with potassium permanganate in water or in acetic acid gave a product corresponding to the empirical formula $C_{15}H_9N_5O_2 \cdot H_2O$ and containing a carboxy group (it was impossible to obtain the analogous product from VIIb under the same conditions). In an attempt to split out water by heating the substance above its melting point, it decomposed. The structure of the product obtained may, in view of the results of preceding investigations [3], be illustrated by formula VIII with a covalently bound molecule of water.

Thus, it has been shown that even when a phenyl residue is present in position 5 of tetrazolo[1,5-c]-quinazoline, covalent hydration becomes possible if there is an electron-accepting group in the benzene nucleus. The latter obviously compensates the electron-donating influence of the phenyl radical and raises the δ^+ charge on the C-5 carbon atom facilitating nucleophilic attack in this position.

EXPERIMENTAL

N-Tolylbenzimidoyl Isothiocyanates (IIa, b). To a solution of 0.1 mole of N-tolylbenzimidoyl chloride (Ia, b) [9] in 100 ml of dry benzene was added 32 g of lead thiocyanate, and the mixture was boiled in the water bath with stirring for 2 h. Then it was filtered and the benzene was distilled off from the filtrate.

TABLE 2. Quinazolines and Tetrazolo[1,5-c]quinazolines

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IIIa	234—235	$C_{15}H_{12}N_2S$	71,93	4,85	11,45	71,40	4,79	11,10	39
IIIб	241—243	$C_{15}H_{12}N_2S$	71,52	4,78	11,39	71,40	4,79	11,10	35
IVa	256—258	$C_{15}H_{12}N_2O$	76,74	5,20	11,74	76,25	5,12	11,86	90
IVб	252—254	$C_{15}H_{12}N_2O$	76,43	5,16	12,44	76,25	5,12	11,86	90
VIa	208—210	$C_{15}H_{14}N_4$	72,37	5,68	22,83	71,98	5,64	22,38	75
VIб	215—217	$C_{15}H_{14}N_4$	72,68	5,79	22,09	71,98	5,64	22,38	65
VIIa	175—176	$C_{15}H_{11}N_5$	69,18	4,54	27,64	68,95	4,24	26,81	82
VIIб	168—169	$C_{15}H_{11}N_5$	69,23	4,21	27,56	68,95	4,24	26,81	87
VIII	310—313	$C_{15}H_{11}N_5O_3$	58,16	3,84	22,47	58,25	3,58	22,65	12

N-(p-Tolyl)benzimidoyl isothiocyanate forms yellow crystals with mp 75-80°C, while N-(o-tolyl)benzimidoyl isothiocyanate gives a red oil. Yield 85-90%. The products obtained were used for the preparation of IIIa and b without further purification.

6(8)-Methyl-2-phenylquinazoline-4-thiones (IIIa, b). A solution of 0.1 mole of IIa or b in 60 ml of m-xylene was boiled for 2 h. On cooling, a precipitate deposited, and it was filtered off and crystallized from ethanol or benzene. Yellow crystals soluble in alkalis, sparingly soluble in ethanol and benzene (Table 2).

6(8)-Methyl-2-phenylquinazolin-4-ones (IVa, b). A solution of 0.02 mole of IIIa or b in 10% KOH solution (2- to 3-fold excess) was heated to 80°C and, with stirring, a 30% solution of hydrogen peroxide was gradually added. The initially faintly yellow reaction mixture became more strongly colored and then the color disappeared. After this, it was cooled and the quinazolinone was precipitated with acetic acid. Colorless crystals (from isopropanol) soluble in alkalis, sparingly soluble in the usual organic solvents (Table 2).

