SYNTHESIS OF 4-OXO-3,4,5,6-TETRAHYDROSPIRO(BENZO[*h*]QUINAZOLINE-5,1′-CYCLOHEXANE) DERIVATIVES

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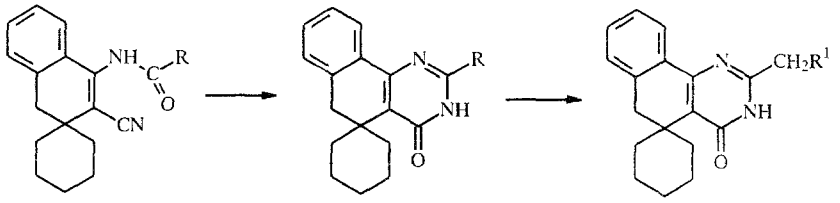
The reaction of 4-acylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1′-cyclohexanes) with hydrogen chloride yields 2-substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexanes). It was found that when the latter are condensed with methyl iodide, N-alkylation takes place exclusively. Alkylation with ethyl iodide in analogous conditions yields a mixture of O- and N-substituted products.

Benzoquinazoline derivatives exhibit antispasmodic, antidepressant, and anti-inflammatory activity [1-4]. There are absolutely no published data on the methods of synthesis and biological properties of benzoquinazolines spiro-bound with other rings. From this point of view, it was interesting to develop a method for synthesis of benzo[*h*]quinazoline derivatives spiro-bound with a cyclohexane ring. We showed that passing hydrogen chloride through an alcohol solution of 4-acylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1′-cyclohexanes) I-IV yields the target 2-substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) V-VIII. Difficulties related to the poor solubility of these compounds arose in taking the ESR spectra, and for this reason their structure was demonstrated by IR and mass spectroscopic data (Tables 1 and 2). There were no absorption bands of a nitrile group and there was absorption in the 1640-1660 cm^{-1} region characteristic of the C=O group in the IR spectra of compounds V-VIII.

The presence of a mobile halogen atom in 4-oxo-2-chloromethyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) V makes it possible to synthesize aminomethyl compounds IX-XI by nucleophilic substitution. Synthesis was conducted by condensation of halide V with secondary cyclic amines.

In condensation of quinazolines VI-VIII with alkyl iodides, formation of O- or N-alkylated products or mixtures of them could have been predicted. It was found that exclusively N-alkylated compounds XII-XIV were formed in methylation of these quinazolines in alcohol solution of potassium hydroxide, and the methyl group protons in their ESR spectra resonate as a singlet signal at 3.33-3.46 ppm. A mixture of O- and N-substituted products is formed in ethylation of quinazolines VI-VIII in similar conditions.



I-IV V-VIII IX-XI

I, V R=CH_2Cl; II, VI R=Et; III, VII R=Ph; IV, VIII R=CH_2Ph; IX R^1= pyrrolidino; X R^1=piperidino; XI R^1=morpholino

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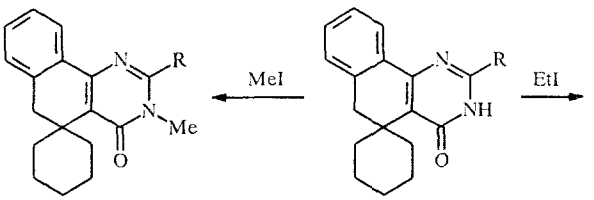
TABLE 1. Mass Spectra of 2-Substituted 4-Oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) V-VIII

