9. V. A. Kaminskii, I. V. Stepanchenko, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 9, 1251 (1979).
10. A. N. Saverchenko, Z. R. Bekkerova, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 2, 243 (1974).
11. A. R. Katritzky, K. Horvath, and B. Plau, J. Chem. Soc., Chem. Commun., No. 6, 300 (1979).

SYNTHESIS OF N-(8-METHOXY-5-QUINOLYLSULFONYL)AZIRIDINE AND ITS REACTIONS WITH SECONDARY AMINES. PMR SPECTRA AND STRUCTURES OF THE DERIVATIVES OBTAINED

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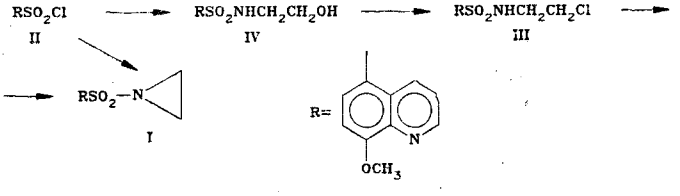
A method for the synthesis of a new fluorescent derivative of ethyleneimine, viz., N-(8-methoxy-5-quinolylsulfonyl)-aziridine, starting from 8-methoxyquinoline-5-sulfonyl chloride was developed. The quinolylsulfonylaziridine reacts smoothly with secondary aliphatic amines to give 8-methoxy-5-[N-(2-N-dialkylethylamino)] quinolinesulfonamides. In a study of the PMR spectra of these compounds it was established that significant deshielding of the 4-H proton (0.8 ppm) and a substantial increase (by 0.8 ppm) in $^3J_{(6,7)}$ are characteristic signs of the introduction of aziridinylsulfonyl or N-(2-N-dialkylamino)sulfonamido substituents into the 5 position of 8-methoxyquinoline.

N-Sulfonylaziridines are activated alkylating compounds that react readily with nucleophilic groups [1]. The reactions of N-sulfonylaziridines can be used as a mild method for the introduction of sulfonamidoethyl groups into organic compounds [2].

N-Sulfonylaziridines of the quinoline series could be used as fluorescent probes for the study of the structures of proteins and enzymes and as analytical reagents for amino and sulfhydryl groups in analog with 1-dimethylamino-5-naphthylsulfonylaziridine (dansylaziridine) [3] and 1-dimethylamino-naphthalene-5-sulfonyl chloride (dansyl chloride) [4].

In the present paper we report the synthesis and reactions with secondary amines of N-(8-methoxy-5-quinolylsulfonyl)aziridine (I), which was obtained on the basis of the previously described 8-methoxyquinoline-5-sulfonyl chloride (II), which is a highly sensitive, photostable, fluorescent reagent for amines, amino acids, and peptides [5].



Like other arylsulfonyl derivatives of ethyleneimine, quinolylsulfonylaziridine I is formed in good yield by the reaction of sulfonyl chloride II with ethyleneimine in chloroform [2] or by cyclization of 8-methoxy-5-[N-(2-chloroethyl)]quinoline-sulfonamide (III) under the conditions of the Gabriel reaction in aqueous acetone or methanol in the presence of KOH or NaOH [6]. Chloroethyl derivative III is synthesized by treatment of 8-methoxy-5-[N-(2-hydroxyethyl)]quinolinesulfonamide (IV), obtained by the reaction of sulfonyl chloride

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TABLE 1. Properties of 8-Methoxy-5-[N(2-N-dialkylethylamino)] quinolinesulfonamides VIa-g

Compound	mp, deg C	R_f	Fluorescence spectrum, nm		IR spectrum, cm^{-1}	Found, %				Empirical formula	Calculated, %				Yield, %
			λ_{exc}	λ_{em}		C	H	N	S		C	H	N	S	
VIa	Oil	0,21	320	380	1060, 3178 (NH)	54,5	6,3	13,5	10,5	$C_{14}H_{19}N_3O_3S$	54,4	6,1	13,6	10,4	90
VIb	141—142	0,25	335	380	1060, 3090 (NH)	57,2	6,7	12,6	9,7	$C_{16}H_{23}N_3O_3S$	57,0	6,8	12,5	9,5	85
VIc	128—129	0,59	320	380	1060, 3090 (NH)	59,6	7,1	11,6	8,8	$C_{18}H_{27}N_3O_3S$	59,7	7,1	11,5	8,7	95
VId	109—110	0,62	320	380	1060, 3090 (NH)	59,2	7,6	11,8	9,0	$C_{20}H_{31}N_3O_3S$	61,1	7,9	10,7	8,1	87
VIe	102—103	0,21	330	380	1060, 3090 (NH)	57,7	6,5	12,6	9,7	$C_{16}H_{21}N_3O_3S$	57,3	6,5	12,6	9,6	98
VIf	133—139	0,35	330	380	1060, 3090 (NH)	58,1	6,7	12,1	9,2	$C_{17}H_{23}N_3O_3S$	58,4	6,6	12,0	9,2	75
VIg	Oil	0,7	330	380	1060, 3090 (NH), 2090 (C≡C), 3220 (C≡CH)	57,9	5,2	12,1	9,1	$C_{16}H_{18}N_3O_3S$	57,8	5,5	12,6	9,6	52

