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HETEROCYCLES WITH A BRIDGED NITROGEN ATOM. 13.* AN ANOMALOUS EXAMPLE OF THE SULFONATING ACTION OF DIMETHYL SULFATE DURING AN ATTEMPT AT THE METHYLATION OF 5-AMINOINDOLIZINE. CRYSTAL STRUCTURE OF METHYL 5-MORPHOLYL-2-(*p*-NITROPHENYL)INDOLIZINE-1-SULFONATE

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The reaction of 5-morpholino-2-(p-nitrophenyl)indolizine with dimethyl sulfate gives the sulfonation product – methyl 5-morpholyl-2-(p-nitrophenyl)indolizine-1-sulfonate. Its structure was proved by X-ray crystallographic analysis.

Keywords: indolizine, oxazole, oxazolo[3,2-a]pyridine, pyridine, pyrrole, X-ray crystallographic analysis, recyclization with acetylacetone, 5-methyl-2-(*p*-nitrophenyl)oxazolo[3,2-*a*]pyridinium perchlorate, 1-acetyl-2,5-dimethylindolizine.

Earlier we proposed a new approach to the synthesis of an unknown subclass of 5-aminoindolizines by the recyclization of oxazolo[3,2-*a*]pyridinium salts [2-4]; no further study of the reactivity of such indolizines was undertaken. Alkylation of 5-aminoindolizines at the amino group could lead to the formation of quaternary salts with the leaving group at the $C_{(5)}$ atom, and this would open up the possibility of varying the substituent at this position by nucleophilic substitution reactions. Although the possibility of nonselective alkylation of alkylindolizines in the ring has been mentioned in the literature [5], the low degree of conjugation of the 5-NR_2 group with the indolizine residue [4] made it possible to expect selective attack by the alkylating agent at the amino group.

We attempted methylation of 5-morpholyl-2-(*p*-nitrophenyl)indolizine **1**. When methyl iodide was used as alkylating agent only regeneration of the initial substance was observed. In the reaction of indolizine **1** with dimethyl sulfate the initial substance entered fully into the reaction. In order to isolate the ionic alkylation component (5-indolizyltrialkylammonium salt) the reaction mixture was treated with ether, and the formed precipitate was dissolved in sulfuric acid and reprecipitated with perchloric acid. According to X-ray crystallographic analysis, the isolated substance was methyl 5-morpholino-2-(*p*-nitrophenyl)indolizine-1-sulfonate (**2**).

* For Communication 12, see [1].

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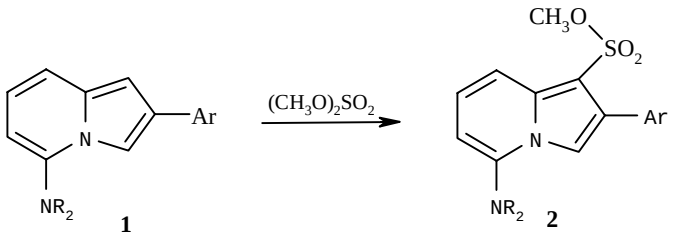
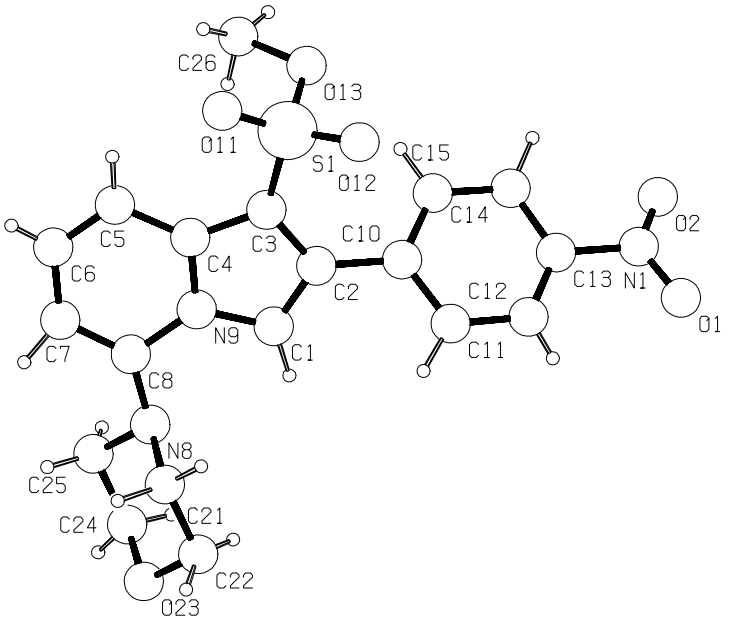
The structure of the obtained compound was confirmed conclusively by X-ray crystallographic analysis. According to this the SO_2OMe group is bonded covalently to the $C_{(1)}$ atom, although the declination of the sulfur atom from the plane of the indolizine ring is fairly large and amounts to almost 20°.



