STRUCTURE AND AMBIPHILIC REACTIVITY OF INDOLIZINES.

1. ISOMERIC 6- AND 8-NITROINDOLIZINES

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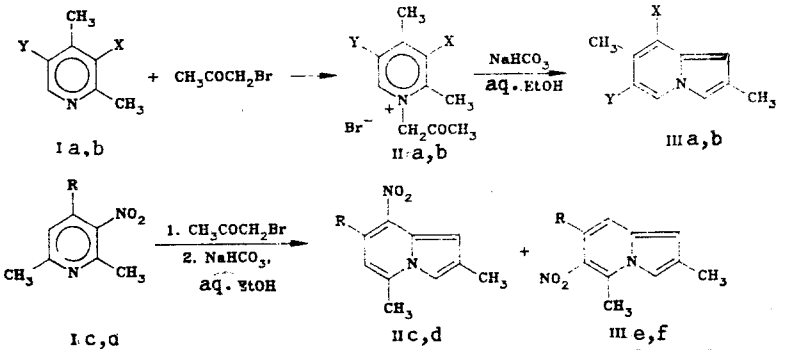
UDC 547.754.04:543.422

Reaction of bromoacetone with the accessible methyl-β-nitropyridines has given some 6- and 8-nitroindolizines. In the case of α,α'-dimethyl-β-nitropyridines, both the 8- and 6-nitroindolizines were obtained.

Indolizines, which are quasiaromatic systems in which the pyrrole ring, which is π-excessive, is condensed with the π-deficient pyridine system, readily undergo electrophilic substitution in the 3 (and 1) position [1], whereas nucleophilic attack on unsubstituted indolizine does not occur. It has, however, been found that the activated 6- and 8-nitroindolizines readily add nucleophiles (amines and hydroxy ion), isomerizational recyclization taking place to give nitroindoles [2]. A detailed study of isomerizational recyclization and other "nucleophilic" reactions in the indolizine series has been prevented by the relative inaccessibility of the starting 6(8)-nitroindolizines, the synthesis of which requires several steps [3].

The aim of this study was to synthesize (and subsequently to examine the ambiphilic reactivity of) the potentially recyclizable 6- and 8-nitroindolizines by the Chichibabin reaction, from bromoacetone and accessible methyl-β-nitropyridines.



I a,b II a,b III a,b

I c,d II c,d III e,f

I—III a X=NO_2, Y=H; b X=H, Y=NO_2; c,e R=H; d,f R=CH_3

The reaction of the nitrolutidines (Ia, b) with bromoacetone in ethyl methyl ketone solution gave good yields of the salts (IIa, b). On treatment with aqueous-alcoholic sodium bicarbonate, these salts were converted into the nitroindolizines (IIIa, b) (Table 1), which were isolated and purified by TLC. The reaction of bromoacetone with the mixture of nitrolutidines (Ia, b) gave a mixture of indolizines (IIIa, b), which were separated by chromatography. Since the separation of the isomeric nitroindolizines is simpler than that of the starting isomers (Ia, b) (see Experimental), this method was more convenient for the preparation of small amounts of the nitroindolizines (IIIa, b).

The nitropyridines (Ic, d) could give isomeric 6- or 8-nitroindolizines, depending on which methyl group in the bromoacetonylate (para- or ortho- to the nitro-group) undergoes cyclocondensation. It was found that the intermediate salts (II) could not be isolated as a result of considerable resinification. Following treatment of the reaction mixtures with base, low yields of mixtures of the 6- and 8-nitroindolizines (IIIc, e) and (IIId, f) were

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0009-3122/87/2302-0169$12.50

TABLE 1. Properties of Methylnitroindolizines (III)

