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HETEROCYCLIC COMPOUNDS WITH A BRIDGE NITROGEN ATOM. 14*. CYCLOADDITION OF ACETYLENE-DICARBOXYLIC ACID ESTER TO 2-CHLORO-N-PHENACYLPYRIDINIUM YLIDE. CRYSTAL STRUCTURE OF DIMETHYL ESTER OF 5-CHLORO-3-(*p*-NITROBENZOYL)-INDOLIZINE-1,2-DICARBOXYLIC ACID*[2]

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Derivative of 5-chloroindolizine is formed in the reaction of 2-chloro-1-(p-nitrophenacyl)pyridinium ylide with acetylenedicarboxylic acid dimethyl ester, the structure of which was demonstrated by X-ray diffraction analysis. According to data of ^{1}H NMR and mass spectra indolizine obtained undergoes an unusual intramolecular cyclization with the formation of benz[e]cycl[3.3.2]azine nucleus.

Keywords: benz[*e*]cycl[3.3.2]azine, acetylenedicarboxylic acid dimethyl ester, condensed heterocycles, indolizine, pyridine, pyridinium ylide, pyrrole, 5-chloroindolizine, 2-chloro-1-(*p*-nitrophenacyl)-pyridinium bromide, intramolecular cyclization of 3-aroyl-5-chloroindolizines, 1,3-dipolar cycloaddition, X-ray diffraction analysis.

Recently we discovered new interesting conversions of 2-halo-N-phenacylpyridinium salts by the action of potassium thiocyanate (with the formation of 3-acyl-2-aminothiazolo[3,2-*a*]pyridinium derivatives [2]) and by reaction with secondary amines (with the formation of oxazolyldienes [3,4]). In the latter case only the intermediate formation of pyridinium ylide **A** may be assumed to explain the mechanism of forming the oxazole nucleus from pyridine ring. Intermediate **A** undergoes closure of the oxazole ring and fission of the pyridine ring.

A similar ylide is probably the intermediate in the conversion of 2-chloro-N-phenacylpyridinium salts into 1-nitroindolizines by the action of ω-nitrostyrenes [5]. In this reaction ylides **A** generated by the action of base undergo Michael addition to the activated multiple bonds with subsequent intramolecular closure of the pyrrole fragment and oxidative aromatization.

* For Part 13 see [1].

*[2] Dedicated to the memory of A. N. Kost in connection with his birthday 85 years ago.

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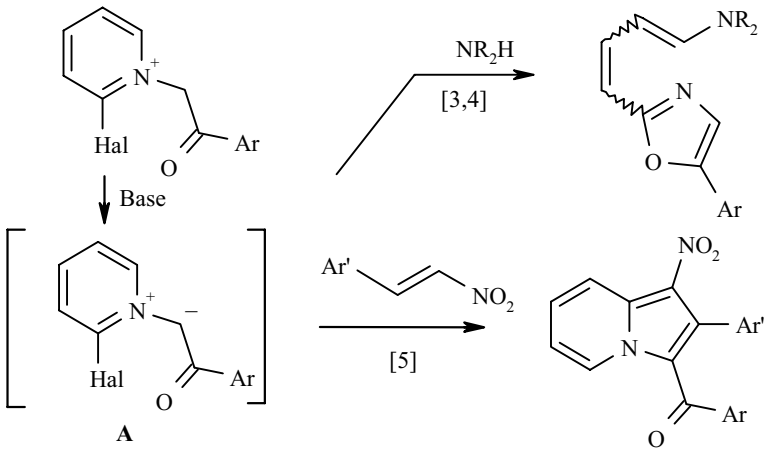
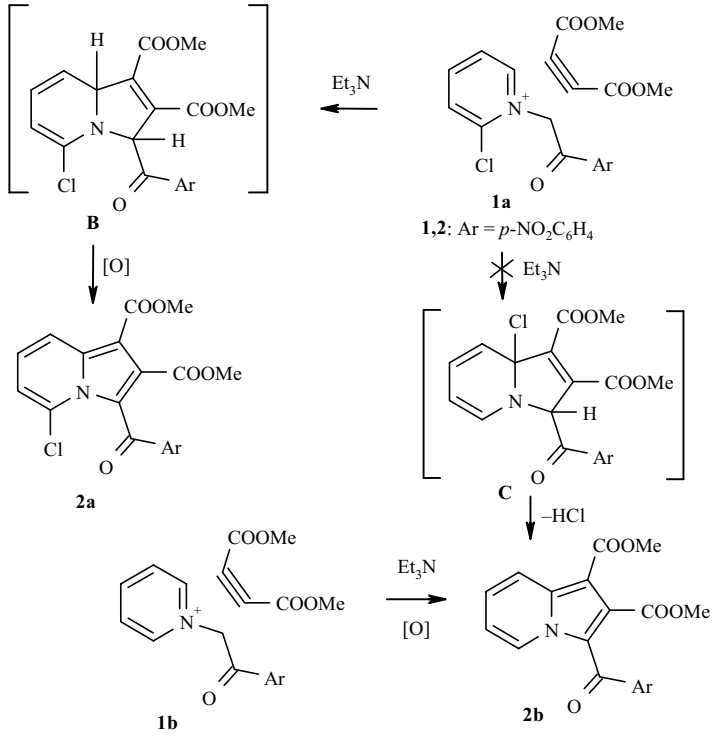


