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RESEARCHES ON BENZODIAZINES

VI. Synthesis of 2-R-4-Hydrazinoquinazolines, 5-R- [3,4-c]-s-Triazolo- and 5-R [1,5-c] Tetrazoloquinazolines*

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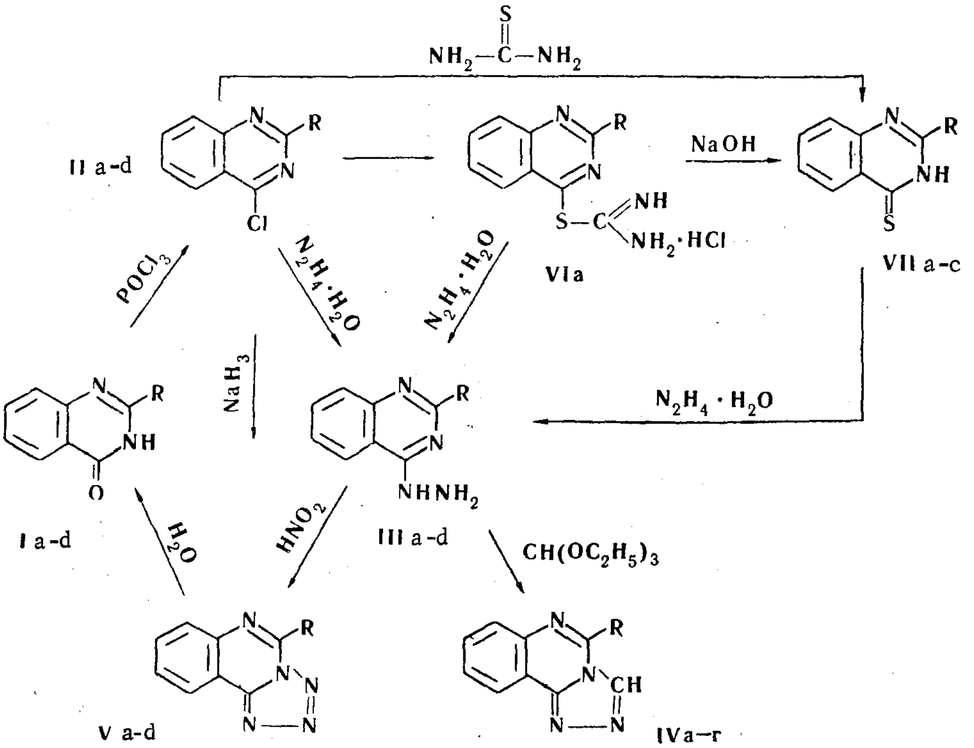
2-R-Quinazolones have been synthesized (R = Me, Ph, γ-pyridyl, α-furyl), and subsequently the 4-chlorides and the corresponding 2-R-4-hydrazinoquinazolines were obtained. By the reaction of orthoformic ester and nitric acid on the hydrazines, 5-R- [3, 4-c]-s-triazoloquinazolines and 5-R- [1, 5-c] tetrazoloquinazolines were prepared, respectively. The compounds in which R = Me differ considerably from compounds with other groups, both in color and stability of intermediate reaction products. 5-R- [1, 5-c] tetrazoloquinazolines are hydrolyzed by HCl into quinazol-4-ones.

We have previously prepared quinazoline compounds with tetrazoline and triazoline rings fused at the a side of the pyrimidine part of the quinazoline ring [1]. In the present paper syntheses are given for triazolo-c- and tetrazolo-c-quinazolines with methyl, phenyl, γ-pyridyl, or α-furyl (IV, V) at position 2. The syntheses were carried out as follows.

The starting compounds, the quinazolones Ib, c, d were prepared from thioamides of acids and anthranilic acid by the method of [2]. Compound Ic has not been described in the literature. 2-Methylquinazol-4-one (Ia) is prepared from acetylanthranil by the Nimentovskii reaction [3]. Chlorides IIa, b, d were prepared by the method of [4], described for IIa, namely reacting $POCl_3$ in benzene with the corresponding quinazolones in the presence of dimethylaniline. Using this method yields could be improved and purer chlorides obtained than when using the method described for IIb and d [2]. The chloride IIc, hitherto undescribed in the literature, was prepared by reacting 2-(γ-pyridyl) quinazol-4-one with $POCl_3$-PCl_5 mixture.