Compound	Reaction time, h	Mp, deg C (from hexane)	R_f (Silufol, hexane–ether, 4:1)	Found, % C (H)	Found, % N	Empirical formula	Calculated, % C (H)	Calculated, % N	M^+	Yield, %
IIIa	15	101—102	0,24	63,4 (5,5)	14,7	$C_{10}H_{10}N_2O_2$	63,2 (5,3)	14,7	190	100
IIIb	22	98—100	0,48	62,1 (5,3)	14,4	$C_{10}H_{10}N_2O_2$	63,2 (5,3)	14,7	190	62
IIIc	34	115	0,25	—	14,7	$C_{10}H_{10}N_2O_2$	—	14,7	190	1
IIId	34	143—145	0,31	—	13,3	$C_{11}H_{12}N_2O_2$	—	13,7	204	3
IIIe	34	92—93	0,47	—	—	$C_{10}H_{10}N_2O_2$	—	—	190	0,1
IIIf	34	66—68	0,50	—	—	$C_{11}H_{12}N_2O_2$	—	—	204	0,6

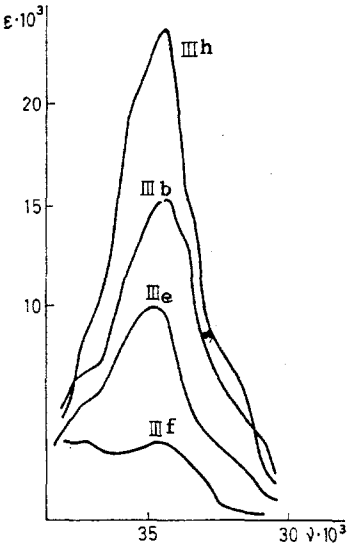


Fig. 1. Electronic absorption spectra of nitroindolizines (IIIb, e, f, h) in the 260–330 nm region (in hexane).

obtained,* the 8-isomers being present in much greater amounts. Although these results do not, of course, enable the reactivities of the ortho- and para-methyl groups to be compared, it is nonetheless noteworthy that both experimental [4] and calculated data [5] are in accordance with the greater acidity of the ortho-methyl group (in the 2-position) in 3-nitro-1,2,4,6-tetramethylpyridinium cation. The low yields of the nitroindolizines (IIIc-f) may be due to steric hindrance by the second α-methyl group at the quaternization stage. For example, 2,5-dimethylindolizine was obtained in low yield ($\leq$5%) [6].

The mixtures of 6- and 8-nitroindolizines were separated by TLC, and it was shown that in all the compounds obtained here, and in their lower homologs 2-methyl-8- and 6-nitroindolizines (IIIg, h), the chromatographic mobility of the 6-nitro-compounds was greater than that of the 8-nitro-isomers (see Table 1, and [7]).

For the interpretation of the PMR spectra of (IIIa-f) (Table 2), it was useful to compare them with those of the indolizines (IIIg, h). The introduction of methyl groups simplifies the appearance of the aromatic region of the spectrum, the signals for the protons in the ortho-position to the methyl group being shifted to slightly lower field. The resonance signals of the 1-H protons in 8-nitroindolizines (but not in the 6-nitro compounds) are shifte to considerably lower field under the influence of the peri-oriented magnetically anisotropic nitro-group. It was thus possible to assign isomers (IIIc, e), and to assign fully the resonance signals for (IIIa-c, e). In the case of the trimethyl nitroindolizines (IIId, f), however, such comparison was insufficiently diagnostic.

*The reaction was carried out in a polar solvent (acetonitrile). The yields were lower in ethyl methyl ketone and toluene, and in ethanol solution no nitroindolizines whatever were formed.