Ar = *p*-$O_2NC_6H_4$; NR_2 = N-morpholyl

The phenyl ring forms an angle of 44° with the planar indolizine fragment and of 16° with the nitro group. As in the case of other indolizines (see the discussion in [4]), clearly defined alternation of the lengths of the single and double bonds in the $C_{(5)}C_{(6)}C_{(7)}C_{(8)}C_{(9)}C_{(1)}C_{(2)}C_{(3)}$ chain is observed in the skeleton of the molecule **2**. The amino group at position 5 is separated from the 1-methylsulfonyl group by three double bonds, and the substituents are in formal conjugation with each other. Such conjugation can be revealed at the structural level by comparison of the geometry of the $N–C_{(5)}C_{(6)}C_{(7)}C_{(8)}C_{(9)}C_{(1)}$ fragments in indolizine **2** and 5-aminoindolizine not containing an acceptor at position 1 (cf., the data from X-ray crystallographic analysis for 5-hexamethyleneimino-2-(*p*-nitrophenyl)indolizine [4]). It is found that the introduction of an acceptor group at position 1 leads to shortening of the $N–C_{(5)}$, $C_{(6)}–C_{(7)}$, and $C_{(9)}–C_{(1)}$ bonds, whereas the $C_{(5)}–C_{(6)}$ and $C_{(8)}–C_{(9)}$ bonds are slightly lengthened.

It is quite difficult to explain the discovered direction of the reaction rationally. It must be supposed that the 2-*p*-nitrophenyl group seriously deactivates the pyrrole fragment of indolizine **1** toward electrophilic attack. Thus, we were unable to realize the acylation reactions standard for indolizines (acetylation by acetic anhydride or benzoylation by benzoyl chloride) with compound **1**. The amino group at position 5 is also deactivated on account possibly not so much of conjugation but of steric factors. (According to X-ray crystallographic analysis, the unshared pair in the aminoindolizines is directed toward the side of the *peri*-located proton 3-H.) Moreover, the



The numbering of the atoms and the structure of compound **2**

TABLE 1. The Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Parameters ($U_{eq} \times 10^3$) in the Investigated Structure