TABLE 2. PMR Spectra of N-(8-Methoxyquinolylsulfonyl)-aziridine (I) and 8-Methoxyquinoline (VII)

Compound	Chemical shift, δ, ppm								^nJ (H, H), Hz					
	2-H	3-H	4-H	5-H	6-H	7-H	OCH_3	CH_2	$^3J_{(2,3)}$	$^4J_{(2,4)}$	$^3J_{(3,4)}$	$^5J_{(5,6)}$	$^4J_{(5,7)}$	$^5J_{(6,7)}$
I	9,03	7,64	9,25	—	8,21	7,08	4,17	2,42	4,2	1,7	8,8	—	—	8,5
VII	8,91	7,37	8,07	7,36	7,41	7,01	4,06	—	4,2	1,7	8,6	8,5	2,4	6,7

TABLE 3. PMR Spectra of 8-Methoxy-5-[N-(2-N-dialkylethyl-amino)]quinolinesulfonamides

Compound	Chemical shift, δ, ppm								$^5J_{(6,7)}$, Hz
	2-H, 4-H	3-H	6-H	7-H	OCH_3	CH_2—CH_2	NH	1-R	
VIa	8,90—9,10	7,60	8,28	7,08	4,16	2,20; 2,92	4,89	1,93	8,5
VIb	8,90—9,10	7,60	8,40	7,16	4,19	2,37; 2,89	5,08	0,81 (CH_3), 2,31 (CH_2)	8,5
VIc	8,90—9,10	7,60	8,28	7,09	4,16	2,38; 2,89	—	0,70 (CH_3), 1,24 (CH_2), 2,15 (NCH_2)	8,5
VId	8,90—9,10	7,73	8,42	7,20	4,22	2,40; 2,88	—	0,82 (CH_3), 1,18 (CH_2), 2,17 (NCH_2)	8,5
VIe	8,90—9,10	7,60	8,28	7,18	4,21	2,40; 2,95	5,25	1,57 (CH_2), 2,21 (NCH_2)	8,5
VIf	8,90—9,10	7,62	8,28	7,16	4,22	2,20; 2,91	—	1,30 (CH_2), 2,03 (NCH_2)	8,5

II with 2-aminoethanol in chloroform, with thionyl chloride. Aziridine I is completely stable during storage and during chromatography in systems that contain acid and ammonia.

The introduction of an arylsulfonyl residue into ethyleneimine significantly increases the reactivity of the aziridine ring with respect to nucleophilic reagents [7]. Opening of the aziridine ring in I in reactions with secondary amines (Va-g) proceeds smoothly in alcohol or chloroform without the catalysts that are normally used (for example, NH_4Cl or Lewis acids) [1], is not accompanied by side reactions, and leads to 8-methoxy-5-[N-(2-N-dialkylethylamino)]quinolinesulfonamides (VIa-g). The reaction

$$\xrightarrow{R^1H} \underset{\text{VIa-g}}{RSO_2NHCH_2CH_2R^1}$$

a $R^1=N(CH_3)_2$; b $R^1=N(C_2H_5)_2$; c $R^1=N(C_3H_7)_2$; d $R^1=N(C_4H_9)_2$; e. $R^1=$ 1-pyrrolidino f $R^1=$ 1-piperidine; g $R^1=CH_3NCH_2C\equiv CH$

with primary amines requires more severe conditions and is less unambiguous: products of further substitution are formed along with monoalkyl derivatives, as is characteristic for other activated aziridines [8].

The fluorescence spectra of VIa-g in solution in ethanol contain a λ_{max} band at 380 nm; in the case of excitation with UV light the λ_{max} band is located at 320-330 nm. The yields and properties of derivatives VIa-g are presented in Table 1.