TABLE 2. PMR Spectral Data for Methylnitroindolizines and Their Cations

Compound	Solvent	PMR spectrum, δ, ppm						
		1-H	2-CH_3	3-H	5-H (5-CH_3)	6-H	7-H (7-CH_3)	8-H
IIIa	CCl_4	6,75	2,40	7,20	7,95	6,35	(2,60)	—
	CF_3COOH	7,53	2,93	5,90	9,21	8,03	(2,50)	
IIIb	CCl_4	6,25	2,35	7,25	8,95	—	(2,65)	7,05
	CF_3COOH	6,60	2,10	5,25	9,37	—	(2,66)	7,60
IIIc	CCl_4	7,10	2,38	7,15	(2,51)	6,39	7,80	—
	CF_3COOH	7,85	3,06	5,50	(2,67)	7,90	9,23	—
IIId	CCl_4	6,77	2,41	6,99	(2,58)	6,18	(2,58)	—
	CF_3COOH	7,12	2,79	5,27	(2,79)	7,52	(2,45)	—
IIIe	CCl_4	6,37	2,37	7,20	(2,90)	—	7,36	7,20
IIIf	CCl_4	6,33	2,34	7,11	(2,56)	—	(2,36)	7,11
IIIg	CCl_4	7,05	2,35	7,20	8,05	6,45	7,25	—
	CF_3COOH	8,14	3,00	6,10	9,72	8,40	9,62	—
IIIh	CCl_4	6,35	2,35	7,25	8,90	—	7,12—7,42	
	CF_3COOH	6,75	2,20	5,30	9,50	—	8,80	7,80

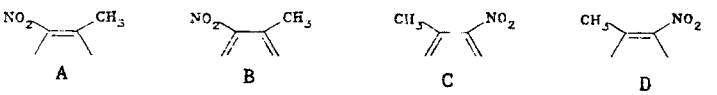
TABLE 3. Electronic Spectra of Nitroindolizines (II) and Their Cations

Compound	Solvent*	λ_{max}, nm	lg ε
IIIa	E	211, 261, 268, 345, 468	4,47; 4,23; 4,25; 3,57; 3,38
	A	287	3,06
IIIb	E	233, 302, 440	4,30; 4,09; 2,97
	H	234, 297, 422	4,33; 4,18; 2,98
	A	327	4,05
IIIc	E	210, 260—267, 351, 477	4,48; 4,17; 4,18; 3,52; 3,47
	A	300	4,00
IIId	E	219, 263—270, 345, 465	4,37; 4,17; 4,20; 3,37; 3,37
	A	310	3,96
IIIe	H	234, 293, 410	4,12; 3,98; 2,96
IIIf	H	241, 298, 401	4,34; 3,81; 2,78
IIIg	E	203, 258—265, 353, 480	4,34; 4,17; 4,18; 3,55; 3,33
	A	293	3,11
IIIh	E	226, 303, 436	4,53; 4,51; 3,36
	H	230, 297, 418	4,38; 4,45; 3,16
	A	332	4,37

*E — 96% ethanol; A — 1 N HCl in 50% ethanol; H — hexane.

Differences have previously been reported [3] between the electronic absorption spectra of 6- and 8-nitroindolizines, the 8-nitro compounds being more deeply colored (see, also [8]). The compounds synthesized here have the same type of spectra as their lower homologs (Table 3), thus enabling the nitroindolizines to be assigned unambiguously to the 6- or 8-series from their electronic spectra. In this way, the correctness of the assignment of the isomeric indolizines (IIIc, e) was confirmed, and assignment of isomers (IIId, f) carried out.

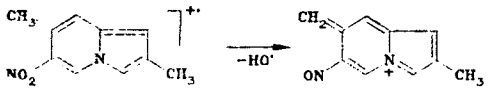
In the case of 6-nitroindolizines, there is a decrease in the intensities of the first and second absorption bands in the higher homologs (Fig. 1). This hypochromic effect, which increases in the sequence (IIIg) → (IIIb) → (IIIe) → (IIIf), may be due to the differing extents of rotation of the NO_2 group (relative to the plane of the indolizine nucleus) as a result of steric repulsion by the ortho-oriented methyl groups. The greater effect of the CH_3 group in the 5-position (in (IIIe)) as compared with the 7-position (IIIb) could be due to the smaller distance between the CH_3 and NO_2 groups in structures of type A as compared with those of type B.