Ylides of type **A** generated from 2-halopyridinium salts should possibly react by 1,3-dipolar cycloaddition. Such reactions of ylides, obtained from the usual N-phenacylpyridinium salts, are used widely in organic synthesis [6]. However, investigations in this area are limited to a single publication [7], where the possibility of carrying out cycloaddition for 2-bromo-N-phenacylpyridinium ylide was demonstrated.

We have found that the 3-acyl-5-chloroindolizine derivative **2a** is formed in the reaction of 2-chloro-1-(*p*-nitrophenacyl)pyridinium bromide (**1a**) with acetylenedicarboxylic acid dimethyl ester in the presence of triethylamine:



The structure of indolizine **2a** was confirmed by spectral data (^{1}H NMR, mass spectra) and X-ray diffraction analysis (see Fig. 1, Tables 1-3). According to the X-ray diffraction data the ester group at position 1 in the **2a** molecule lies in the plane of the indolizine bicycle, while the same group at position 2 is turned by 84° relative to this plane. The carbonyl fragment of the benzoyl group is turned by 56° and the phenyl fragment by 35° relative to the indolizine plane. The angle between the nitro group and the phenyl ring is 13°.

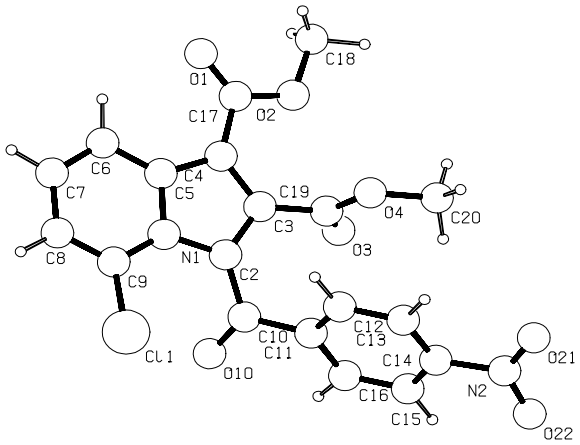


Fig. 1. Numbering of atoms and structure of compound **2a**.

Evidently the mechanism of conversion necessarily implies the formation of ylide of type **A**. Further 1,3-dipolar cycloaddition with the participation of such an ylide should proceed in two ways, through the cycloadducts **B** or **C**, leading to formation of indolizine **2a** or **2b** respectively. As is seen attack of the dipolarophile occurs leading to the cycloadduct **B**. Subsequent aromatization of the molecule to indolizine is of an oxidative character. In this way not even traces of indolizine **2b** are formed in the reaction mixture (compound **2b** should be obtained by the nonoxidative aromatization of cycloadduct **C**). To confirm this we carried out a directed synthesis of indolizine **2b** by cycloaddition to the "usual" pyridinium ylide obtained from salt **1b** and the substance isolated was used as a chromatographic and spectral standard.

