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# SYNTHESIS, STRUCTURE, AND CHEMICAL PROPERTIES OF SOME N-(3-CHLORO-2-QUINOXALYL)ARYLSULFONAMIDES

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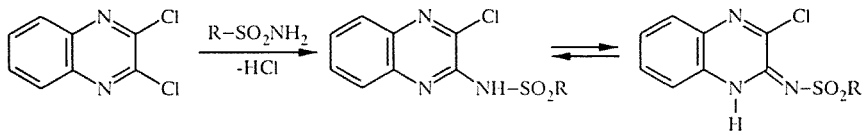
*We have developed a method for synthesis of N-(3-chloro-2-quinoxalyl)sulfonamides by reaction of 2,3-dichloroquinoxaline with substituted arylsulfonamides. Based on the IR spectra, we have established that in the solid state, the synthesized compounds exist in the form of amide tautomers. Alkylation of these compounds leads to N-methyl-N-(3-chloro-2-quinoxalyl)arylsulfonamides. We demonstrate the possibility of nucleophilic substitution of the halogen upon treatment with O- and N-nucleophiles. The use of bifunctional nucleophiles leads to condensed quinoxalines.*

New methods have been developed for synthesis of sulfonamide derivatives and study of their chemical properties because of the widespread application of these compounds as drugs with a complex spectrum of action [1]. Continuing investigations in the area of the chemistry of sulfones of the heterocyclic series [2, 3], we have studied the reaction of 2,3-dichloroquinoxaline with different aromatic sulfonamides and some chemical properties of the compounds obtained in this case.

The products of reaction of 2,3-dichloroquinoxaline with arylsulfonamides were described earlier in [4], but the synthesis conditions (fusion of the reagents at 180°C in the presence of $K_2CO_3$ and metallic copper over the course of 8 h) and the low yields of the target compounds do not make it possible to consider this method as preparative. We have found that upon brief heating of the reagents in DMF or DMSO in the presence of $K_2CO_3$, N-(3-chloro-2-quinoxalyl)arylsulfonamides I-IV are formed in yields close to quantitative, which can exist in the amide (A) or imide (B) forms:

Scheme I




A I, III B II, IV

I R = $C_6H_5$; II R = 4-$CH_3C_6H_4$; III R = 4-$NO_2C_6H_4$; IV R = 4-$CH_3CONHC_6H_4$

We can choose between the tautomeric forms A and B of compounds I-IV on the basis of analysis of their IR spectra. Earlier in [5] the position of the tautomeric equilibrium of the sulfonamide–sulfonimide type was studied for 2-substituted thiadiazoles, and clear criteria were developed for estimating the position of the tautomeric equilibrium on the basis of IR spectroscopy data. Thus, the presence of intense absorption bands in the region 870-890, 1160-1190, and 1350-1380 $cm^{-1}$ (which is characteristic for the IR spectra of compounds I-IV) and the absence of such bands in the region 1250-1280 $cm^{-1}$ allows us to say that in the solid form, the chloro derivatives I-IV exist as amide tautomers A. In the UV spectra of all the compounds obtained, there are two close long-wavelength maxima at 335 ($\varepsilon$ = 3500) and 348 nm ($\varepsilon$ = 3300), the position and intensity of which are practically independent of the nature of R.

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TABLE 1. Characteristics of Compounds I-XVIII