Both sulfonylaziridine I itself and all of the VI derivatives on silica gel have bright blue fluorescence, the intensity of which is not inferior to the intensity of the fluorescence of the dansyl derivatives of the corresponding amines and, in contrast to the latter, does not decrease in an acidic medium.

The structures of I and VIa-f were proved by data from the PMR spectra, which are presented in Tables 2 and 3. For comparison, we also studied the spectrum of 8-methoxyquinoline (VII) (Table 2). The assignment of the lines in the spectra was made on the basis of the chemical shifts and the spin-spin coupling constants (SSCC) (J), the form of the spectra, and comparison of the spectra with one another. The data previously obtained for quinoline and a number of its derivatives [9-11] were taken into account in the assignment.

In the spectra of I and VIa-f as compared with the spectrum of VII one observes significant deshielding of the 4-H protons under the influence of substituents in the 5 position (the peri effect), the magnitude of which exceeds 0.8 ppm. Since in this case the chemical shifts of the 2-H protons change only slightly, and the signals of the 4-H protons are overlapped with the 2-H signals, in the spectrum of aziridine I they are found at even weaker field than the 2-H signals. Overlapping of the 2-H and 4-H signals in the spectra of VIa-f leads to pronounced deviation of the spectrum of the protons of the heterocyclic part from first order, and this makes it impossible to determine the accurate values of the chemical shifts of the 2-H and 4-H protons, as well as the $^3J_{(2,3)}$, $^4J_{(2,4)}$, and $^3J_{(3,4)}$ values. The pronounced deshielding of the 4-H proton is evidently due not so much to the effect of the magnetic anisotropy of the substituents in the 5 position as much as to the steric factor of these bulky substituents. It is known that the so-called γ effect, which leads to polarization of the charge along the γ-C—γ-H bond joining the carbon atom in the γ position relative to the bulky substituent and the γ-H atom, arises under the influence of the steric factor. As a result, significant shielding of the γ-C in the ^{13}C spectra and deshielding of the γ-H atom are observed [12-14]. Specifically for quinolines let us note that a significant (several parts per million) shift of the $C_{(4)}$ signal to strong field under the influence of bulky substituents in the 5 position is actually observed in the ^{13}C spectra (an exception is observed only when heavy atoms such as iodine are introduced into this position) [11, 15, 16]. The assignment of the signals of the 6-H and 7-H protons in I and VIa-f was made on the basis of the following data. Broadening of the 7-H signals, which is recorded in experiments involving double resonance in the case of irradiation with a second rf field of the protons of the OCH_3 group, is observed in the spectrum of 8-methoxyquinoline (VII) (Table 2). This made it possible to establish the existence of ^5J long-range spin-spin coupling (7-H, OCH_3). The noted coupling in all of the remaining cases (in the AB spectrum of the 6-H and 7-H protons broadening of the signal located at stronger field is also similarly recorded) made it possible to make the desired assignment. Let us note that the $^3J_{(6,7)}$ values in the spectra of derivatives I and VIa-f are substantially greater (by 1.8 Hz) as compared with $^3J_{(6,7)}$ in the spectrum of VII; this is in complete agreement with the fact of the introduction of an electronegative substituent into the 5 position [11].

The spectrum of the methylene protons of the aziridine ring is a singlet. In the case of ring opening the spectrum of these protons in VIa-f has a characteristic form, which, within a first-order approximation, can be regarded as two triplets with $^3J(CH_2,CH_2) \sim 6$ Hz. The protons of the NC_2H_5, NC_3H_7, and NC_4H_9 groups give a spectrum that also has deviations from first order with a distance of ~7 Hz between the components of the multiplets; the chemical shifts of the two methylene groups in the butyl radical virtually coincide. The spectra of the methylene protons of the pyrrolidine and piperidine rings are observed as virtually two singlets with integral intensity ratios of 4:4 for VIe and 4:6 for VIf.

The exceptional ease and selectivity in the preparation of fluorescent 8-methoxy-5-[N-(2-N-dialkylethylamino)]quinoline-sulfonamides make it possible to use N-(8-methoxy-5-quinolylsulfonyl)aziridine as an analytical reagent for secondary amino groups. The synthesized derivatives have high photostability during chromatographic analysis on Silufol plates, in contrast to the corresponding amine derivatives obtained by means of dansyl chloride, which decompose under similar conditions.