TABLE 1. Coordinates of Atoms ($\times 10^4$) and Equivalent Isotropic Parameters ($U_{eq} \times 10^3$) in the Investigated Structure **2a**

Atom	*x*	*y*	*z*	U_{eq}
1	2	3	4	5
$Cl_{(1)}$	2066(2)	5672(1)	5206(1)	59(1)
$N_{(1)}$	2269(4)	8331(3)	4743(2)	40(1)
$C_{(2)}$	3042(5)	8347(3)	3672(2)	37(1)
$C_{(3)}$	3659(5)	9591(3)	3298(2)	38(1)
$C_{(4)}$	3260(5)	10365(3)	4121(3)	40(1)
$C_{(5)}$	2389(5)	9573(3)	5024(3)	42(1)
$C_{(6)}$	1658(5)	9805(5)	6075(3)	53(1)
$C_{(7)}$	905(6)	8810(5)	6786(3)	61(1)
$C_{(8)}$	951(5)	7532(5)	6521(3)	59(1)
$C_{(9)}$	1682(5)	7287(4)	5517(3)	49(1)
$C_{(10)}$	2762(5)	7410(3)	2995(2)	42(1)
$O_{(10)}$	1230(4)	6973(3)	3064(2)	59(1)
$C_{(11)}$	4403(5)	7075(3)	2145(2)	39(1)
$C_{(12)}$	6297(5)	6967(3)	2310(3)	47(1)
$C_{(13)}$	7823(6)	6720(3)	1499(3)	49(1)
$C_{(14)}$	7387(5)	6585(3)	532(3)	46(1)
$C_{(15)}$	5541(6)	6624(4)	364(3)	51(1)
$C_{(16)}$	4044(6)	6860(3)	1176(3)	46(1)
$C_{(17)}$	3520(5)	11774(4)	4075(3)	47(1)

TABLE 1 (continued)

1	2	3	4	5
$O_{(2)}$	4104(4)	12334(2)	3073(2)	60(1)
$C_{(18)}$	4325(10)	13753(4)	2909(5)	76(2)
$C_{(19)}$	4416(6)	10057(3)	2158(3)	44(1)
$O_{(3)}$	3433(4)	10400(3)	1482(2)	68(1)
$O_{(4)}$	6324(4)	9989(2)	1988(2)	51(1)
$C_{(20)}$	7258(9)	10337(6)	903(4)	73(1)
$N_{(2)}$	8964(6)	6442(3)	-367(3)	62(1)
$O_{(21)}$	10544(5)	6689(4)	-307(3)	93(1)
$O_{(22)}$	8627(5)	6073(3)	-151(2)	91(1)
$H_{(6)}$	1748(50)	10700(37)	6208(27)	61(12)
$H_{(7)}$	408(57)	9019(39)	7493(32)	82(13)
$H_{(8)}$	579(52)	6772(39)	7087(30)	72(12)
$H_{(12)}$	6568(52)	7047(34)	2991(28)	65(12)
$H_{(13)}$	9193(57)	6629(36)	1603(28)	72(12)
$H_{(15)}$	5225(45)	6480(31)	-335(26)	52(10)
$H_{(18A)}$	5230(88)	13982(60)	2067(50)	177(25)
$H_{(18B)}$	5029(72)	13924(48)	3406(39)	107(18)
$H_{(18C)}$	3166(77)	14236(52)	2897(40)	116(21)
$H_{(20A)}$	6592(81)	10024(54)	410(42)	138(23)
$H_{(20B)}$	7281(66)	11237(51)	777(36)	101(18)
$H_{(20C)}$	8695(88)	10035(52)	926(40)	138(22)