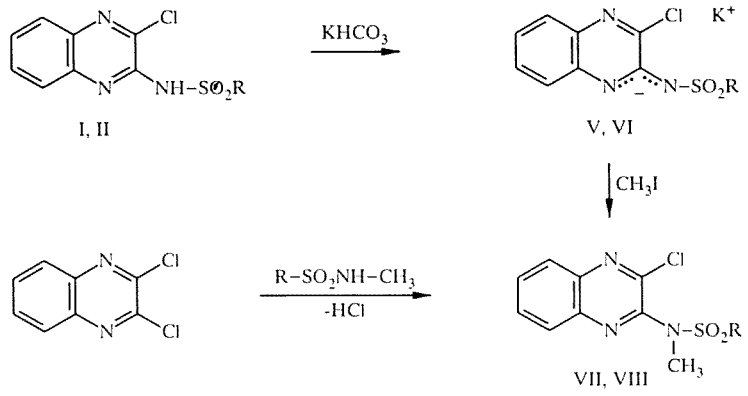
| Compound | Empirical formula | Mp, °C | Characteristic signals in PMR spectrum (δ, ppm, J, Hz)*2 | Yield, % |
|---|---|---|---|---|
| I | $C_{14}H_{10}ClN_3O_2S$ | 174 | 5,4 (1H, br. s, NH-); 7,57...8,35 (8H, m, aromatic H atoms) | 98 |
| II | $C_{15}H_{12}ClN_3O_2S$ | 251 | 2,31 (3H, s, $CH_3$-); 7,37 (2H, d, 8,0, H atoms *ortho* to $CH_3$ group $CH_3$-); 7,6...7,9 (4H, m, 4H, 5-H, 6-H, 7-H, 8-H); 8,02 (2H, d, 8,0, H atoms *ortho* to $SO_2$ group) | 95 |
| III | $C_{14}H_9ClN_4O_4S$ | 252 | 5,82 (1H, br. s, NH-); 7,56...7,97 (4H, m, 5-H, 6-H, 7-H, 8-H); 8,43 (4H, s, hydrogen atoms of the benzene ring) | 78 |
| IV | $C_{14}H_8ClN_5O_6S$ | 224 (разл.) | 7,49...8,12 (5H, m, H atoms of the benzene ring); 8,51 (1H, s, 6-H); 8,88 (1H, s, 7-H) | 92 |
| VII | $C_{15}H_{12}ClN_3O_2S$ | 168 | 3,51 (3H, s, $CH_3$); 7,38...8,27 (9H, m, aromatic H atoms) | 80 |
| VIII | $C_{16}H_{14}ClN_3O_2S$ | 128 | 2,26 (3H, s, $CH_3$-); 3,45 (3H, s, N—$CH_3$); 7,32 (2H, d, 8,0, H atoms *ortho* to $CH_3$ group 7,61...7,89 (4H, m, 4-H, 5-H, 6-H, 7-H, 8-H); 8,01 (2H, d, 8,0, H atoms *ortho* to $SO_2$ group) | 91 |
| IX | $C_{15}H_{13}N_3O_3S$ | 173 | 4,34 (3H, s, O—$CH_3$); 7,62...8,24 (9H, m, aromatic H atoms) | 93 |
| X | $C_{16}H_{16}N_4O_3S$ | 234 | 1,7 (3H, t, $CH_3$-); 4,95 (2H, d, $CH_2$-); 7,89...8,53 (8H, m, aromatic H atoms) | 61 |
| XI | $C_{17}H_{17}N_3O_3S$ | 163 | 1,55 (6H, d, $(CH_3)_2$); 5,56 (1H, m, CH-); 7,67...8,21 (9H, m, aromatic H atoms) | 78 |
| XII | $C_{18}H_{15}N_4O_2S$ | 127 | 1,02 (3H, t, $CH_3$-); 1,49 (2H, m, $CH_3$—$CH_2$-); 1,88 (2H, m, $CH_3$—$CH_2$—$\underline{CH_2}$—$CH_2NH$); 3,75 (2H, t, $\underline{CH_2}$—NH); 7,58...8,15 (4H, m, aromatic H atoms) | 94 |
| XIII | $C_{22}H_{20}N_4O_3S$ | 188 | 4,01 (3H, s, O—$CH_3$); 7,22 (2H, d, 8,0, H atoms *ortho* to $CH_3$ group); 7,72 (2H, d, 8,0, H atoms ortho to $SO_2$ group); 7,37...8,2 (8H, m, aromatic H atoms) | 90 |
| XIV | $C_{22}H_{16}ClF_3N_4O_2O_2S$ | 267 | 2,57 (3H, s, $CH_3$-); 7,42...8,1 (11H, m, aromatic H atoms) | 83 |
| XV | $C_{18}H_{18}N_4O_2S$ | 187 | 4,14 (4H, t, $(CH_2)_2N$); 4,41 (4H, t, $(CH_2)_2O$); 7,70...8,09 (4H, m, aromatic H atoms) | 96 |
| XVI | $C_{22}H_{15}F_3N_4O_2S$ | >300 | 2,60 (3H, s, $CH_3$-); 7,70...8,41 (11H, m, aromatic H atoms) | 43 |
| XVII | $C_{14}H_{10}N_4$ | >300 | 7,39 (2H, s, H-1, H-4); 7,50...8,09 (6H, m, 3-H, 4-H, 7-H, 8-H, 9-H, 10-H) | 96 |
| XVIII | $C_{14}H_9N_3O$ | >300 | 7,20...7,89 (8H, m, aromatic H atoms) | 87 |

*The spectra of compounds I-IV were recorded in DMSO-$d_6$, the spectra of the rest of the compounds were recorded in $CF_3COOD$.

