ADDITION OF NUCLEOPHILES TO 3-METHYLQUINAZOLINIUM IODIDE

T. L. Pilicheva, O. N. Chupakhin, and
I. Ya. Postovskii

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3-Methylquinazolinium iodide adds alkyl- and arylamines, pyrroles, and indoles to give the corresponding 4-substituted 3,4-dihydroquinazolines. A hydroxyl group in the 3-methylquinazolinium pseudobase is replaced by residues of these nucleophiles.

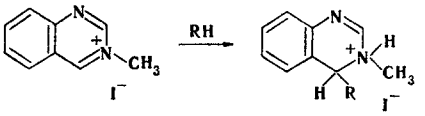
Reactions of quinazolines with uncharged nucleophiles have not been described. It is known that quinazolines preferably exist as stable 3,4-dihydro compounds (for example, covalent hydrates [1]), and it therefore might have been expected that quinazoline methiodide on reaction with nucleophiles would give stable products of addition at the 4 position.

A mixture of 1-methyl- and 3-methylquinazolinium iodide in a ratio of 1:5 is formed in the quaternization of quinazoline [2]. Inasmuch as separation of the isomers by cyrstallization is difficult, a mixture of the isomers was used in the reaction described below.

A crystalline precipitate of the addition product was formed when the mixture of quinazoline methiodides was refluxed in alcohol with dialkylanilines. The base of the addition product was isolated from the filtrate when it was made alkaline to pH 8, and at pH 10 an oil, which was found to be the pseudobase of the 1-methyl isomer, was liberated. The amount of the oil corresponded to the amount of 1-methylquinazolinium iodide formed during quaternization. Thus of the two isomers, only 3-methylquinazolinium iodide (I) proved to be reactive.

Iodide I is also capable of adding arylamines that have a free amino group (aniline and 1-naphthylamine), and this reaction gives low yields of N-addition products (XIII and XIV). A similar addition product (XX) is formed in the reaction of I with morpholine. In the latter case, morpholine hydriodide, which is formed as a result of an exchange reaction of hydriodide XX with the more basic morpholine, is also isolated from the reaction mixture.

Like arylamines, π-surplus heterocycles — indole, 1- and 2-methylindoles, pyrrole, and 1-methylpyrrole (Table 1) — add to 3-methylquinazolinium iodide.



I II–VIII

II R = 4-dimethylaminophenyl; III R = 4-diethylaminophenyl; IV R = 3-indolyl; V R = 2-methyl-3-indolyl; VI R = 1-methyl-3-indolyl; VII R = 2-pyrrolyl; VIII R = methyl-2-pyrrolyl

The 4-substituted 3-methyl-3,4-dihydroquinazolinium iodides obtained can be considered to be complexes of the Meisenheimer type in the case of nucleophilic substitution of hydrogen in the azinium cations. Meisenheimer complexes are usually difficult to isolate [3] or record spectrally [4]. On the other hand, the compounds that we synthesized are interesting with respect to their anomalously high (for dihydro compounds) stability. They do not undergo

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TABLE 1. 3-Methyl-4-substituted-3,4-dihydroquinazolinium Iodides (II-VIII) and 3-Methyl-4-substituted-3,4-dihydroquinazolines (IX-XI, XIII-XX)