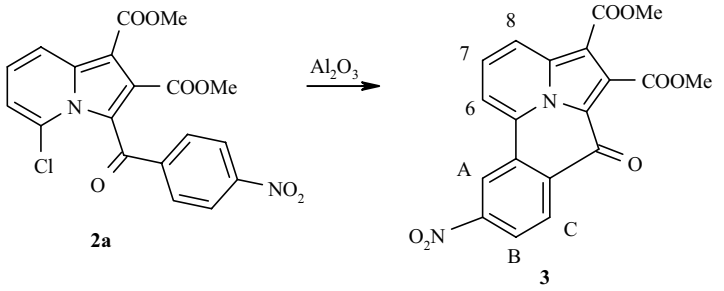
Derivatives of 5-chloroindolizine subclass have not been described. Comparison of the ^{1}H NMR spectra of indolizines **2a,b** showed that the chlorine atom in position 5 has an insignificant effect on the chemical shift of the protons of the pyridine fragment. A special feature of the mass spectral behavior of indolizine **2a** is the intense [M-HCl] peak. In addition a sample of indolizine **2b** purified by TLC, according to data of chromato-mass spectrometry, includes a compound containing one molecule of HCl less than the initial substance. It turned out that indolizine **2b** on extended storage (in the dry state or in chloroform solution), but also under the action of aluminum oxide, is converted into a compound to which the tetracyclic structure **3** may be assigned.

TABLE 2. Bond Lengths (*l*) in the **2a** Molecule

Bond	*l*, Å	Bond	*l*, Å
$Cl_{(1)}$–$C_{(9)}$	1.729(4)	$C_{(11)}$–$C_{(16)}$	1.391(4)
$N_{(1)}$–$C_{(9)}$	1.382(4)	$C_{(11)}$–$C_{(12)}$	1.392(5)
$N_{(1)}$–$C_{(2)}$	1.392(4)	$C_{(12)}$–$C_{(13)}$	1.387(5)
$N_{(1)}$–$C_{(5)}$	1.394(4)	$C_{(13)}$–$C_{(14)}$	1.383(5)
$C_{(2)}$–$C_{(3)}$	1.380(4)	$C_{(14)}$–$C_{(15)}$	1.369(5)
$C_{(2)}$–$C_{(10)}$	1.465(4)	$C_{(14)}$–$N_{(2)}$	1.468(4)
$C_{(3)}$–$C_{(4)}$	1.398(4)	$C_{(15)}$–$C_{(16)}$	1.374(5)
$C_{(3)}$–$C_{(19)}$	1.495(4)	$C_{(17)}$–$O_{(1)}$	1.202(4)
$C_{(4)}$–$C_{(5)}$	1.397(4)	$C_{(17)}$–$O_{(2)}$	1.340(4)
$C_{(4)}$–$C_{(17)}$	1.463(5)	$O_{(2)}$–$C_{(18)}$	1.450(5)
$C_{(5)}$–$C_{(6)}$	1.411(5)	$C_{(19)}$–$O_{(3)}$	1.197(4)
$C_{(6)}$–$C_{(7)}$	1.346(5)	$C_{(19)}$–$O_{(4)}$	1.329(4)
$C_{(7)}$–$C_{(8)}$	1.397(6)	$O_{(4)}$–$C_{(20)}$	1.446(5)
$C_{(8)}$–$C_{(9)}$	1.358(5)	$N_{(2)}$–$O_{(21)}$	1.211(5)
$C_{(10)}$–$O_{(10)}$	1.224(4)	$N_{(2)}$–$O_{(22)}$	1.222(4)
$C_{(10)}$–$C_{(11)}$	1.489(4)		