*2Compounds I-IV, VII-XIII were recrystallized from isopropanol, XIV, XV — from *o*-xylene, XVI-XVIII — from DMF.

The presence of two electron-acceptor substituents bonded to the nitrogen atom of the sulfonamide group is responsible for the high NH-acidity of the synthesized compounds. Thus, they dissolve easily in an aqueous solution of potassium carbonate with formation of the corresponding potassium salts V, VI. Alkylation of the salts (we used methyl iodide as the alkylating reagent) can lead to two isomeric compounds, but in all cases the reaction proceeds unambiguously and N-methyl-N-(3-chloro-2-quinoxalyl)arylsulfonamides VII, VIII are formed. We clearly proved the orientation of methylation of compounds I and II using an alternate synthesis of the derivatives VII and VIII from 2,3-dichloroquinoxaline and N-methylarylsulfonamides:

Scheme 2

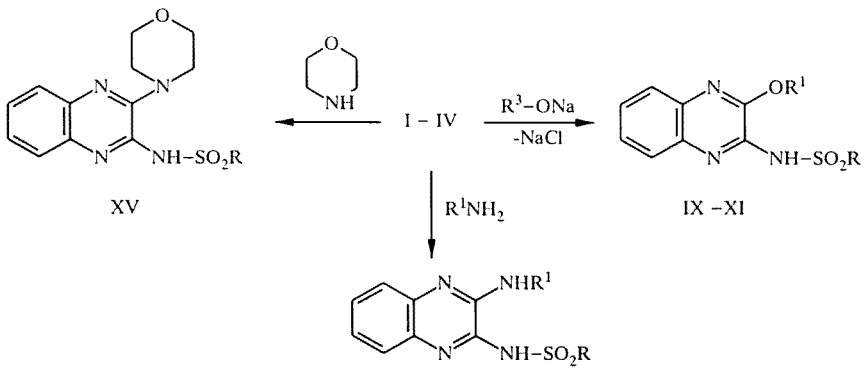



I, II V R = $C_6H_5$; VI R = 4-$CH_3C_6H_4$; VII R = $C_6H_5$; VIII R = 4-$CH_3C_6H_4$

In the IR spectra of the methylated derivatives VII and VIII, we observe the same regularities as in the spectra of compounds I-IV: the absence of appreciable absorption in the region 1250-1280 and strong bands at 880, 1360, and 1180 $cm^{-1}$. This confirms the conclusions drawn above concerning the existence of compounds I-IV in the solid state in the form of amide tautomers A, since for derivatives VII and VIII such tautomerism is impossible. The UV spectra of compounds I-VIII are very close in position and extinction coefficients of the absorption bands. Thus, the long-wavelength maximum in the spectra of all the compounds is found at 360-365 nm ($\varepsilon = (3.1\text{-}3.5)\cdot 10^4$).

We have studied the possibility of substitution of the active chlorine atom in compounds I-IV upon treatment with different nucleophiles. Thus alcoholates of alkali metals easily react with them with formation of the corresponding alkoxy derivatives IX-XI. Upon treatment with different primary and secondary monofunctional amines, substitution of the chlorine by an amine residue occurs (compounds IX-XV):

Scheme 3

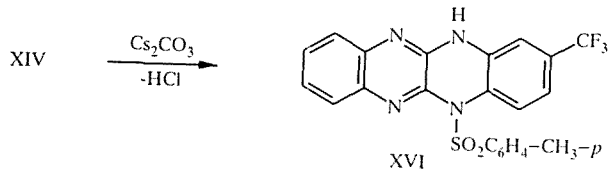



IX R = $C_6H_5$, $R^1$ = $CH_3$; X R = 4-$NH_2C_6H_4$, $R^1$ = $C_2H_5$; XI R = $C_6H_5$, $R^1$ = *i*-$C_3H_7$; XII R = $C_6H_5$, $R^1$ = *n*-$C_4H_9$; XIII R = 4-$CH_3C_6H_4$, $R^1$ = *p*-$CH_3OC_6H_4$; XIV R = 4-$CH_3C_6H_4$, $R^1$ = 2-Cl-5-$CF_3C_6H_3$; XV R = $C_6H_5$

The structure of the synthesized compounds, considering their spectral characteristics (see Table 1) and elemental analysis data, is not in doubt.