Compound	R	mp, °C	Solvent	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
II	4-Dimethylaminophenyl	130—131	Ethanol—benzene (1 : 20)	$C_{17}H_{19}N_3 \cdot HI$	52,4	5,0	10,3	51,9	5,1	10,7	58
III	4-Diethylaminophenyl	140—142	Ethanol—benzene (1 : 20)	$C_{19}H_{23}N_3 \cdot HI$	54,4	5,9	10,1	54,2	5,7	10,0	50
IV	3-Indolyl	315	Water	$C_{17}H_{15}N_3 \cdot HI$	52,7	4,2	11,1	52,5	4,1	10,8	75
V	2-Methyl-3-indolyl	237—238	DMFA	$C_{18}H_{17}N_3 \cdot HI$	53,8	4,7	10,5	53,5	4,8	10,4	96
VI	1-Methyl-3-indolyl	234—236	Ethanol—xylene (1 : 20)	$C_{18}H_{17}N_3 \cdot HI$	53,8	4,5	10,0	53,5	4,8	10,4	89
VII	2-Pyrrolyl	226—228	Butanol	$C_{13}H_{13}N_3 \cdot HI$	46,1	4,1	12,3	46,0	4,2	12,4	58
VIII	1-Methyl-2-pyrrolyl	220—222	Butanol	$C_{14}H_{15}N_3 \cdot HI$	47,4	4,6	11,6	47,6	4,6	11,9	74
IX	3-Indolyl	246—248	Aqueous ethanol	$C_{17}H_{15}N_3$	78,5	5,7	16,1	78,1	5,8	16,1	83
X	4-Dimethylaminophenyl	167—168	Aqueous ethanol	$C_{17}H_{19}N_3$	77,1	7,3	15,8	77,0	7,2	15,5	95
XI	2-Pyrrolyl	200—202	Aqueous ethanol	$C_{13}H_{13}N_3$	73,7	6,3	19,8	73,9	6,2	19,9	98
XIII	Phenylamino	159—160	Anhydrous ethanol	$C_{15}H_{15}N_3$	75,4	6,7	—	75,9	6,4	—	55
XIV	1-Naphthylamino	196—197	Anhydrous benzene	$C_{19}H_{17}N_3$	79,4	5,7	14,5	79,4	5,9	14,6	68
XV	2-Naphthylamino	194—195	Anhydrous toluene	$C_{19}H_{17}N_3$	79,4	6,0	14,6	79,4	5,9	14,6	56
XVI	2-Methylphenylamino	155	Anhydrous xylene	$C_{16}H_{17}N_3$	76,2	6,7	—	76,5	6,8	—	77
XVII	3-Methylphenylamino	176—178	Anhydrous toluene	$C_{16}H_{17}N_3$	76,1	6,7	—	76,5	6,8	—	64
XVIII	4-Methylphenylamino	180—181	Anhydrous toluene	$C_{16}H_{17}N_3$	76,8	6,7	—	76,5	6,8	—	77
XIX	1-Piperidino	105—106	Anhydrous ligroin	$C_{14}H_{19}N_3$	73,3	8,2	18,3	73,4	8,3	18,3	43
XX	1-Morpholino	102—103	Anhydrous ligroin	$C_{13}H_{19}N_3O$	67,6	7,3	18,6	67,5	7,4	18,2	71

TABLE 2. PMR Spectra in DMSO

	Compound	Chemical shifts, δ, ppm	
		2-H	4-H
Salts	I	9,45	9,96
	II	8,60	6,01
	IV	8,75	6,50
	VIII	8,81	6,55
Bases	IX	7,24	5,97
	X	6,94	5,37
	XI	7,15	5,60
	XII	7,23	5,77

aromatization under the influence of sulfur, $KMnO_4$, chloranil, and other oxidizing agents.

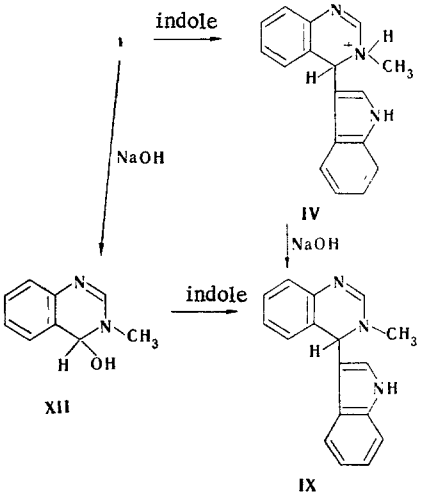
The disruption of the aromatic character of the pyrimidine portion of the molecule in the addition products is manifested as a hypsochromic shift of the absorption maxima in the UV spectra: the absorption band with λ_{max} 230 nm (log ε 1.3) ($n \rightarrow \pi^*$ transition) vanishes, and an absorption maximum develops at 218-220 nm (log ε 1.3).