TABLE 3. Bond Angles (ω) in the **2a** Molecule

Angle	ω, deg.	Angle	ω, deg.
$C_{(9)}$–$N_{(1)}$–$C_{(2)}$	130.8(3)	$C_{(2)}$–$C_{(10)}$–$C_{(11)}$	116.7(3)
$C_{(9)}$–$N_{(1)}$–$C_{(5)}$	120.0(3)	$C_{(16)}$–$C_{(11)}$–$C_{(12)}$	119.5(3)
$C_{(2)}$–$N_{(1)}$–$C_{(5)}$	108.7(3)	$C_{(16)}$–$C_{(11)}$–$C_{(10)}$	119.7(3)
$C_{(3)}$–$C_{(2)}$–$N_{(1)}$	107.2(3)	$C_{(12)}$–$C_{(11)}$–$C_{(10)}$	120.8(3)
$C_{(3)}$–$C_{(2)}$–$C_{(10)}$	124.4(3)	$C_{(13)}$–$C_{(12)}$–$C_{(11)}$	120.6(4)
$N_{(1)}$–$C_{(2)}$–$C_{(10)}$	126.3(3)	$C_{(14)}$–$C_{(13)}$–$C_{(12)}$	117.6(4)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	109.3(3)	$C_{(15)}$–$C_{(14)}$–$C_{(13)}$	122.9(3)
$C_{(2)}$–$C_{(3)}$–$C_{(19)}$	123.9(3)	$C_{(15)}$–$C_{(14)}$–$N_{(2)}$	118.2(4)
$C_{(4)}$–$C_{(3)}$–$C_{(19)}$	126.5(3)	$C_{(13)}$–$C_{(14)}$–$N_{(2)}$	118.8(4)
$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	107.1(3)	$C_{(14)}$–$C_{(15)}$–$C_{(16)}$	118.8(4)
$C_{(3)}$–$C_{(4)}$–$C_{(17)}$	128.6(3)	$C_{(15)}$–$C_{(16)}$–$C_{(11)}$	120.4(4)
$C_{(5)}$–$C_{(4)}$–$C_{(17)}$	124.2(3)	$O_{(1)}$–$C_{(17)}$–$O_{(2)}$	123.6(3)
$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	107.7(3)	$O_{(1)}$–$C_{(17)}$–$C_{(4)}$	125.7(4)
$N_{(1)}$–$C_{(5)}$–$C_{(6)}$	119.1(3)	$O_{(2)}$–$C_{(17)}$–$C_{(4)}$	110.7(3)
$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	133.2(3)	$C_{(17)}$–$O_{(2)}$–$C_{(18)}$	116.4(3)
$C_{(7)}$–$C_{(6)}$–$C_{(5)}$	119.1(4)	$O_{(3)}$–$C_{(19)}$–$O_{(4)}$	124.7(3)
$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	121.2(4)	$O_{(3)}$–$C_{(19)}$–$C_{(3)}$	124.2(3)
$C_{(8)}$–$C_{(9)}$–$N_{(1)}$	119.6(4)	$O_{(4)}$–$C_{(19)}$–$C_{(3)}$	111.1(3)
$C_{(8)}$–$C_{(9)}$–$Cl_{(1)}$	121.3(3)	$C_{(19)}$–$O_{(4)}$–$C_{(20)}$	116.9(4)
$N_{(1)}$–$C_{(9)}$–$Cl_{(1)}$	118.9(3)	$O_{(21)}$–$N_{(2)}$–$O_{(22)}$	122.4(4)
$O_{(10)}$–$C_{(10)}$–$C_{(2)}$	122.9(3)	$O_{(21)}$–$N_{(2)}$–$C_{(14)}$	119.3(4)
$O_{(10)}$–$C_{(10)}$–$C_{(11)}$	120.2(3)	$O_{(22)}$–$N_{(2)}$–$C_{(14)}$	118.3(4)



The structure of compound **3** was confirmed by ^{1}H NMR spectra. The mechanism of this unusual cyclization will form the subject of a separate publication.