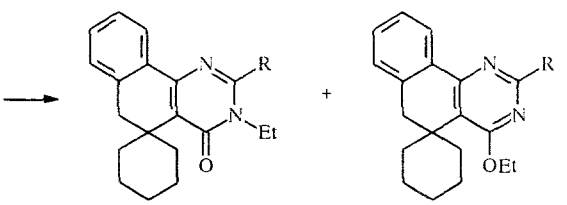
Compound	m/z (relative intensity of ion peaks, % of maximum)
V	317(8), 316(38), 315(25), 314(100), 313(15), 299(11), 297(28), 287(3), 285(11), 280(8), 279(5), 273(25), 271(61), 260(28), 259(29), 258(84), 257(25), 245(18), 220(15)
VI	295(20), 294(100), 293(18), 277(17), 265(11), 252(14), 251(63), 239(17), 238(73), 237(35), 225(15), 208(5)
VII	243(20), 242(100), 341(15), 325(15), 313(12), 300(15), 299(64), 287(15), 286(70), 285(25), 273(15), 256(6)
VIII	357(30), 356(100), 355(20), 339(22), 327(12), 314(14), 313(54), 301(18), 300(54), 299(24), 287(12)

TABLE 2. Properties of the Compounds

Compound	Empirical formula	MP, °C (solvent)	R_f (system)	IR spectrum, ν, cm^{-1}			Yield, %
				C=C arom	C=O	C=N	
V	$C_{18}H_{19}N_2ClO$	297...298 (DMF)	0,61 ( )	1590	1650	1615	95,5
VI	$C_{19}H_{22}N_2O$	264 (DMF)	0,62 ( )	1580	1640	1610	91,8
VII	$C_{23}H_{22}N_2O$	304...305 (DMF)	0,60 ( )	1570	1640	1610	93,6
VIII	$C_{24}H_{24}N_2O$	325...326 (DMF)	0,63 ( )	1580	1660	1630	92,7
IX	$C_{22}H_{27}N_3O$	178...180 (ethanol)	0,55 ( )	1590	1650	1610	82,8
X	$C_{23}H_{29}N_3O$	215...217 (butanol)	0,61 ( )	1590	1650	1605	82,6
XI	$C_{22}H_{27}N_3O_2$	226...227 (butanol)	0,75 ( )	1595	1640	1615	57,6
XII	$C_{20}H_{24}N_2O$	168...170(dioxane-water)	0,56 ( )	1580	1650	1610	64,9
XIII	$C_{24}H_{24}N_2O$	199...201 (ethanol)	0,68 ( )	1580	1655	1615	56,2
XIV	$C_{25}H_{26}N_2O$	156...157 (ethanol)	0,64 ( )	1570	1650	1605	64,9
XV	$C_{21}H_{26}N_2O$	250...252(ethanol-water)	0,49 ( )	1590	1650	1615	24,8
XVI	$C_{26}H_{28}N_2O$	124...126(ethanol)	0,65 ( )	1580	1660	1610	31,2



XII-XIV VI-VIII



XV, XVII XVI, XVIII

XII R=Et; XIII R=Ph; XIV R=CH_2Ph; XV R=Et; XVI R=CH_2Ph; XVII, XVIII R=Ph

The products of O-ethylation of 2-ethyl- and 2-benzyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) VI and VIII are an uncrystallizable oil and we did not isolate it in the pure form. Both an O-ethylated (compound XVIII) and a N-ethylated product (compound XVII) was isolated in pure form in ethylation of quinazoline VII.