Atom	*x*	*y*	*z*	U_{eq}
$C_{(1)}$	3360(7)	698(13)	3745(3)	23(2)
$C_{(2)}$	4426(7)	398(14)	3635(3)	23(2)
$C_{(3)}$	4817(7)	137(13)	3230(3)	24(2)
$C_{(4)}$	3962(7)	-1430(14)	3121(3)	30(2)
$C_{(5)}$	3910(8)	-3325(14)	2815(3)	31(3)
$C_{(6)}$	2962(8)	-4591(15)	2844(3)	38(3)
$C_{(7)}$	2046(8)	-4108(14)	3131(3)	35(3)
$C_{(8)}$	2060(7)	-2325(14)	3429(3)	30(2)
$N_{(9)}$	3071(5)	-1028(11)	3433(2)	26(2)
$C_{(10)}$	5084(6)	3103(11)	3940(3)	26(2)
$C_{(11)}$	4501(7)	4924(11)	4091(3)	32(3)
$C_{(12)}$	5110(6)	6386(14)	4414(3)	38(3)
$C_{(13)}$	6259(6)	6013(12)	4581(3)	36(3)
$C_{(14)}$	6861(7)	4212(12)	4444(3)	42(3)
$C_{(15)}$	6259(6)	2793(14)	4105(3)	41(3)
$N_{(1)}$	6901(7)	7512(13)	4938(3)	50(2)
$O_{(1)}$	6434(6)	9239(12)	4985(2)	71(2)
$O_{(2)}$	7789(6)	6928(10)	5178(2)	60(2)
$N_{(8)}$	1269(6)	-1609(11)	3763(2)	36(2)
$C_{(21)}$	443(8)	-24(16)	3552(4)	45(3)
$C_{(22)}$	-233(10)	878(18)	3975(4)	67(4)
$O_{(23)}$	-867(6)	-808(11)	4207(2)	71(2)
$C_{(24)}$	-91(11)	-2400(20)	4406(5)	73(4)
$C_{(25)}$	594(9)	-3346(17)	3982(4)	55(3)
$S_{(1)}$	5954(2)	561(4)	2858(1)	43(1)
$O_{(11)}$	5722(5)	-513(10)	2380(2)	52(2)
$O_{(12)}$	6192(5)	2762(11)	2845(2)	65(2)
$O_{(13)}$	7068(5)	-347(10)	3163(2)	48(2)
$C_{(26)}$	7112(10)	-2710(18)	3204(4)	58(3)
$H_{(1)}$	2850(50)	1140(90)	4020(20)	7(17)
$H_{(5)}$	4540(60)	-3600(110)	2590(20)	40(20)
$H_{(6)}$	2980(70)	-5490(130)	2620(30)	60(30)
$H_{(7)}$	1190(60)	-4630(110)	3120(20)	40(20)
$H_{(11)}$	3650(70)	5020(130)	3950(30)	70(30)
$H_{(12)}$	4750(80)	7360(150)	4560(30)	90(30)
$H_{(14)}$	7760(70)	3810(140)	4620(30)	80(30)
$H_{(15)}$	6660(80)	1540(170)	4030(30)	100(30)
$H_{(211)}$	-170(70)	-430(120)	3200(30)	60(20)
$H_{(212)}$	860(70)	1220(140)	3370(30)	70(30)
$H_{(221)}$	230(50)	1060(100)	4280(20)	20(20)
$H_{(222)}$	-850(60)	1360(110)	3740(20)	30(20)
$H_{(241)}$	-330(170)	-2700(300)	4560(70)	240(90)
$H_{(242)}$	410(50)	-1720(100)	4650(20)	13(19)
$H_{(251)}$	40(60)	-3910(120)	3690(30)	50(20)
$H_{(252)}$	1120(60)	-4000(120)	4240(30)	50(20)
$H_{(261)}$	6430(80)	-2970(130)	3450(30)	80(30)
$H_{(262)}$	6900(50)	-2950(100)	2870(20)	20(20)
$H_{(263)}$	7730(70)	-2770(130)	3490(30)	70(30)

5-amino group probably prevents attack by the electrophile at position 3 sterically. Thus, according to our preliminary data, trifluoroacetylation of indolizine **1** leads to a mixture of 1- and 3-trifluoroacetyl derivatives, whereas 2-arylindolizines usually form the 3-isomer exclusively [6]. Thus, position 3 of the indolizine ring (and the molecule as a whole) is deactivated toward methylation. However, it is not quite clear why in this case dimethyl sulfate exhibits untypical sulfonating characteristics.

