REACTION OF INDOLIZINES WITH ELEMENTAL SULFUR

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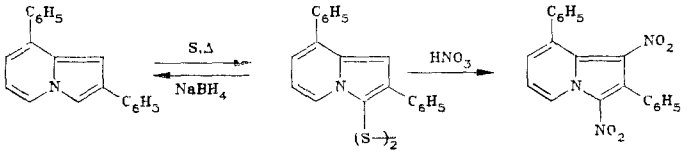
The fusion of 3,8-diphenyl-, 1,2-diphenyl-, and 6-methyl-2,7-diphenyl-indolizines with sulfur results in the formation of bis(indolizin-3-yl) disulfides with the respective substituents. Bis(2,8-diphenylindolizin-3-yl) disulfide is reduced to the original indolizine, and its treatment with nitric acid gives 2,8-diphenyl-1, 3-dinitroindolizine. Bis(dibenzo[b,g]indolizin-11-yl) disulfide is obtained from dibenzo[b,g]indolizine. The formation of the disulfides is apparently a general region of indolizines without substituents at C_3 or C_1 of the pyrrole ring. The structures of the disulfides obtained have been confirmed by data from x-ray diffraction analysis and NMR spectroscopy.

In the chemistry of heterocyclic compounds elemental sulfur is employed as a dehydrogenating agent and in syntheses of sulfur-containing heterocycles [1-5]. The literature, however, offers no data on the reaction of indolizines with elemental sulfur.

We found that the fusion of sulfur with 2,8-diphenylindolizine (I), which was obtained according to Chichibabin's method [6], results in the formation of garnet red crystals of bis(2,8-diphenylindolizin-3-yl) disulfie (II) as the main reaction product, which was isolated chromatographically with a 41% yield. The reaction is completed in 1 h with a ratio of the indolizine to sulfur ranging from 1:2 to 1:10.



I II III

The formation of disulfide II was confirmed by spectral data. The location of the sulfur at $C_{(3)}$ was established on the basis of PMR and ^{13}C NMR data (250 and 360 MHz for protons) in a comparison with the original indolizine I. The PMR spectrum of disulfide II does not show a signal for the 3-H proton, while the remaining indolizine protons are displayed and have chemical shifts differing only slightly from those for the original indolizine (see Experimental). Disulfide II is characterized by location of the signals of the protons of the phenyl substituent in the $C_{(2)}$ position at a higher field than in the case of the phenyl group at $C_{(8)}$ and broadening of these signals, as well as the signal from the 5-H proton to the point of the complete disappearance of the find structure upon cooling in $CDCl_3$ and $(CD_2)_2CO$ to −40 to −50°C (250 MHz). In the ^{13}C NMR spectrum (90,5 MHz, without decoupling from the protons at −50°C) the characteristic signals for disulfide II were assigned to the $C_{(3)}$—S (138.6 ppm) and $C_{(2)}$ (109.0 ppm) indolizine carbon atoms (in the original indolizine the $C_{(2)}$ signal appears at 129.5 ppm).

The structure of disulfide II was also proved with the aid of x-ray diffraction analysis.*

*The x-ray diffraction investigation was carried out by D. S. Yufit and Yu. T. Struchkov (the unit-cell parameters and the intensities of 3574 reflections were measured on a Hilger-Watts diffractometer).

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TABLE 1. Proton Chemical Shifts of Dibenzo[b,g]indolizine IX and Disulfide X

Compound	Chemical shifts, δ, ppm (in DMSO-d_6)									
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H
IX	8,13	7,3	7,3	7,80	6,87	8,54	8,27	7,5	7,5	7,72
X	8,66	6,40	7,18	7,24	6,62	8,07	7,81	7,24	7,26	7,62
Δδ*	−0,53	+0,9	+0,12	+0,46	+0,25	+0,47	+0,46	+0,26	+0,24	+0,10

*Here Δδ is the change in the shielding upon the transition from IX to X, ppm.