The reaction of I and II with some bifunctional primary amines does not stop at the stage of primary substitution of the chlorine atom. Thus, upon heating the amine XIV with $Cs_2CO_3$ in N-methylpyrrolidone, arylation of the sulfamide nitrogen atom occurs and 11,12-dihydro-2-trifluoromethyl-12-(4-methylphenylsulfonyl)quinoxalino[2,3-*b*]quinoxaline (XVI) is formed:

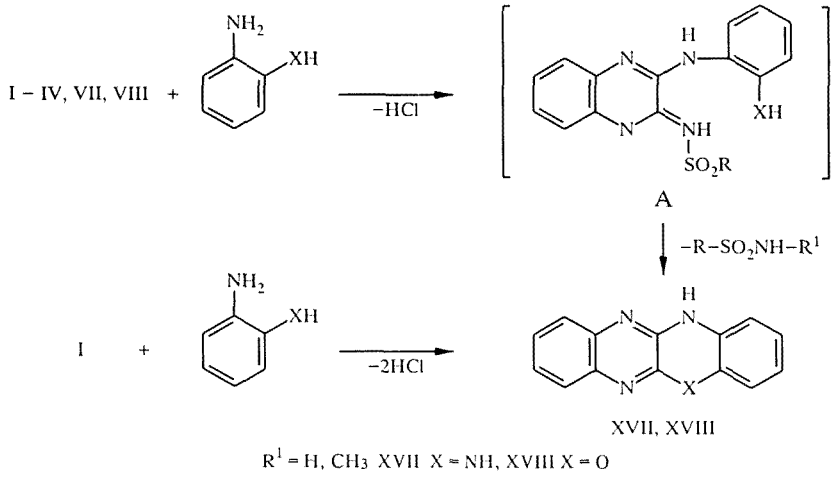
Scheme 4




XVI

Upon heating the chloro derivatives I-IV with *o*-phenylenediamine, we isolate the same product from the reaction mixture, independently of the aryl substituent R: 7,11-dihydroquinoxalino[2,3-*b*]quinoxaline (XVII). Introduction of *o*-aminophenol into this reaction leads accordingly to 12-n-quinoxalino[2,3-*b*]-[1,4]benzoxazine (XVIII). The reaction goes to completion after boiling the reagents in dimethylformamide for 10 min, and the yields of the target compounds XVII and XVIII are close to quantitative. The characteristics of the products obtained coincide with the constants of the cyclic compounds synthesized earlier in reaction of 2,3-dichloroquinoxaline with *o*-phenylenediamine and *o*-aminophenol respectively [6]:

Scheme 5




It is interesting that the reaction of *o*-phenylenediamine and *o*-aminophenol with N-methyl derivatives VII and VIII also leads to the cyclic compounds XVII and XVIII, but in this case the reaction proceeds significantly more slowly (boiling 6-8 h in DMF). Attempts to stop the reaction at the stage of formation of the proposed product of primary substitution of the halogen proved to be unsuccessful: in all cases, we could isolate only the cyclic compounds XVII and XVIII from the reaction medium.

We isolated arylsulfonamides from the reaction medium when carrying out this reaction, and they were identical with known samples.

## EXPERIMENTAL

The IR spectra were recorded on the Pye Unicam SP3-300 in KBr disks. The PMR spectra were recorded on the Bruker WP-100 Fourier spectrometer with TMS as the internal standard. The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates, the eluent was a 9:1 chloroform–methanol mixture.