TABLE 2. The Bond Lengths *d* (Å) in the Molecule of the Investigated Compound

Bond	*d*	Bond	*d*
$C_{(1)}$–$C_{(2)}$	1.352(10)	$C_{(12)}$–$C_{(13)}$	1.371(7)
$C_{(1)}$–$N_{(9)}$	1.382(9)	$C_{(13)}$–$C_{(14)}$	1.390(8)
$C_{(2)}$–$C_{(3)}$	1.420(10)	$C_{(13)}$–$N_{(1)}$	1.475(10)
$C_{(2)}$–$C_{(10)}$	1.499(10)	$C_{(14)}$–$C_{(15)}$	1.394(8)
$C_{(3)}$–$C_{(4)}$	1.404(11)	$N_{(1)}$–$O_{(2)}$	1.205(8)
$C_{(3)}$–$S_{(1)}$	1.709(8)	$N_{(1)}$–$O_{(1)}$	1.225(9)
$C_{(4)}$–$N_{(9)}$	1.378(10)	$N_{(8)}$–$C_{(21)}$	1.452(11)
$C_{(4)}$–$C_{(5)}$	1.434(11)	$N_{(8)}$–$C_{(25)}$	1.483(12)
$C_{(5)}$–$C_{(6)}$	1.354(11)	$C_{(21)}$–$C_{(22)}$	1.508(13)
$C_{(6)}$–$C_{(7)}$	1.372(12)	$C_{(22)}$–$O_{(23)}$	1.447(12)
$C_{(7)}$–$C_{(8)}$	1.364(11)	$O_{(23)}$–$C_{(24)}$	1.411(13)
$C_{(8)}$–$N_{(8)}$	1.382(10)	$C_{(24)}$–$C_{(25)}$	1.526(15)
$C_{(8)}$–$N_{(9)}$	1.418(10)	$S_{(1)}$–$O_{(12)}$	1.416(7)
$C_{(10)}$–$C_{(15)}$	1.391(7)	$S_{(1)}$–$O_{(11)}$	1.418(6)
$C_{(10)}$–$C_{(11)}$	1.402(7)	$S_{(1)}$–$O_{(13)}$	1.553(6)
$C_{(11)}$–$C_{(12)}$	1.393(8)	$O_{(13)}$–$C_{(26)}$	1.495(12)