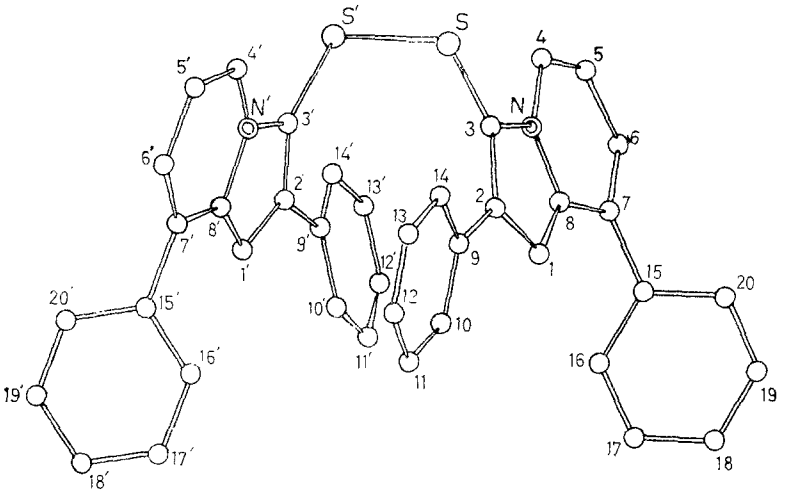
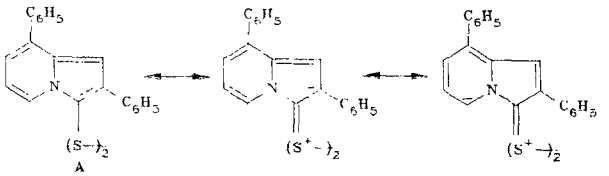


Fig. 1. Geometry of the bis(2,8-diphenylindolizin-3-yl) disulfide molecule (II).

The value of the N—C—S—S angle of torsion (~80°) attests to the axial conformation of the two halves of this molecule. The length of the C—S bond, which is equal to 1.71 Å, is smaller than in aliphatic disulfides (~1.82 Å) and coincides with the length of the bond in thiophene and the C=S bond in thiourea [7]. The increased multiplicity of the C—S bond in disulfide II is confirmed by the presence in its UV spectrum of a long-wavelength absorption maximum at 450 nm, which corresponds to zwitterionic form B or C.

When the disulfide forms, the PMR spectra do not reveal any increase in the shielding of the 5-H proton, while the ^{13}C NMR spectra displays strong shielding of the $C_{(2)}$ carbon (Δδ = 20.5 ppm relative to the original compound), which is an indication of the absolute predominance of zwitterionic form B.



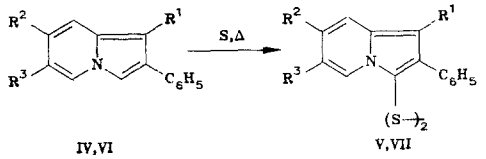
A

The unusual elongation of the S—S bond to 2.141 Å is consistent with the significant contribution of the zwitterionic structure and is apparently a consequence of the repulsion between the positive charges of the sulfur atoms. The stretching of the S—S bond is also caused by the decrease in the C—S—S—C angle of torsion (to 62.8°), whose significant deviation from the optimal value (90°) is apparently attributable to the interaction through space between the phenyl substituent at $C_{(2)}$ (an acceptor) in one half of the molecule and the pyrrole ring (a donor) in the other half. These two fragments of the disulfide molecule are oriented almost parallel to one another (Fig. 1). The dihedral angle between them is ~7.9°, the interplanar distance is ~3.8 Å, and they form a twin charge-transfer (CT) complex.

The phenyl rings at $C_{(8)}$ are rotated through a 45.6° angle relative to the planar indolizine bicycle, and the phenyl substituents at $C_{(2)}$ are rotated through a significantly smaller angle of ~24.3° (as a consequence of the formation of the CT complex).