X-ray diffraction examination has in fact shown that there is considerable alternation in the C—C bond lengths in the pyridine moiety of 2-phenyl-6-nitroindolizine [9]. The

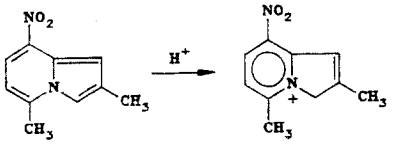
hypochromic effect is at a maximum in the nitroindolizine (IIIf), which has two ortho-methyl groups. Using the well-known equation $\cos^2\phi = \varepsilon/\varepsilon_0$ [10], in which ε_0 relates to compound (IIIh), the angles of rotation of the NO_2 group ϕ can be calculated to be 43, 54, and 61° for compounds (IIIb, e, and f) respectively. (The calculation was carried out for the more intense second absorption band in the electronic spectra; cf. Table 3).

The nature of the mass spectra of these nitroindolizines is determined by the participation of the NO_2 group in the fragmentation of the molecular ion, which is typical of aromatic and heteroaromatic nitro-compounds. For example, elimination of the NO_2 group ($[M - 46]^+/M^{+\cdot} = 0.38 - 0.76$) is seen, cleavage of oxygen and the NO radical being less marked. In compounds (IIIā, b, and d) the principal mode of mass spectra fragmentation is elimination of hydroxyl ($[M - 17]^+/M^+ = 0.46$, 0.97, 0.47, 0.39, and 0.91 respectively) as a result of the "ortho-effect" [11], for example:



In the case of the indolizine (IIIc), which does not contain ortho-oriented CH_3 and NO_2 groups, this mode of fragmentation does not occur, thus enabling the isomeric nitroindolizines (IIIc, e) to be distinguished by their mass spectra (a similar mass spectral criterion has been employed previously to assign the isomeric 1,2,7-trimethyl-3-ethoxycarbonyl-4- and -6-nitroindoles [12]). It was found that for compounds (IIIb, f), in which the 7-CH_3 and 6-NO_2 groups are ortho-oriented, separated by system C, the "ortho-effect" is greater than in the nitroindolizines (IIIa, d, e), which have type D structures. A similar situation is encountered in 2-phenyl-7-methyl-6- and -8-nitroindolizines [13], and in some 1- and 3-nitroindolizines [14].

We have also examined the protonation of the nitroindolizines obtained. It has previously been found that the protonation of 2-methyl, 2-phenyl-, and some other indolizines in kinetically-controlled reactions gives a mixture of 3H- and 1H-indolizinium cations (∿3:1). Under thermodynamic control, the 1H-isomer is irreversibly converted into the more stable 3H-cation [15, 16]. It has been shown that 6-, 7-, and 8-ethoxycarbonylindolizines in trifluoroacetic acid solution give the 3H-indolizinium cations as the sole protonation products [17, 18]. Using PMR and electronic spectroscopy (Tables 2 and 3), we have found that the nitroindolizines (III) are protonated exclusively at the 3-position, for example:



In the PMR spectrum, the protons of the CH_2 group appear at 5.25-6.10 ppm, showing conclusively [19] that protonation takes place at $C_{(3)}$. In the cationic forms of the 8-nitroindolizines (IIIa, c, e, g) the low-field shift of the 1-H proton under the influence of the peri-oriented NO_2 group persists. Generally speaking, the changes in the PMR and UV spectra on protonation of indolizines (IIIa-h) are what would be expected (see, for example, [8, 17-21]).

The isomerizational recyclization of methylnitroindolizines will be reported in a subsequent publication.

EXPERIMENTAL*

The purities of the compounds obtained were checked by TLC on Silufol plates. Separation of the isomers was carried out by column chromatography (silica gel L 40/100) and on plates (Silpearl UV-254). UV spectra were obtained on Specord M-40 UV-VIS and Cary-219 instruments in 96% ethanol, hexane, or 1 N HCl (in 50% ethanol), and PMR spectra in Tesla BS-467 (60 MHz) and XL-100 instruments in CCl_4 and CF_3COOH, internal standard TMS. Mass spectra were obtained on a Varian MAT-212 (E = 100 eV), with direct sample introduction.