4-Chloro-6(8)-methyl-2-phenylquinazolines (Va, b). A mixture of 0.02 mole of IVa or b, 6 ml of $POCl_3$, and 9 ml of dimethylaniline was boiled in 100 ml of absolute benzene for 2 h. The reaction mixture was cooled, diluted with 100 ml of benzene, and washed with an equal volume of water, then with 10% sodium carbonate solution, and then with water again. The benzene solution was dried with calcium chloride, passed through a column of alumina (layer height 3-4 cm) to free it from colored impurities, and the benzene was distilled off. Colorless or faintly yellowish crystals (from n-heptane): mp: Va 111-112°C; Vb 99-101°C. Yield 95%. Found, %: for Va Cl 14.37; for Vb Cl 14.09. Calculated for $C_{15}H_{11}N_2Cl$, %: Cl 13.92.

4-Hydrazino-6(8)-methyl-2-phenylquinazolines (VIa, b). a) A mixture of 0.02 mole of IIIa or b, 150 ml of ethanol, and a 15-fold excess of hydrazine hydrate was boiled until the evolution of hydrogen sulfide ceased (6-8 h). On cooling, a precipitate of the hydrazine deposited. Colorless or faintly yellowish crystals (from ethanol) soluble in dilute hydrochloric acid (Table 2).

b) A mixture of 0.04 mole of Va or b, 200 ml of benzene, and a 5-fold excess of hydrazine hydrate was boiled for 30 min. The products obtained, after recrystallization from ethanol, were identical with those obtained from IIIa and b (mixed mp's).

9(7)-Methyl-5-phenyltetrazolo[1,5-c]quinazolines (VIIa, b). a) At room temperature, a solution of 0.01 mole of sodium nitrite was added dropwise to a solution of 0.01 mole of VIa or b in 2 N hydrochloric acid. After 30 min, the precipitate that had deposited was filtered off. The IR spectra of the compounds in the crystalline state and in chloroform solution showed no characteristic bands corresponding to the asymmetric stretching vibrations of the azide group (2050-2200 cm^{-1}) [10], while they contained bands which can be ascribed with confidence to the vibrations of tetrazole rings: VIIa: 1098, 1108; VIIb: 1050, 1073, 1090 cm^{-1} [11] (Table 2).

b) A solution of 0.5 g of sodium azide in 2 ml of water was added to a solution of 0.005 mole of Va or b in 30 ml of boiling ethanol and the mixture was boiled for 1 h. The precipitate of the tetrazole that deposited on cooling was crystallized from isopropanol. The reaction products were identical with those obtained from VIa and b, respectively (mixed mp's).

Oxidation of 9-Methyl-5-phenyltetrazolo[1,5-c]quinazoline. a) Over 1 h, a solution of 1.3 g of potassium permanganate in 100 ml of water was added to 1 g of VIIa in 0.5 liters of boiling water. The mixture was boiled for 5 h, a small amount of ethanol was added, and the manganese dioxide was filtered off. When the filtrate was acidified with acetic acid, the product precipitated. It was filtered off and dissolved in ammonia, the solution was boiled with carbon and filtered, and the product was reprecipitated from the filtrate with acetic acid. Colorless crystals sparingly soluble in the majority of organic solvents. Its elementary analysis (Table 2) corresponds to a compound with the structure of 5-hydroxy-5-phenyl-5,6-dihydrotetrazolo[1,5-c]quinazoline-9-carboxylic acid (VIII). Its IR spectrum had bands at 1060, 1075, and 1099 cm^{-1}.

b) A solution of 1 g of compound VIIa in 50 ml of glacial acetic acid, was immersed in a boiling water bath, and then 15 ml of water and, over 30 min, 9 g of potassium permanganate were added. The mixture was heated in the water bath for another 2 h. Then the reaction mixture was poured into water, hydrogen peroxide was added until it was decolorized, and the residual solid matter was filtered off. The addition of 10-15 ml of conc. HCl to the filtrate precipitated the product. The IR spectrum in the 700-1700 cm^{-1} region of the compound obtained coincided with that of the product obtained by oxidation in an aqueous medium.

The IR spectra were recorded on an IKS-14 instrument for mulls in paraffin oil (NaCl prism) and in perfluorohydrocarbons (LiF prism).

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