The treatment of disulfide II with concentrated nitric acid at 20°C is accompanied by considerable resinification. 2,8-Diphenyl-1,3-dinitroindolizine (III) was recovered from the reaction mixture with a 17% yield. Disulfide II readily undergoes desulfurization when it is reacted with sodium borohydride in methanol, original indolizine I being regenerated with a high yield.

The reaction resulting in the formation of the disulfide discovered here is apparently a general reaction for indolizine systems. This was confirmed by the conversion of 1,2-diphenylindolizine (IV) [8] into bis(1,2-diphenylindolizin-3-yl) disulfide (V) and of 6-methyl-2,7-diphenylindolizine (VI) [9] into bis (6-methyl-2,7-diphenylindolizin-3-yl)disulfide (VII) under similar conditions.



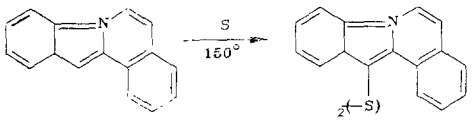
IV,VI V,VII

IV, V $R^1=C_6H_5$, $R^2=R^3=H$; VI, VII $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$

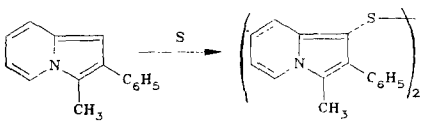
The formation of disulfides at the $C_{(3)}$ position attests to the higher reactivity of this position in comparison to the $C_{(1)}$ position.

It was shown in the case of the reaction of 3,7-dimethyl-1,2-diphenylindolizine (VIII) with sulfur that a disulfide does not form when the $C_{(3)}$ and $C_{(1)}$ positions are occupied (the original compound VIII is recovered with a 73% yield).

The fusion of dibenzo[b,g]indolizine (IX) and 3-methyl-2-phenyl-indolizine (XI) with sulfur gave bis(dibenzo[b,g]indolizin-11-yl) disulfide (X) and bis(3-methyl-2-phenylindolizin-1-yl) disulfide (XII), respectively, with yields up to 20%. In these cases, the reaction takes place at the $C_{(1)}$ position of the indolizine fragment.



IX X



XI XII

An analysis of the PMR spectra of disulfide X at 250 MHz with the use of double resonance made it possible to assign the signals of all the protons and to detect the critical changes in their chemical shifts in comparison to the original dibenzo[b,g]indolizine IX (see Table 1).

As is seen from Table 1, the value of $\Delta\delta$ for the adjacent 1-H and 2-H protons in disulfide X reached a record value of 2.26 ppm (for comparison, it should be noted that its value for α and β protons in pyridine rings usually exceeds 1.5 ppm). Such strong changes in the chemical shifts upon the transition from the original compound IX to the sulfide X may be attributed to the location of a negative charge in the zwitterionic structure on the benzene ring of the quinoline fragment (the strong shielding of 2-H and 4-H), as well to the mutual effects of the magnetic anisotropy of the two identical planar polynuclear aromatic fragments joined by the disulfide "bridge" (the shielding of 7-H and 6-H and the dishielding of 1-H).

The formation of a CT complex apparently strongly hinders the intramolecular rotation in the liquid phase. This is reflected in the broadening of the NMR signals of the protons and carbon-13, which was observed in the case of disulfides II and V and was attributed to the hindered rotation of the phenyl group in the $C_{(2)}$ position, especially at reduced temperatures. In disulfide VII the rotation of the other phenyl group at $C_{(7)}$, which is adjacent to a methyl substituent, is apparently hindered, causing the broadening of all the NMR signals even under normal conditions (a solution in $CDCl_3$, 20-60°C). This disulfide at 360 MHz or a high-resolu-

tion carbon-13 spectrum at 90.5 MHz. A comparatively narrow signal was observed only for the methyl group.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra (TMS served as an internal reference) were recorded on WH-360 and WM-250 spectrometers with superconducting magnets for the protons at 360 and 250 MHz and for ^{13}C at 90.5 and 63 MHz, respectively. The mass spectra were obtained on an MKh-1303 spectrometer at 70 V with direct admission into the source. The UV spectra were recorded on an Hitachi spectrophotometer in ethanol, and the IR spectra were recorded on a UR-20 instrument in KBr tablets.