The ring currents in the pyrimidine fragment vanish when nucleophiles are added to the quaternary quinazolinium salt, and this is manifested in the PMR spectra of II, IV, and VIII as a shift of the 2-H and 4-H† signals to considerably stronger field (Table 2). It is apparent from the data in Table 2 that the position of the 2-H signal depends only slightly on the character of residue R. Protonation of the molecule leads to the appearance of a 3-H signal at weak field (δ 8.75 ppm). The signals of the aromatic protons of the annelated benzene ring in the quinazolines and also in indole compounds show up as a multiplet (δ 6.8-7.7 ppm). According to the literature [5], the splitting of the 3'-H and 4'-H signals of the pyrrole residue at 5.95 ppm and the 5'-H doublet at 6.95 ppm, as well as the ratio of integral intensities, may attest to α substitution in the pyrrole derivatives (VII and VIII). The $3\text{-}CH_3$

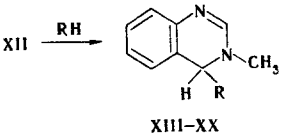
†Here and subsequently, the usual numbering of the atoms in the quinazoline ring is used.

group of quinazoline and the N–CH_3 group of pyrrole were identified in the spectra of solutions in d_7-DMFA as two intense signals at 3.37 ppm and 3.57 ppm. The character of the signal at 6.8 ppm (II and III), which is typical for an AA'BB' spin system, makes it possible to conclude that the phenyl ring in II and III is p-substituted.

We found that 3-methyl-4-hydroxy-3,4-dihydroquinazoline (XII) [2] is capable of undergoing substitution of the hydroxyl group by a nucleophile residue (Table 1). Thus when XII was heated in alcohol or benzene with indole we obtained a compound that was identical with respect to its IR spectrum and melting point to the substance isolated after treatment of addition product IV with alkali. In this connection, we began to suspect that the reaction of nucleophiles with 3-methylquinazolinium iodide proceeds through a step involving the covalent hydrate, which could form due to air moisture [6]. When we carried out the reaction of indole with the quaternary quinazolinium salt under conditions that exclude access to moisture we obtained the same product (IV) as we obtained in air. This makes it possible to consider the reaction of the quaternary salts to be direct addition. Replacement of the hydroxyl group in XII and addition of nucleophiles at the amino group also occur in the reaction of pseudobase XII with primary aromatic amines (aniline, o-, m-, and p-toluidine, and 1,2-naphthylamines) and cyclic alkylamines (morpholine and piperidine). In this case,



3-methyl-4-arylamino-3,4-dihydroquinazolines (XIII-XVIII) and 3-methyl-4-alkylamino-3,4-dihydroquinazolines (XIX and XX), respectively, are formed in good yields (see the experimental section).



XIII–XX

XIII R = phenylamino; XIV R = 1-naphthylamino; XV R = 2-naphthylamino; XVI R = 2-methylphenylamino; XVII R = 3-methylphenylamino; XVIII R = 4-methylphenylamino; XIX R = 1-piperidino; XX R = 1-morpholino

It was found that XIII, XIV, and XX were identical with respect to their melting points and chromatographic mobilities to the compounds previously obtained by reaction of quinazoline methiodide with aniline, 1-naphthylamine, and morpholine, respectively.

The IR spectra confirm the structures proposed for XIII-XX: only one absorption band in the region of stretching vibrations of the N–H bond (3280-3300 cm^{-1}) is observed in the spectra of XIII-XVIII, whereas this band is absent in the spectra of XIX and XX. Products XIII-XX are capable of undergoing hydrolysis in the presence of moisture. They were therefore prepared and purified under anhydrous conditions. The described reactions can be considered to constitute a convenient method for the preparation of previously unknown stable 4-sub-

stituted 3,4-dihydroquinazolines.