EXPERIMENTAL

Reaction of Pyridinium Ylide Salt 1a with Acetylenedicarboxylic Acid Dimethyl Ester. Salt **1a** (0.106 g, 0.3 mmol) was suspended in acetonitrile (4 ml), acetylenedicarboxylic acid dimethyl ester (0.078 g, 0.55 mmol), and then triethylamine (0.06 g, 0.6 mmol) were added dropwise. After shaking the mixture for 10 min the solid had dissolved, and the solution had acquired a red-brown color. The mixture was left for 1 day, evaporated, and chromatographed on a silica plate (eluent ethyl acetate–petroleum ether, initial ratio 1 : 1, then 1 : 2, then 1 : 1). The plate with the substance was dried for 12 h, and the substance was washed off the sorbent with ethyl acetate. Indolizine **2a** (0.063 g, 54%) was isolated, yield after recrystallization from benzene was 17%; mp 178-180°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, J (Hz): 8.34 (3H, m, p-$NO_2C_6H_4$, 8-H); 8.15 (2H, m, p-$NO_2C_6H_4$); 7.50 (1H, dd, 7-H); 7.31 (1H, d, J_{67} = 7.5, 6-H); 3.86 [3H, s, 1(2)-COOMe]; 3.47 [3H, s, 2(1)-COOMe].

3-Oxo-3H-6-nitrobenz[e]cycl[3.3.2]azine-1,2-dicarboxylic Acid Dimethyl Ester (3). Indolizine **2a** (20 mg) was dissolved in chloroform (30 ml) at boiling, aluminum oxide (acid, Brockmann grade III) (0.5 g) was added, and the mixture left in an open vessel. After evaporation to dryness the residue was stored for 14 d, checking for the final disappearance of the initial indolizine by TLC. The mixture was washed with chloroform (20 ml) and the obtained solution evaporated. Cyclazine **3** (0.017 g, 90%) was isolated; mp 353-355°C, R_f 0.42 (Silufol, benzene–acetone, 10 : 1). For comparison R_f of the initial indolizine 0.24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm, J (Hz): 9.33 (1H, br. s, H_A); 8.30 (1H, d, J_{BC} = 2.8, H_B); 8.20 (2H, m, 7-H, 8-H); 7.05 (1H, d, J_{BC} = 2.8, H_C); 6.93 (1H, d, J_{67} = 5, 6-H); 2.77 [3H, s, 1(2)-COOMe]; 2.42 [3H, s, 2(1)-COOMe].

The synthesis of salt **1b** (92% yield; mp 272-274°C) and of indolizine **2b** (17% yield, mp 174-176°C) has been described previously [8]. ^{1}H NMR spectrum of indolizine **2b** (400 MHz, DMSO-d_6, δ, ppm, J (Hz): 9.65 (1H, d, J_{56} = 7, 5-H); 8.38 (3H, m, p-$NO_2C_6H_4$, 8-H); 7.83 (2H, m, p-$NO_2C_6H_4$); 7.67 (1H, dd, 7-H); 7.34 (1H, dd, 6-H); 3.84 [3H, s, 1(2)-COOMe]; 3.30 [3H, s, 2(1)-COOMe].

X-ray Structural Investigation of Compound 2a was carried out on a CAD-4 automatic monocrystal diffractometer [9] using MoKα radiation. The unit cell parameters were determined and refined in the θ angle range of 14-16° using 25 reflections (crystal 0.3 × 0.12 × 0.12 mm). Crystals of the compound studied were assigned to the triclinic system [space group P(-1)] with unit cell parameters a = 7.132(3), b = 10.172(2), c = 12.981(1) Å, α = 79.81(1), β = 78.96(2), γ = 81.02(2)°, V = 902.4(5) Å^3, Z = 2. Initial treatment of the diffraction data was carried out with the WinGX-96 set of programs [10]. The structure was solved by the direct method using 3549 reflections lying in the θ angle range of 1-28° and refined by a full-matrix least-squares method using the SHELX-97 set of programs [11] with an anisotropic approach for the non-hydrogen atoms. The coordinates of the hydrogen atoms were found from electron density difference synthesis and were refined in an isotropic approach. The final R factor had the value of 0.0561 for 3414 independent reflections with $I > 2\sigma(I)$.

The coordinates of atoms in the investigated compound and the isotropic thermal parameters equivalent to the corresponding anisotropic parameters are given in Table 1, interatomic distances and bond angles are reported in Tables 2 and 3. The spatial disposition of atoms in the molecule and their numbering are given in Fig. 1 [12].

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