TABLE 3. ESR Spectra of Compounds IX-XVI

Compound	Chemical shifts, δ, ppm
IX	1,2...2,1 (14H, m, $(CH_2)_5$ and $(CH_2)_2$); 2,46...2,93 (4H, m, CH_2—N—CH_2); 3.03 (2H, s, 6-CH_2); 3,7 (2H, s, 2-CCH_2); 7,2...8,36 (4H, m, C_6H_4)
X	1,33...2,0 (16H, m, $(CH_2)_5$ and $(CH_2)_3$); 2,33...2,9 (4H, m, CH_2—N—CH_2); 3,0 (2H, s, 6-CH_2); 3,5 (2H, s, 2-CCH_2); 7,2...8,33 (4H, m, C_6H_4)
XI	1,26...1,9 (10H, m, $(CH_2)_5$); 2,5...2,9 (4H, m, CH_2—N—CH_2); 3,03 (2H, s, 6-CH_2); 3,60 (2H, s, 2-C—CH_2); 3,7...4,0 (4H, m, CH_2—O—CH_2); 7,2...8,33 (4H, m, C_6H_4)
XII	1,23...1,7 (13H, m, $(CH_2)_5$ and CH_2CH_3)); 2,66 (2H, q, J = 7 Hz, 2-CH_2CH_3); 2,96 (2H, s, 6-CH_2); 3,46 (3H, s, N—CH_3); 7,1...8,33 (4H, m, C_6H_4)
XIII	1,2...2.0 (10H, m, $(CH_2)_5$); 3,1 (2H, s, 6-CH_2); 3,5 (3H, s, N—CH_3); 7,2...8,3 (9H, m, C_6H_4 and C_6H_5)
XIV	1,1...2,8 (10H, m, $(CH_2)_5$); 3,0 (2H, s, 6-CH_2); 3,33 (3H, s, N—CH_3); 4.06 (2H, s, $CH_2C_6H_5$); 7,06...8,16 (9H, m, C_6H_5 C_6H_4)
XV	1,1...1,9 (16H, m, $(CH_2)_5$ 2-CH_2CH_3); 2,73 (2H, q, J = 7Hz, 2-CH_2CH_3); 3,0 (2H, s, 6-CH_2); 3,73 (2H, q, J = 7 Hz, N—CH_2CH_3); 7,10...8,4 (4H, m, C_6H_4)
XVI	1,1 (3H, t, J = 8 Hz, N—CH_2CH_3); 1,16...1,83 (10H, m, $(CH_2)_5$); 2,96 (2H, s, 6-CH_2); 3,86 (2H, q, J = 8 Hz, N—CH_2CH_3); 4,1 (2H, s, $CH_2C_6H_5$); 7,03...8,23 (9H, m, C_6H_4 and C_6H_5)

In the ESR spectra of compounds XV-XVII, the methylene protons of the N—CH_2CH_3 fragment appear as a quadruplet signal at 3.73-3.86 ppm, while the methylene protons of the O—CH_2CH_3 fragment resonate at 4.76 ppm in the ESR spectrum of compound XIII.

EXPERIMENTAL

The IR spectra were made on a UR-20 in petrolatum. The ESR spectra were made on a Varian T-60 spectrometer (60 MHz) in deuterated chloroform using TMS as the internal standard. The mass spectra were made on a MX-1320 spectrometer using a system for direct introduction of the sample in the ion source. The purity of the compounds was verified by TLC on Silufol UV-254 plates in nonane—ethyl acetate, 1:1 (A), and acetic acid—water systems, 3:4 (B).

The data from elemental analysis of the compounds for C, H, and N corresponded to the calculations.

2-Substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) V-VIII. A mixture of 0.1 mole of 4-acylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) and 200 ml of abs. ethanol was heated to 70°C while stirring and a current of dry hydrogen chloride was passed through for 2 h. It was cooled, the sediment was filtered off, washed three times wtih 300 ml portions of water, and recrystallized from dimethylformamide (see Table 2).

2-Aminomethyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) IX-XI. A mixture of 3.1 g (0.01 mole) of chloromethylquinazoline V and 3 ml of amine was boiled with a reflux condenser for 7 h. It was cooled, 50 ml of water was added, and the crystals were filtered and recrystallized from butanol (see Tables 2 and 3).

2-Substituted 3-alkyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) XII-XVI. Here 0.01 mole of quinazoline was added to a solution of 0.56 g (0.01 mole) of potassium hydroxide in 20 ml of absolute ethanol and heated until dissolved. Then 0.02 mole of alkyl iodide was added and boiled for 6 h with a reflux condenser. The mixture was cooled, washed with water, and recrystallized (see Tables 2 and 3).