EXPERIMENTAL METHOD

The PMR spectra of DMSO and deuterated DMFA solutions of the compounds were measured with a Chart S-60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The UV spectra of alcohol solutions (c $2 \cdot 10^{-5}$ mole/liter) were obtained with a Perkin-Elmer 420 spectrophotometer. The IR spectra of mineral oil and perfluorohydrocarbon suspensions of the compounds were recorded with a UR-20 spectrometer.

The characteristics of II-XI and XIII-XX are presented in Table 1.

3-Methyl-4-(p-N,N-dialkylaminophenyl)-3,4-dihydroquinazolinium Iodides (II, III). A 20-mmole sample of the appropriate dialkylaniline and 20 mmole of a mixture of quinazoline methiodides were refluxed for 1 h in 5 ml of DMFA, after which the mixture was cooled, and 1 ml of water was added to the solution. The resulting precipitate was removed by filtration, dried, and crystallized.

3-Methyl-4-(3-indolyl)-3,4-dihydroquinazolinium Iodides (IV-VI). A 20-mmole sample of a mixture of quinazoline methiodides and 20 mmole of the appropriate indole were refluxed for 1 h in 5 ml of butanol, after which the mixture was cooled. The resulting precipitate was removed by filtration, washed with ether, dried, and crystallized.

3-Methyl-4-(2-pyrrolyl)-3,4-dihydroquinazolinium Iodide (VII). A solution of 0.5 g (20 mmole) of a mixture of quinazoline methiodides and 0.1 g (20 mmole) of pyrrole in 5 ml of butanol was allowed to stand for 5-6 h at room temperature, after which the resulting precipitate was removed by filtration, washed with ether, dried, and crystallized.

3-Methyl-4-(1-methylpyrrolyl)-3,4-dihydroquinazolinium Iodide (VIII). The method used to prepare IV-VI was used to obtain this compound from 0.5 g (20 mmole) of a mixture of quinazoline methiodides and 0.1 g (20 mmole) of 1-methylpyrrole.

3-Methyl-4-(indolyl)-3,4-dihydroquinazoline (IX). A solution of 0.3 g (18 mmole) of 3-methyl-4-hydroxy-3,4-dihydroquinazoline and 0.2 g (18 mmole) of indole in 4 ml of anhydrous alcohol was refluxed for 2 h, after which it was cooled and treated with 1 ml of water. The resulting precipitate was removed by filtration, washed with ether, dried, and crystallized.

3-Methyl-4-(p-dimethylaminophenyl)-3,4-dihydroquinazoline (X). Sodium hydroxide (5% solution) was added carefully to pH 8 to a solution of 0.3 g (7.7 mmole) of II in 4 ml of alcohol, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized.

3-Methyl-4-(2-pyrrolyl)-3,4-dihydroquinazoline (XI). The procedure used to obtain X was used to prepare this compound from 0.6 g (18 mmole) of VII.

3-Methyl-4-R-3,4-dihydroquinazolines (XIII, XIV, and XVI-XVIII). A 0.5-g (30 mmole) sample of XII and 30 mmole of the appropriate amine were refluxed in 4 ml of anhydrous alcohol for 1 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration, dried, and crystallized.

3-Methyl-4-(2-naphthylamino)-3,4-dihydroquinazoline (XV). A solution of 0.5 g (30 mmole) of XII and 0.4 g (30 mmole) of 2-naphthylamine in 4 ml of DMFA was refluxed for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration, dried, and crystallized.

3-Methyl-4-R-3,4-dihydroquinazolines (XIX, XX). A 0.5-g (30 mmole) sample of XII and 30 mmole of the appropriate alkylamine were refluxed in 15 ml of anhydrous ligroin for 2 h, after which the precipitate was removed by filtration. The precipitate that formed from the cooled solution was removed by filtration, dried, and crystallized.

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