Reaction of benzene solutions of the chlorides with hydrazine hydrate gives the corresponding hydrazines III (Table 1). There is a characteristic color reaction for the hydrazines: if a solution of an alkali is added to an ethanol



a $R=CH_3$; b $R=C_6H_5$; c R = γ-pyridyl; d R = α-furyl

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* For Part V see [1].

solution of the hydrazine, the color rapidly changes from yellow to dark cherry. Possibly the color reaction is due to formation of hydrazine oxidation products, as no reaction is observed if it is carried out in a CO_2 atmosphere.

When carrying out the syntheses described here, observations were made which showed that the nature of the group R considerably influences the properties of the substance, especially the reactivity of the group at position 4. Thus the chloride IIa, with R = Me, is bright yellow, and has an intense smell of acetamide, while the other chlorides (IIb, c, d) are colorless and odorless. As was mentioned above, in benzene all the chlorides react with hydrazine hydrate, to give mono-substituted hydrazines. In ethanol the main reaction product from IIa and hydrazine hydrate is 4, 4'-N, N'-bis-quinazolylhydrazine, while under the same conditions compounds IIb, c, d give only mono-substituted hydrazines. Reaction of chlorides IIa, b, c with thiourea gave the corresponding quinazolin-4-thiones (VII, Table 1). Reaction of 2-methyl-4-chloroquinazoline (IIa) with thiourea gives, firstly, the isothiuronium chloride VIa, which has a brick-red color. It was unstable, and merely by the action of alkali was converted to thione.* On reaction with hydrazine hydrate it gives the mono-substituted hydrazine VIa. With the other chlorides (IIb, c) it is not possible to separate the isothiuronium chlorides, as during the condensation process they are already converted to the corresponding quinazoline-4-thiones. On heating with hydrazine hydrate all the thiones give the hydrazines III.

Table 1

2-R-4-Hydrazinoquinazolines and 2-R-Quinazoline-4-thiones

Compound Number	Mp, °C (crystallization solvent)	Formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IIIa	180—182 ($CHCl_3$)	$C_9H_{10}N_4$	62.36	5.65	31.76	62.05	5.79	32.17	80
IIIb	214—215 ($CHCl_3$)	$C_{14}H_{12}N_4$	71.37	5.31	23.88	71.16	5.12	23.72	81
IIIc	249—250 (dioxane or EtOH)	$C_{13}H_{11}N_5$	65.48	4.83	29.69	65.81	4.67	29.52	76
IIId	200—202 ($CHCl_3$ or EtOH)	$C_{12}H_{10}N_4O$	63.38	4.39	24.98	63.70	4.46	24.77	97
VIIb	216—218 (EtOH)	$C_{14}H_{10}N_2S$*	—	—	11.86	—	—	11.76	63
VIIc	219—220 (dioxane)	$C_{13}H_9N_3S$**	65.44	4.08	17.24	65.26	3.79	15.57	85

* Found: S 13.04%. Calculated: S 13.43%.

**Found: S 13.21%. Calculated: S 13.38%.

2-Methyl-4-hydrazinoquinazoline (IIIa) behaves differently towards nitrous acid than hydrazines with phenyl, γ-pyridyl and α-furyl (IIIb, c, d). While these hydrazines give tetrazoles (V, Table 2), a hydrazine with a methyl group (IIIa) under the same conditions gives a product of composition $C_9H_9N_5O$ (VIIIa) which, only when it is heated above the melting point (198°), loses a molecule of water, to give the tetrazole $C_9H_7N_5$, mp 163-164° (Va). Initially it was assumed that the compound with melting point 198° was the tetrazole, crystallizing with a molecule of water. However, the tetrazole prepared by reacting the chloride with sodium azide is identical with the tetrazole melting point 163-164°, and on crystallizing from water-ethanol, there is no tendency to form a crystal hydrate. Determination of the structure of the product formed is the subject of a separate research.

All the hydrazines III react with orthoformic ester to give the expected triazoles IV (Table 2), colorless compounds which crystallize well.

It is of interest to note that the triazoles, and also all the tetrazoles, fluoresce brightly in the near ultraviolet. The tetrazoles, whether in the solid crystalline state, or in benzene solution, give IR spectra with intense absorption bands in the 1100 cm^{-1} region, ascribed to the tetrazole group [6]. The spectra do not show bands characteristic of asymmetric vibrations of the azide group (2100-2150 cm^{-1}) [7]. Thus with the compounds prepared the tetrazole rings are not

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* The thione VIIa is described in the literature, though it was obtained by another route [5].

unlocked on solution, in the way that, for example, they are with 2-cycloalkylamino [1, 5-c] tetrazoloquinazolines [8]. At the same time it was shown that the tetrazole compounds V (b, c, d) are converted to 2-R-quinazolones (I) by heating with hydrochloric acid. Hence it can be concluded that the bond between nitrogen atoms 1 and 2 in the adjacent tetrazole ring is strongly polarized, and is broken by a hydrolytic agent. The resultant azide compound is further hydrolyzed to quinazoline [9].