4-Oxo-2-phenyl-3-ethyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′cyclohexane) (XVII, $C_{25}H_{26}N_2O$) and 2-phenyl-4-ethoxy-5,6-dihydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (XVIII, $C_{25}H_{26}N_2O$). Here 3.4 g (0.01 mole) of quinazoline VI was added to a solution of 0.56 g (0.01 mole) of potassium hydroxide in 20 ml of abs. ethanol and heated until dissolved while stirring. Then 3.1 g (0.02 mole) of ethyl iodide was added and boiled for 7 h. It was cooled, 30 ml of water was added, and the precipitated crystals were filtered off and recrystallized from nonane, yielding 0.8 g (21.6%) of quinazoline XVIII. Mp 133-134°C, R_f 0.79 (A). IR spectrum: 1580 cm^{-1} (C=C, arom.). ESR spectrum: 1.1-1.8 (13H, m, $(CH_2)_5$ and OCH_2CH_3); 2.96 (2H, s, 6-CH_2); 4.56 (2H, q, J = 7 Hz, OCH_2CH_3); 6.8-8.7 ppm (9H, m, C_6H_4 and C_6H_5).

Nonane was distilled from the filtrate, and the sediment was recrystallized from ethanol, yielding 1 g (27.0%) of quinazoline XVII, mp 164-165°C, R_f 0.64 (A). IR spectrum: 1595 (C=C, arom.); 1645 cm^{-1} (C=O). ESR spectrum: 1.1-

1.9 (13H, m, $(CH_2)_5$ and NCH_2CH_3); 2.96 (2H, s, 6-CH_2); 3.86 (2H, q, J = 7 Hz, NCH_2CH_3); 7.00-8.20 ppm (9H, m, C_6H_4 and C_6H_5).

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REACTION OF QUINAZOLINE DERIVATIVES WITH QUATERNARY SALTS OF HETEROCYCLIC BASES

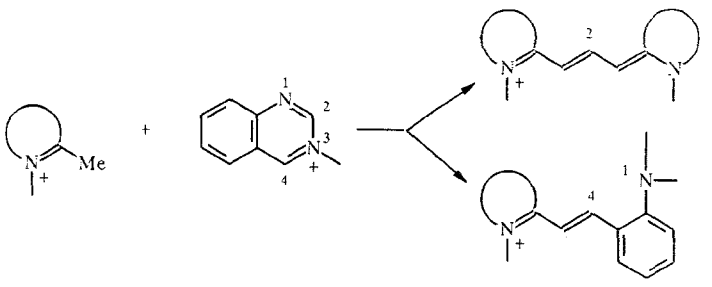
S. P. Gromov and M. A. Razinkin

The formation of carbocyanine and styryl dyes from quinazoline derivatives and quaternary salts of heterocyclic bases was detected. The intermediate compounds were separated and mechanisms of the reactions were proposed.

We proposed opening of the *sym*-triazine ring after addition of a nucleophile according to an electrocyclic mechanism as the basic direction in conversion of *sym*-triazine into pyridine and pyrimidine derivatives by enaminones. This reaction can take place with inclusion of a different number of *sym*-triazine atoms, including one carbon atom [1]. There is also information that trimethinecyanines are formed with extremely high yields in the reactions of quaternary salts of 2-methyl derivatives of heterocyclic bases with *sym*-triazine, which serves as a donor of a central carbon atom in construction of the polymethine chain of the dye [2]. Pentamethine dyes with three atoms in the pyrimidine ring in the polymethine chain are formed in the reaction of pyrimidine derivatives and the quaternary salt of the corresponding methyl derivative of the heterocycle [3].

Quinazoline derivatives can simultaneously be considered as pyrimidine derivatives for which reactions of nucleophilic addition at positions 2 and 4 [4] or cyclotransformation reactions are characteristic [5] and as a condensed diazine system similar to *sym*-triazine derivatives in electron deficiency [6].

It was possible to hypothesize that the diazine ring of the quinazoline nucleus will also be able to act as a donor of one or three carbon atoms in reactions with quaternary salts of heterocyclic bases, respectively forming cyanine and styryl dyes:



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