EXPERIMENTAL

The PMR spectra were obtained with a Tesla BS-567 spectrometer (100 MHz) under continuous conditions. Stabilization of the resonance conditions was realized with respect to the signal of tetramethylsilane (TMS), which was used as the internal standard. The investigated samples were solutions of the compounds in $CDCl_3$ with a concentration of 0.2 mole/liter. The chemical shifts are presented on the δ scale. The fluorescence spectra were recorded with a Hitachi spectrometer (ethanol solutions). The IR spectra were obtained with a Unicam SP-1000 spectrometer (KCl pellets). Monitoring of the course of the reactions and the purity of the compounds obtained was realized by thin-layer chromatography (TLC) on Silufol plates in chloroform–acetone (4:1) (system A), acetonitrile–25% NH_4OH (6:1) (system B), chloroform–2-propanol (4:1) (system C), and chloroform–methanol (4:1) (system D).

8-Methoxy-5-[N-(2-hydroxyethyl)]quinolinesulfonamide (IV). A solution of 1.28 g (5 mmole) of 8-methoxyquinoline-5-sulfonyl chloride in 20 ml of chloroform was added in the course of 10 min to a solution of 360 mg (6 mmole) of aminoethanol and 0.4 ml of triethylamine in 30 ml of chloroform, and the mixture was maintained at 20°C for 30-40 min. The precipitated sulfonamide IV was separated to give 1.25 g (92%) of a product with mp 181-183°C (ethanol). The substance was homogeneous in systems A and C. IR spectrum: 1060, 3092 (NH); 3228 cm^{-1} (OH). Found: C 50.9; H 5.3; N 10.3; S 12.1%. $C_{12}H_{11}N_2O_4S$. Calculated 51.1; H 5.0; N 9.9; S 11.7%.

8-Methoxy-5-[N-(2-chloroethyl)]quinolinesulfonamide (III). A mixture of 1.41 g (6 mmole) of hydroxyethyl derivative IV and 5 ml of thionyl chloride was refluxed for 1 h, after which it was evaporated, and the residue was dissolved in water. The aqueous solution was made alkaline to pH 9 by the addition of 25% ammonium hydroxide, and 1.28 g (81%) of derivative III, with mp 158-159°C (ethanol), was separated. The substance was homogeneous in systems A and C. IR spectrum: 1060 and 3092 cm^{-1} (NH). Found: C 48.2; H 4.3; Cl 11.0; N 9.3; S 11.2%. $C_{12}H_{13}ClN_2O_3S$. Calculated 47.9; H 4.3; Cl 11.8; N 9.3; S 10.6%.

N-(8-methoxy-5-quinolylsulfonyl)aziridine (I). A) A 430-mg (10 mmole) sample of ethyleneimine and 1 ml of triethylamine were added with ice cooling to a solution of 2.56 g (10 mmole) of 8-methoxyquinoline-5-sulfonyl chloride in 50 ml of dry benzene, and the mixture was stirred for 3 h, during which the temperature was gradually raised to ~20°C. The resulting precipitate was removed by filtration and extracted on the filter with benzene and chloroform. The extract was washed with water and combined with the filtrate, and the resulting solution was dried with $MgSO_4$. The solvent was evaporated to give 2.58 g (98%) of aziridine I with mp 200-201°C (n-propanol). The substance was homogeneous in systems A and B. IR spectrum: 947, 1050, and 1055 cm^{-1} (aziridine ring). Found: C 54.8; H 4.4; N 10.6%. $C_{12}H_{12}N_2O_3S$. Calculated: C 54.5; H 4.7; N 10.6%.

B) A suspension of 290 mg (1 mmole) of the hydrochloride of III and 114 mg (2 mmole) of KOH in 10 ml of ethanol and stirred for 20 h, after which the precipitate was separated and washed with cold water to give 2.1 g (70%) of I, which, with respect to its melting point, R_f value, and spectral data, was identical to the aziridine obtained by method A.

8-Methoxy-5-[N-(2-N-dialkylethylamino)]quinolinesulfonamides (VIa-g) (Table 1). A 132-mg (0.5 mmole) sample of I was refluxed with 0.5 mmole of the corresponding amine Va-g in 5 ml of ethanol or chloroform. After 20 min, the solvent was evaporated to give derivatives that were homogeneous in systems A and B.