TABLE 3. The Bond Angles ω (deg) in the Molecule of the Investigated Compound

Angle	ω	Angle	ω
$C_{(2)}$–$C_{(1)}$–$N_{(9)}$	108.0(7)	$C_{(12)}$–$C_{(13)}$–$C_{(14)}$	122.9(8)
$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	108.7(7)	$C_{(12)}$–$C_{(13)}$–$N_{(1)}$	120.1(7)
$C_{(1)}$–$C_{(2)}$–$C_{(10)}$	123.0(7)	$C_{(14)}$–$C_{(13)}$–$N_{(1)}$	116.9(7)
$C_{(3)}$–$C_{(2)}$–$C_{(10)}$	128.0(7)	$C_{(13)}$–$C_{(14)}$–$C_{(15)}$	117.1(8)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	106.6(7)	$C_{(10)}$–$C_{(15)}$–$C_{(14)}$	121.2(8)
$C_{(4)}$–$C_{(3)}$–$S_{(1)}$	123.3(6)	$O_{(2)}$–$N_{(1)}$–$O_{(1)}$	125.2(8)
$C_{(2)}$–$C_{(3)}$–$S_{(1)}$	129.4(6)	$O_{(2)}$–$N_{(1)}$–$C_{(13)}$	118.9(7)
$N_{(9)}$–$C_{(4)}$–$C_{(3)}$	106.9(7)	$O_{(1)}$–$N_{(1)}$–$C_{(13)}$	115.8(7)
$N_{(9)}$–$C_{(4)}$–$C_{(5)}$	118.7(8)	$C_{(8)}$–$N_{(8)}$–$C_{(21)}$	115.5(7)
$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	134.0(8)	$C_{(8)}$–$N_{(8)}$–$C_{(25)}$	113.0(7)
$C_{(6)}$–$C_{(5)}$–$C_{(4)}$	117.1(8)	$C_{(21)}$–$N_{(8)}$–$C_{(25)}$	108.0(7)
$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	123.6(9)	$N_{(8)}$–$C_{(21)}$–$C_{(22)}$	110.1(8)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	121.2(9)	$O_{(23)}$–$C_{(22)}$–$C_{(21)}$	109.4(9)
$C_{(7)}$–$C_{(8)}$–$N_{(8)}$	130.5(8)	$C_{(24)}$–$O_{(23)}$–$C_{(22)}$	110.7(8)
$C_{(7)}$–$C_{(8)}$–$N_{(9)}$	116.7(7)	$O_{(23)}$–$C_{(24)}$–$C_{(25)}$	111.1(9)
$N_{(8)}$–$C_{(8)}$–$N_{(9)}$	112.7(7)	$N_{(8)}$–$C_{(25)}$–$C_{(24)}$	107.8(9)
$C_{(4)}$–$N_{(9)}$–$C_{(1)}$	109.7(7)	$O_{(12)}$–$S_{(1)}$–$O_{(11)}$	118.1(4)
$C_{(4)}$–$N_{(9)}$–$C_{(8)}$	122.4(7)	$O_{(12)}$–$S_{(1)}$–$O_{(13)}$	102.8(4)
$C_{(1)}$–$N_{(9)}$–$C_{(8)}$	127.9(7)	$O_{(11)}$–$S_{(1)}$–$O_{(13)}$	110.7(4)
$C_{(15)}$–$C_{(10)}$–$C_{(11)}$	120.0(7)	$O_{(12)}$–$S_{(1)}$–$C_{(3)}$	108.9(4)
$C_{(15)}$–$C_{(10)}$–$C_{(2)}$	119.4(7)	$O_{(11)}$–$S_{(1)}$–$C_{(3)}$	109.0(4)
$C_{(11)}$–$C_{(10)}$–$C_{(2)}$	120.4(6)	$O_{(13)}$–$S_{(1)}$–$C_{(3)}$	106.7(4)
$C_{(12)}$–$C_{(11)}$–$C_{(10)}$	119.0(7)	$C_{(26)}$–$O_{(13)}$–$S_{(1)}$	115.2(6)
$C_{(13)}$–$C_{(12)}$–$C_{(11)}$	119.6(8)		

EXPERIMENTAL

Reaction of Indolizine 1 with Dimethyl Sulfate. Indolizine **1** (0.165 g, 0.51 mmol) was heated in solution of dimethyl sulfate (2.8 g) at 80°C for 36 h. The transparent solution was poured into ether (50 ml), the formed precipitate was filtered off, dried, and dissolved in concentrated sulfuric acid (4 ml), perchloric acid (5 ml) was

added, and the mixture was diluted to 80 ml with water. After the solution had cooled to 5°C the precipitated indolizine **2** was filtered off, and the single crystals were used for X-ray crystallographic analysis. Yield (before treatment with acid) 0.14 g (65%).

X-ray Crystallographic Analysis of Compound 2. The investigation was conducted on an automatic single-crystal CAD-4 diffractometer with $\lambda MoK\alpha$ radiation. The unit cell parameters were determined and refined in the range of 8-10 angles θ in 25 reflections. The crystals of the compound belong to the monoclinic syngony (space group $P2_1/n$) with unit cell parameters: a = 11.456(3), b = 6.309(3), c = 25.952(13) Å, β = 94.91(3)°, Z = 4. The structure was solved by direct methods using SHELXS-97 software [7] and refined by full-matrix least-squares treatment with the SHELXL-97 software [8] in anisotropic approximation for the sulfur atom. Other atoms were refined in isotropic approximation. All the hydrogen atoms were localized from a Fourier difference synthesis of electron density and were refined isotropically. The final R factor was 0.0705 in 903 unique reflections with $I > 2\sigma(I)$.

The position parameters of the atoms in the studied compound and the isotropic temperature parameters, equivalent to the corresponding anisotropic values, are given in Table 1. The interatomic distances and the bond angles are given in Tables 2 and 3 respectively. The three-dimensional arrangement of the atoms in the molecule and their numbering are shown in Fig. 1 [9].

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