2,8-Diphenylindolizine (I). A 2.2-g proton (6 mmole) of 1-phenacyl-2-methyl-3-phenylpyridinium bromide in 50 ml of a 40% potassium carbonate solution is boiled for 3 h. The precipitate is separated, washed with 100 ml of water, dried, and crystallized from a 1:1 hexane–ether mixture. This gives 1.3 g (81%) of indolizine I in the form of pale yellow crystals with mp 134-135°C. PMR spectrum ($CDCl_3$): 6.82 (s, 1-H), 7.50 :s, 3-H;, 7.66 (d. d, 5-H), 6.40 (t, 6-HO, 6.58 (d. d, 7-H), 7.1-7.4 ppm (10 H, m, phenyl protons). Spin–spin coupling constant: $J_{56} = J_{67} = 6.7$ Hz, $J_{57} = 1$ Hz. ^{13}C NMR spectrum ($CDCl_3$): 97.0 ($C_{(1)}$), 129.5 ($C_{(5)}$), 110.7 ($C_{(3)}$), 124.1 ($C_{(5)}$, 110.7 ($C_{(6)}$), 116.9 ($C_{(7)}$), 132.6 ($C_{(8)}$), 132.8 ppm $C_{(9)}$). Found: C, 89.4; H, 5.9; N. 5.1%: M^+ 269. Calculated for $C_{20}H_{15}N$: C, 89.2; H, 5.5; N, 5.21; M 269.

Bis(2,8-diphenylindolizin-3-yl) Disulfide (II). A mixture of 1 g (3.7 mmole) indolizine I and 0.24 g (7.5 mmole) of crystalline sulfur is heated for 1 h at 150-160°C in a nitrogen atmosphere. At 145-150°C the reaction mass becomes dark red; hydrogen sulfide is evolved. The residue, which hardens after cooling, is dissolved in 3 ml of benzene and chromatographed on aluminum oxide (H = 30 cm, d = 1.9 cm, a 1:1 mixture of ether with hexane as the eluent). This gives 0.45 g (40.5%) of disulfide II in the form of garnet red crystals with a flat prismatic shape, mp 167-168°C (from 1:1 ether–hexame mixture). UV spectrum, λ_{max} (log ε): 262 (4.42), 320 (3.84), sh, 380 (3.46), 450 nm (3.50). IR spectrum: 454 (C–S–S–C), 697, 753 (C–S), 1338, 1370, 1457 cm^{-1}. Mass spectrum, m/z (%): 600 (3), 302 (15), 300 (10), 269 (100), 256 (21), 192 (65), 158 (51), 128 (56). PMR spectrum ($CDCl_3$): 6.82 (s, 1-H), 7.86 (d. d, 5-H), 6.66 (t, 6-H), 6.54 (d. d, 7-h), 6.9-7.1 ppm (m, 5-h, C_6H_5 at $C_{(2)}$), 7.4-7.6 ppm (5H, C_6H_5 protons at $C_{(8)}$). Spin–spin coupling constants: $J_{56} = J_{67} = 6.7$ Hz, $J_{57} = 1$ Hz. ^{13}C NMR spectrum ($CDCl_3$): 101.6 ($C_{(1)}$, 109.0 ($C_{(2)}$), 138.6 ($C_{(3)}$), 123.3 ($C_{(5)}$), 111.4 ($C_{(6)}$), 120.4 ($C_{(7)}$), 134.7 ($C_{(8)}$), 132.4 ppm ($C_{(9)}$). Found: C, 79.7; H, 5.0; N, 4.8%. Calculated for $C_{40}H_{28}N_2S_2$: C, 80.1; H, 4.7; M. 4.7%; M 600.