**3-Chloro-2-(N-arylsulfonamido)quinoxalines (I-IV).** 0.01 moles of the corresponding arylsulfonamide and 1.4 g (0.01 moles) of calcined, finely ground potassium carbonate were added to a solution of 1.99 g (0.01 moles) 2,3-dichloroquinoxaline in 20 ml DMF. The reaction mixture was boiled with stirring for 1 h. Then the excess solvent was driven off under vacuum and 20 ml water was added to the residue. The solution obtained was acidified with 3 ml acetic acid and the residue was filtered off.

**Synthesis of Potassium Salts V and VI.** 0.012 moles of the corresponding compounds I, II were added to a solution of 0.70 g (0.005 moles) potassium carbonate in 50 ml water. The suspension formed was stirred for 1 h at a temperature of 50°C and the insoluble residue was filtered off. The filtrate was evaporated to dryness under vacuum. The yields of salts V, VI were quantitative. For additional purification, we used the method of reprecipitation of salts V,VI from their aqueous solutions (1 g salt in 20 ml water) in 30 ml acetone.

**3-Chloro-2-($NCH_3\tilde{N}$N-arylsulfonamido)quinoxalines (VII, VIII). A.** 0.01 moles potassium carbonate and 1 ml methyl iodide was added to a solution of 0.01 moles of the corresponding compound I, II in 10 ml dry DMSO. The reaction mixture was heated on a water bath at 40°C for 5-6 h. The solvent was driven off under vacuum, 20 ml water was added to the residue, and the precipitate was filtered off.

**B.** 0.01 moles N-methylarylsulfonamide and 1.4 g (0.01 moles) calcined potassium carbonate were added to a solution of 1.99 g (0.01 moles) 2,3-dichloroquinoxaline in 20 ml dry DMF. The reaction mixture was boiled for 3 h. Subsequent treatment of the product was analogous to method A.

**3-Alkoxy-2-(N-arylsulfonamides) (IX-XI).** 0.01 moles compounds I-IV was added to a solution of sodium alkoxide (0.23 g (0.01 moles) metallic sodium in 50 ml of the corresponding alcohol). The reaction mixture was boiled for 1 h and the excess alcohol was evaporated under vacuum. 30 ml water was added; the solution obtained was acidified with 3 ml acetic acid and the precipitate was filtered.

**3-Amino-2-(N-arylsulfonamides) (XII-XV).** 0.02 moles of the amine was added to a solution of 0.01 moles of the corresponding chloro derivative I-IV in 10 ml DMF. The solution obtained was boiled for 1-3 h (monitored by TLC). Subsequent treatment of the reaction mixture was analogous to the treatment in synthesis of compounds IX-XI.

**11,12-Dihydro-2-trifluoromethyl-12-(4-methylphenylsulfonyl)quinoxalino[2,3-*b*]quinoxaline (XVI).** A solution of 1 g compound XIV in 10 ml N-methylpyrrolidone was mixed with 2 g calcined cesium carbonate. The mixture obtained was boiled for 16 h, 50 ml water was added, and the residue was filtered.

**Condensed quinoxalines (XVII, XVIII).** 0.02 moles *o*-phenylenediamine or *o*-aminophenol was added to a solution of 0.01 moles compound I or II in 5 ml DMF. The reaction mixture was boiled for 10-15 min and then the solvent was evaporated under vacuum to dryness. 10 ml 40% KOH solution was added to the residue and the mixture obtained was heated at 60°C for 10 min. The residue of compounds XVII or XVIII was filtered off, the filtrate was acidified with hydrochloric acid to pH 3, and the residue of sulfonamide was filtered off.

## REFERENCES


1. M. Nagwer, Organo-Chemical Drugs and Their Synonyms, Akad. Verlag, Berlin (1987), p. 2470.
2. S. V. Litvinenko, Yu. M. Volovenko, and F. S. Babichev, Khim. Geterotsikl. Soedin., No. 3, 167 (1993).
3. S. V. Litvinenko, Yu. M. Volovenko, and F. S. Babichev, Khim. Geterotsikl. Soedin., No. 2, 224 (1993).
4. S. H. Dandegaonker and C. K. Mesta, J. Med. Chem., **8(6)**, 884 (1965).
5. V. P. Shchipachev, Yu. N. Sheinker, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 2, 350 (1966).
6. G. Riedel and W. Deuschel, Brit. Pat. 971048; Chem. Abstr., **62**, P1774h.