Table 2

5-R- [3, 4-c]-s-Triazoloquinazolines and 5-R- [1, 5-c] Tetrazoloquinazolines

Compound number	Mp, °C	Formula	Found, %			Calculated, %			Color of fluorescence	Yield, %
			C	H	N	C	H	N		
IV a	>280	$C_{10}H_8N_4$	—	—	30.30	—	—	30.42	Yellow	50
IV b	204—206	$C_{15}H_{10}N_4$	72.93	4.32	22.64	73.15	4.09	22.75	Bright violet	97
IV c	260—262	$C_{14}H_9N_5$	68.03	3.94	28.88	68.00	3.67	28.33	Bright violet	98
IV d	206—207	$C_{13}H_8N_4O$	66.25	3.43	24.04	66.09	3.41	23.72	Violet	80
V a	163—165	$C_9H_7N_5$	—	—	37.81	—	—	37.82	Bright yellow	60
V b	162—163	$C_{14}H_9N_5$	68.42	3.89	28.45	68.00	3.67	28.33	Violet	70
V c	194—196	$C_{13}H_8N_6$	62.81	3.10	33.87	62.89	3.25	33.86	White	73
V d	200—202	$C_{12}H_7N_5O$	61.14	3.02	29.55	60.75	2.97	29.53	Violet	80

Experimental

2-(γ-Pyridyl) quinazol-4-one (Id). 12.5 g thioisonicotinamide (mp 209-210° [10]) and 12.5 g anthranilic acid were heated together in a flask immersed in Wood metal at 150-160°. After 1 hr the thickening mass was cooled, and crystallized from dioxane. Yield 7.5 g (37%). The quinazolone melts above 250°; it is insoluble in cold benzene, EtOH, and $CHCl_3$. Found: C 69.75; H 4.21; N 18.95%. Calculated for $C_{13}H_9N_3O$: C 69.94; H 4.06; N 18.83%.

2-(γ-Pyridyl)-4-chloroquinazoline (IId). 7.5 g 2-(γ-pyridyl) quinazol-4-one, 60 ml $POCl_3$, and 10 g PCl_5 were refluxed together for 4 hr. Excess $POCl_3$ was distilled off, the residual suspension poured on to ice, and neutralized with ammonia. The precipitate was filtered off, washed with water, and dried. It was extracted with boiling benzene, the solution filtered to remove inorganic impurities, and the solvent distilled off. Yield of 2-(γ-pyridyl)-4-chloroquinazoline, 6.5 g (80%), slightly greenish plates, mp 164-166°, from n-heptane. The compound is soluble in cold benzene, and ether, less soluble in EtOH. Found: Cl 14.40%. Calculated for $C_{13}H_8ClN_3$: Cl 14.68%.

2-R-4-Chloroquinazolines (IIa, b, c). Prepared by method [4]. For R = Me, mp 86-88° (ex n-heptane); literature 81-83°; for R = Ph, mp 124-126° (ex n-heptane); lit. 122-124°; for R = α-furyl, mp 122-124° (from n-heptane). Found: Cl 15.66%. Calculated for $C_{12}H_7ClN_2O$: Cl 15.40%.

2-R-4-Hydrazinoquinazolines (IIIa, b, c, d). 0.02 mole 2-R-4-chloroquinazoline was dissolved in benzene, the solution filtered, active charcoal being added, and a 5-fold excess of hydrazine hydrate in benzene added gradually, the emulsion being stirred and cooled. A precipitate of hydrazine began to form after 20-30 min. After 2 hr it was filtered off, washed with water, and crystallized. The hydrazines formed colorless or pale cream crystals (Table 1).

They dissolved in 2 N HCl, and evaporation of the solutions gave the hydrochlorides, soluble in water. The hydrochlorides of the hydrazines were pale yellow substances, which crystallized from EtOH.

N, N'-bis (4, 4'-quinazolylhydrazine). 1.8 g 2-methyl-4-chloroquinazoline was dissolved in EtOH, and the solution added to an ethanol solution of 2 ml hydrazine hydrate, when heat was evolved, and a yellow precipitate formed, mass 1.5 g (50%), mp above 280°. Lemon yellow needles from isopropanol. Found: N 26.34%. Calculated for $C_{18}H_{16}N_6$: N 26.57%.