A solution of 0.15 g (0.25 mmole) of disulfide II in 30 ml of ethanol is given an addition of 0.2 g (4.2 mmole) of sodium borohydride over the course of 30 min with stirring. The mixture is stirred for 30 min at 20°C and then for 1 h at the boiling point. It is then cooled and diluted with 30 ml of water. The precipitate is separated and crystallized from ether. This gives 0.96 mg (72%) of compound I, according to the mp (134-135°C), the mass spectrum, and the PMR spectrum of identical 2,8-diphenylindolizine (I).

1.3-Dinitro-2,8-diphenylindolizine (III). A 1-g portion (1.6 mmole) of disulfide II is gradually added to 20 ml of conc. HNO_3 at 20°C with stirring. The mixture is neutralized by a 20% sodium hydroxide solution and extracted with chloroform. The extract is concentrated to 3 ml and chromatographed on aluminum oxide (H = 25 cm, d = 2 cm, 1:1 ether–hexane as the eluent). This gives 0.1 g (17%) of indolizine III in the form of light yellow crystals, mp 226-228°C (from a 1:1 ether–hexane mixture). PMR spectrum (DMSO-d_6): 9.67 (d. d, 5-H), 7.64 (t, 6-H), 7.72 (d. d, 7-H), 7.4-7.6 ppm (m, 10 H, phenyl protons). Spin–spin coupling constants: $J_{56} = 7.0$, $J_{57} = 1.2$, $J_{67} = 17.2$ Hz. Mass spectrum, m/z (%): 359 (100), 342 (7), 313 (11), 267 (30), 254 (56). IR spectrum: 1530, 1355 cm^{-1}. Found: C, 66.6; H, 4.0; N, 11.6%. Calculated for $C_{20}H_{13}N_3O_4$: C, 66.9; H, 3.61 N, 11.7%; M 359.

Bis(1,2-diphenylindolizin-3-yl) Disulfide (V) and Bis(6-methyl-2,7-diphenylindolizin-3-yl) Disulfide (VII). The reaction of indolizines IV and VI with sulfur and the isolation of the reaction products are carried out as in the case of the synthesis of II. Disulfide V is obtained from indolizine IV with a 38% yield in the form of red crystals, mp 103-105°C (from a 1:1 ether-hexane mixture). PMR spectrum ($CDCl_3$): 7.95 (br. d, 5-H), 6.42 (t, 6-H), 6.79 (d. d. d, 7-h), 7.42 (d. t, 8-H), 6.6-7.3 ppm (10 H, complex spectrum of phenyl protons). Spin–spin coupling constants: $J_{56} = J_{67} = 6.7$ Hz, $J_{57} = J_{58} = 0.8$ Hz, $J_{68} = 1.3$ Hz, $J_{78} = 9$ Hz.

Mass spectrum, m/z (%): 600 (20), 301 (8), 269 (100), 158 (40). UV spectrum, λ_{max} (log ε): 252 (4.40), 310 (3.97) sh, 380 (3.52), 450 nm (3.50). Found: C, 79.8; H, 4.9; N, 4.2%. Calculated for $C_{40}H_{28}N_2S_2$: C, 80.1; H, 4.7; N, 4.7%; M 600.