LITERATURE CITED

1. O. C. Dermer and E. E. Ham, Ethyleneimine and Other Aziridines. Chemistry and Application, New York–London (1967), p. 248.
2. P. A. Gembitskii, D. S. Zhuk, and V. A. Kargin, The Chemistry of Ethyleneimine [in Russian], Moscow (1966).
3. B. Keith, Int. J. Biochem., 10, 259 (1979).
4. N. Seiler, Wiechmann, and A. Arber, Progress in Thin-Layer Chromatography, 10, 259 (1970).
5. A. I. Tochilkin, I. N. Gracheva, I. R. Kovel'man, G. A. Davydova, and S. I. Kirillova, USSR Inventor's Certificate No. 1074869; Byull. Izobret., No. 7, 87 (1984).
6. N. A. Rybakova, N. A. Pochkailo, and L. N. Kiseleva, Izv. Akad. Nauk SSSR, Ser. Khim., 2793 (1973).
7. V. I. Markov, S. I. Burmistrov, and D. A. Danileiko, in: Chemical Technology [in Russian], Vol. 21, Izd. Khar'kovsk. Gos. Univ., Kharkov (1971), p. 97.

8. Y. Iwakura and A. Nabeya, J. Org. Chem., 25, 1118 (1960).
9. P. T. Black and M. L. Heffernan, Aust. J. Chem., 17, 558 (1964).
10. M. Attimonelli and O. Sciacovelli, Org. Magn. Reson., 12, 17 (1979).
11. T. Kidrič, D. Hadži, D. Kocjan, and V. Rutar, Org. Magn. Reson., 15, 280 (1981).
12. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
13. B. V. Cheney and D. M. Grant, J. Am. Chem. Soc., 89, 5319 (1967).
14. E. P. Prokof'ev and Zh. A. Krasnaya, Izv. Akad. Nauk SSSR, Ser. Khim., 15, 1011 (1980).
15. I. V. Zuika, Yu. Yu. Popelis, Z. P. Bruvers, D. E. Zaruma, Ya. É. Leeis, and M. A. Tsirule, Khim. Geterotsikl. Soedin., No. 7, 932 (1981).
16. T.-A. Su, E. Siew, E. V. Brown, and S. L. Smith, Org. Magn. Reson., 10, 122 (1977).

DERIVATIVES OF AZIRIDINE-1,2-DICARBOXYLIC ACID

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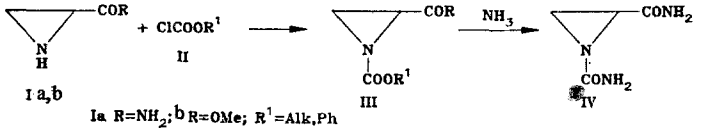
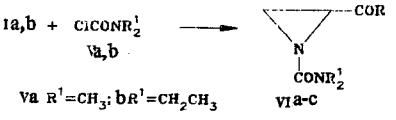
The corresponding esters and amides of aziridine-1,2-di-carboxylic acid were obtained by the reaction of esters and amides of aziridine-2-carbocylic acid with esters and amides of chlorocarbonic acid, isocyanates, and isothiocyanates. The reaction of 2-methoxycarbonylaziridine with diisocyanates and chlorides of the dicarboxylic acids leads to the formation of bisaziridines.

Derivatives of aziridinecarboxylic acids have been studied extensively as immunoregulating and carcinostatic agents [1]. It has already been observed that 2-carbamoylaziridine [2] and 1,2-dicarbamoylaziridine and 1-carbamoyl-2-cyanoaziridine [3] have antineoplastic and immunostimulating properties [3].

In order to obtain new derivatives of aziridinecarboxylic acids for biological studies we carried out reactions of esters and amides of aziridine-2-carboxylic acid with esters and amides of chlorocarbonic acid, as well as with various isocyanates and isothiocyanates. We have shown that aziridine-1,2-dicarboxylic acid esters IIIf, h or 1-alkoxycarbonyl-2-carbamoylaziridines IIIa-e (Table 1) are formed in the reaction of derivatives Ia, b with chlorocarbonic acid esters at low temperatures in the presence of triethylamine. Conclusions regarding the structure of ester IIIf were drawn on the basis of an analysis of the PMR spectra (Table 2), since this compound proved to be thermally unstable and decomposed in an attempt to purify it by vacuum distillation at 120°C (0.003 mm). Compounds IIIa-e were converted to 1,2-dicarbamoylaziridine (IV) by treatment with dry ammonia in methanol at 0-20°C.



1,2-Dicarbamoylaziridines VIa, b and 1-carbamoyl-2-methoxy-carbonylaziridine (VIc) (Table 1) were obtained by the reaction of Ia,b with chloroformic acid amides Va,b. The reactions were carried out as in the case of chlorocarbonic acid esters.



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