3-Nitro-2,6-lutidine and 3-nitro-2,4,6-collidine were obtained by standard methods [22]. 2-Methyl-6- and -8-nitroindolizines have been described [3].

*With the participation of student A. Kossakovskii.

3- and 5-Nitro-2,4-lutidines. A mixture of nitrolutidines, obtained by nitrating 2,4-lutidine [23] was distilled in vacuo. The fraction bp 116-118°C (12 mm) was pure 5-nitro-2,4-lutidine. From the fraction bp 102-106°C (12 mm), precipitation of the acetone-insoluble sulfate [23] followed by treatment with aqueous sodium carbonate and extraction with ether and distillation, there was obtained pure 3-nitro-2,4-lutidine.

1-Acetonyl-2,4-dimethyl-3-nitropyridinium Bromide (IIa). A mixture of 1.54 g (10 mmole) of 3-nitro-2,4-lutidine and 4.10 g (30 mmole) of bromoacetone was boiled in 30 ml of ethyl methyl ketone for 10 h. The gray crystals of (IIa) which separated on cooling were filtered off and washed with ethyl methyl ketone and ether to give 1.75 g (60%) of product, mp 201-202°C (from methanol, decomp.). Found: N 9.7%. $C_{10}H_{13}BrN_2O_3$. Calculated: N 9.7%.

1-Acetonyl-2,4-dimethyl-5-nitropyridinium Bromide (IIb) was obtained as for (IIa), yield 65%, mp 162-163°C (from methanol, decomp.). Found: C 41.9; H 4.5; N 9.6%. $C_{10}H_{13}BrN_2O_3$. Calculated: C 41.5; H 4.5; N 9.7%.

2,7-Dimethyl-8-nitroindolizine (IIIa). A solution of 1.46 g (5 mmole) of (IIa) in 100 ml of 40% ethanol was treated at the boil with an excess of solid sodium bicarbonate. The solution was cooled, extracted with chloroform, and the extract evaporated and chromatographed on a column (SiO_2, hexane–ether, 4:1). The fraction with R_f 0.24 was collected to give 0.95 g (5 mmole) of deep red crystals.

2,7-Dimethyl-6-nitroindolizine (IIIb). Synthesized as for (IIIa), bright red crystals, R_f 0.48 (hexane–ether, 4:1).

Reaction of Bromoacetone with a Mixture of 3- and 5-Nitro-2,4-lutidines. A solution of 3.14 g (20.7 mmole) of a mixture of (Ia) and (Ib) (1:1) and 6.44 g (47.0 mmole) of bromoacetone in 30 ml of ethyl methyl ketone was boiled for 20 h. The mixture was then evaporated, and treated at the boil with HCl (pH 2). Following extraction with chloroform, the aqueous layer was treated with an excess of solid sodium bicarbonate at the boil, cooled, and extracted with ether. The extract was evaporated and chromatographed on a column (SiO_2, hexane–ether, 4:1) to give indolizines (IIIa) (0.19 g; 1.0 mmole) and (IIIb) (0.095 g; 0.5 mmole).

Reaction of Bromoacetone with 3-Nitro-2,6-lutidine. A mixture of 16.9 g (110 mmole) of (Ic) and 27.4 g (200 mmole) of bromoacetone in 80 ml of acetonitrile was boiled for 34 h. The mixture, which underwent considerable resinification, was evaporated and treated with heating with HCl (pH 3), then extracted with chloroform. The aqueous layer was treated with an excess of $NaHCO_3$, boiled for 1 h, then extracted with chloroform and the extract evaporated The residue was chromatographed on a plate (hexane–ether, 4:1) to give 0.209 g (1.10 mmole) of deep red crystals of 2,5-dimethyl-8-nitroindolizine (IIIc) and 0.019 g (0.10 mmole) of orange crystals of 2,5-dimethyl-6-nitroindolizine (IIIe).