5-R- [3, 4-c]-s-Triazoloquinazolines (IVa, b, c, d). 0.002 mole 2-R-4-hydrazinoquinazoline was refluxed with a 5-fold excess of orthoformic ester. After 1 hr the mixture was cooled, the precipitate filtered off, and recrystallized from EtOH. The triazoles were colorless compounds readily soluble in cold $CHCl_3$, less soluble in benzene (Table 2).

5-R- [1, 5-c] Tetrazoloquinazolines (Va, b, c, d). a) 0.002 mole $NaNO_2$ was added dropwise to 0.002 mole 2-methyl-4-hydrazinoquinazoline dissolved in 2 N HCl and cooled to 3-5°. An hour later the precipitate formed was filtered off, and recrystallized from EtOH, to give pale yellow prisms mp 197-198°. The compound was sparingly soluble in cold benzene, $CHCl_3$, dioxane, but soluble in 2 N alkali. Found: N 34.19%. Calculated for $C_9H_9N_5O$: N 34.47%. 0.2 g of the intermediate compound was heated above its melting point until evolution of water ceased. After cooling, the precipitate was recrystallized from EtOH, yield 0.1 g (60%), pale yellow needles of tetrazole Va, mp 162-163°

Undepressed mixed mp with the tetrazole prepared from the chloride and sodium azide. The tetrazoles Vb, c, d (Table 2) were prepared similarly to Va, but with them the tetrazole was formed straight away, in the form of colorless crystals, which crystallized from EtOH. They were readily soluble in $CHCl_3$, less soluble in benzene.

b) 2 g 2-R-4-chloroquinazoline was dissolved in 20 ml EtOH, 1.5 g sodium azide added, along with 2 ml water, and the solution boiled until a precipitate of tetrazole formed.

The IR spectra of the tetrazoles Va, b, c, d were measured with an IKS-14 instrument, with the crystalline compound made into a paste with perfluorohydrocarbons for the 3-5 μ region, a NaCl prism being used, while a paste with vaseline and a LiF prism were used for the 5-14μ one. Further, in the 3-5 μ region, spectra were observed in benzene. Below are data (cm^{-1}) which can be assigned to vibrations of tetrazole rings: Va 1108, 1086; Vb 1108, 1076; Vc 1107, 1092; Vd 1108, 1079. According to [6], tetrazole is characterized by vibrations in the 1110-1000 cm^{-1} region.

2-R-Thioquinazoline-4-thiones (VIIa, b, c). Preparation of the thione VIIa. 0.01 mole 2-methyl-4-chloroquinazoline was added to a solution of 0.01 mole thiourea in 50 ml EtOH, heat was evolved and a brownish red precipitate of isothiuronium chloride was formed. The mixture was boiled for 1 hr, and filtered after cooling. Since the thiuronium chloride is hydrolyzed to thione when water is added, or on heating with EtOH, it was impossible to recrystallize it. Found: Cl 14.53%. Calculayed for $C_{10}H_{10}N_4S \cdot HCl$: Cl 13.97%. Solution of the isothiuronium salt in alkali followed by acidification with AcOH gave a yellow precipitate of thione VIIa, from EtOH mp 217-218° (literature 218-219°) [5].

Preparation of thiones VIIb, c. 0.01 mole 2-R-4-chloroquinazoline and 0.01 mole thiourea in 50 ml EtOH were refluxed for 1 hr, the EtOH distilled off, the residue dissolved in alkali, the solution filtered with addition of active charcoal, then acidified with AcOH. The precipitate of thione was filtered off and crystallized. The quinazolinethiones were pale yellow substances, readily soluble in alkali and $CHCl_3$, less soluble in EtOH (Table 1).

2-R-4-Hydrazinoquinazolines from 2-R-quinazoline-4-thiones. 0.005 mole 2-R-quinazoline-4-thione (VIIb, c), or 0.005 mole isothiuronium chloride (VIIa) was refluxed in EtOH with a 15-fold excess hydrazine hydrate till evolution of H_2S ceased (8-10 hr). The EtOH was distilled off, and the precipitate of hydrazine filtered off and recrystallized.

Hydrolysis of 5-R-[1,5-c] tetrazoloquinazolines. 0.1 g 5-R-[1,5-c]-tetrazoloquinazolines, where R = Ph, γ-pyridyl, α-furyl, was refluxed for 3 hr with HCl (1:1). After cooling the solution was neutralized with Na_2CO_3, the precipitate filtered off, and recrystallized from EtOH. It was 2-R-quinazol-4-one, yield 70-80%.

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