Disulfide VII is obtained from indolizine VI. The yield is 52%, dark red crystals, mp 278-280°C. PMR spectrum (360 MHz, $CDCl_3$): 6.7-7.5 (13H, broad signal), 2.12 ppm (br. s, 3H, 6-CH_3). ^{13}C NMR spectrum ($CDCl_3$, 90.5 MHz): 18.0 (6-CH_3), 101, 112, 117, 121, 123, 127-130, 131, 139 ppm (broad signals). UV spectrum, λ_{max} (log ε): 260 (4.80), 380-440 nm (4.10) broad band. Mass spectrum, m/z (%): 628 (1), 343 (4), 315 (10), 314 (9), 283 (100). Found: C, 80.1; H, 4.7; N, 5.1%. Calculated for $C_{42}H_{32}N_2S_2$: C, 80.3; H, 5.1; N, 4.5%; M 628.

3,7-Dimethyl-1,2-diphenylindolizine (VIII) is obtained from 1-(α-methylphenacyl)-4-methyl-2-benzylpyridinium bromide in analogy to the synthesis of indolizine I. Light brown crystals, 49% yield, mp 143-144°C (from ethanol). PMR spectrum (DMSO-d_6): 7.87 (d, 5-H), 6.47 (d. d, 6-H), 7.19 (d, 8-H), 7.0-7.3 (m, 10 H, phenyl protons), 2.24 (s, 3H, 7-CH_3), 2.36 ppm (s, 3H, 3-CH_3). Spin–spin coupling constants: J_{56} = 6.7, J_{68} = 1.5 Hz. Mass spectrum, m/z (%): 297 (100), M^{2+} 148.5 (10). UV spectrum, λ_{max} (log ε): 254 (4.70), 280 (4.30) sh, 314 (4.02), 324 (4.04), 374 nm (3.58). Found: C, 88.8; H, 6.3; N, 4.6%. Calculated for $C_{22}H_{19}N$: C, 88.9; H, 6.4; N, 4.7%; M 297.

Bis(dibenzo[b,g]indolizin-11-yl) Disulfide (X). This compound is obtained similarly to disulfide II from 0.18 g (0.8 mmole) of dibenzoindolizine IX and 0.05 g (1.6 mmole) of sulfur. This gives 0.04 g (20%) of bright red crystals of disulfide X, mp 210-211°C (from a 1:1 ether–hexane mixture). Mass spectrum, m/z (%): 496 (2), 249 (12), 248 (10), 217 (100), 189 (12), 108.5 (24). Found: C, 77.1; H, 4.2; N, 5.6%. Calculated for $C_{32}H_{20}N_2S_2$: C, 77.4; H, 4.0; N, 5.6%; M 496.

Bis(2-methyl-3-phenylindolizin-1-yl) Disulfide (XII). This compound is obtained similarly to disulfide II from 0.5 g (2.4 mole) of indolizine XI [10] with a 5% yield, yellow crystals, mp 103-104°C. PMR spectrum of the original indolizine XI (DMSO-d_6): 2.51 (s, CH_3). 6.55 ppm (s, 1-H). Protons of the pyridine ring – and ABCD system: 7.96 (5-H), 6.61 (6-H), 6.68 (7-H), 7.41 ppm (8-H); J_{56} = J_{67} = 6.7, J_{78} = 8.5, J_{57} = 1.2, J_{58} = 1.0, J_{68} = 1.5 Hz. Phenyl protons: 7.17 (t. t, 1H, 4'-H), 7.64 (m, 2H, 2',6'-H), 7.32 ppm (m, 2H, 3',5'-H). PMR spectrum of disulfide XII ($CDCl_3$): 2.33(s, CH_3). Protons of the pyridine ring – an ABCD system: 7.63 (5-H), 6.58 (6-H), 6.52 (7-H), 6.98 ppm (8-H); J_{56} = J_{67} = 6.5, J_{78} = 8.5, J_{68} = 1.6 Hz. Phenyl protons: 7.1-7.5 ppm (m). Mass spectrum, m/z (%): 476 (3), 239 (100), 238 (53). Found: C, 75.2; H, 5.3; N, 5.8%. Calculated for $C_{30}H_{24}N_2S_2$: C, 75.6; H, 5.0; N, 5.9%; M 476.

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