Reaction of Bromoacetone with 3-Nitro-2,4,6-collidine. A mixture of 2.52 g (15.2 mmole) of (Id) and 4.11 g (30 mmole) of bromoacetone in 20 ml of acetonitrile was boiled for 34 h. The mixture was then worked up as in the preceding example. Yield 0.086 g (0.42 mmole) of deep red needles of 2,5,7-trimethyl-8-nitroindolizine (IIId) and 0.018 g (0.09 mmole) of 2,5,7 trimethyl-6-nitrindolizine (IIIf) as a yellow powder.

LITERATURE CITED

1. W. Flitsch, in: Comprehensive Organic Chemistry, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, Vol. 4 (1984), p. 443.
2. A. N. Kost, R. S. Sagitullin, and S. P. Gromov, Dokl. Akad. Nauk SSSR, 230, 1106 (1976).
3. A. N. Kost, R. S. Sagitullin, and S. P. Gromov, Khim. Geterotsikl. Söedin., No. 7, 922 (1976).
4. R. S. Sagitullin, S. P. Gromov, and A. N. Kost, Dokl. Akad. Nauk SSSR, 236, 634 (1977).
5. Yu. B. Vysotskii, B. P. Zemskii, T. V. Stupnikova, T. S. Sagitullin, A. N. Kost, and O. P. Shvaika, Khim. Geterotsikl. Soedin., No. 11, 1496 (1979).
6. A. E. Tschitschibabin, Chem. Ber., 60, 1607 (1927).
7. E. V. Babaev and D. E. Lushnikov, in: Current Topics in the Synthesis and Study of Organic Compounds. Proc. 12th Intercollegiate Conf. of Young Scientists [in Russian], Leningrad (1985).
8. S. I. Bobrovskii, E. V. Babaev, S. P. Gromov, K. A. Paseshnichenko, and Yu. G. Bundel', Khim. Geterotsikl. Söedin., No. 2, 209 (1987).
9. V. A. Tafeenko and L. A. Aslanov, Zh. Selsk. Khim., 21, 69 (1980).

10. L. A. Kazitsina and N. B. Kupletskaya, Application of UV, IR, NMR, and Mass Spectroscopy in Organic CHemistry [in Russian], MGU Press, Moscow (1979), p. 44.
11. R. A. Khmel'nitskii and P. B. Tetrent'ev, Usp. Khim., No. 5, 854 (1979).
12. A. N. Kost, L. G. Yudin, E. Ya. Zinchenko, A. B. Belikov, and O. A. Solov'ev, Khim. Geterotsikl. Soedin., No. 3, 375 (1974).
13. S. I. Bobrovskii, E. V. Babaev, Yu. O. Vasil'ev, and Yu. G. Bundel', Vestn. Mosk. Gos. Univ., Khim., No. 1 (1987).
14. S. I. Bobrovskii, E. V. Babaev, and Yu. G. Bundel', Vestn. Mosk. Gos. Univ., Khim., No. 2 (1985).
15. L. M. Alekseeva, G. G. Dvoryantseva, Yu. N. Sheinker, A. A. Druzhinina, R. M. Palei, and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 1, 70 (1976).
16. N. S. Prostakov, V. I. Kuznetsov, A. A. Savina, M. A. Ryashchentseva, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 5, 649 (1977).
17. L. M. Alekseeva, G. G. Dvoryantseva, M. S. Goizman, T. S. Loseva, A. D. Yanina, E. E. Mikhlina, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 11, 1540 (1976).
18. T. S. Loseva, M. S. Goizman, L. M. Alekseeva, O. R. Shvarts, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 6, 802 (1978).
19. M. Fraser, S. McKenzie, and D. H. Reid, J. Chem. Soc., B, No. 1, 44 (1966).
20. W. L. F. Armarego, J. Chem. Soc., B, No. 1, 191 (1966).
21. W. L. F. Armarego, J. Chem. Soc., No. 11, 4226 (1964).
22. E. Plazek, Ber. Chem. Ges., 72B, 577 (1939).
23. L. Achremovicz, T. Batkowski, and Z. Scrowaczewska, Rocnz. Chem., 38, 1317 (1964).