STRUCTURE AND AMBIPHILIC REACTIVITY OF INDOLIZINES. 3 SYNTHESIS AND ISOMERIZING RECYCLIZATION OF 7-METHYL-6(8)-NITRO-2-PHENYLINDOLIZINES*

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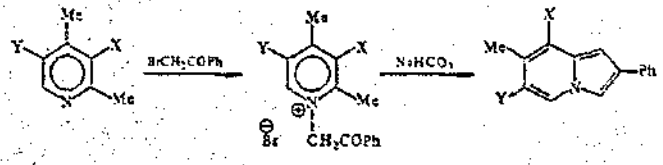
Vestnik Moskovskogo Universiteta. Khimiya, Vol. 42, No. 1, pp. 82-85, 1987

UDC 547.759.4.07

This paper describes 7-methyl-6- and -8-nitro-2-phenylindolizines as objects of isomerizing recyclization with the formation of nitroindoles, by analogy with the 6- and 8-nitro-2-phenolindolizines. The absence of a recyclization product in the case of 8-nitroindolizine and the successful preparation of 6-methyl-5-nitro-3-phenylindole from the 6-nitro isomer permit the limits of applicability of the Kost-Sagitullin reaction in the nitroindolizine series to be marked out. A relatively short route to obtaining the previously inaccessible 6-methyl-5-nitro-3-phenylindole may be mentioned.

It has been established previously that 6- and 8-nitro-2-phenyl(methyl)-indolizines take part under the action of alkali in an isomerizing recyclization reaction with the formation of 5- and 7-nitro-3-phenyl(methyl)indoles. The wide use of this reaction for obtaining nitroindoles has been hindered by the poor accessibility of the initial 6- and 8-nitroindolizines, the synthesis of which requires several stages [3].

Continuing investigations devoted to the structure and ambiphilic reactivity of the indolizines [1,4], we have synthesized 7-methyl-6- and -8-nitro-2-phenylindolizines as objects for isomerizing recyclization. The initial compounds were the readily accessible nitrolutidines (Ia, b) which, unlike the 3- and 5-nitro-2-picolines, can be obtained by the direct nitration of 2,4-lutidine [5]



Ia, b IIa, b IIIa, b

I, II, III: a X=H, Y=NO2; b X=NO2, Y=H.

The quaternization of the nitrolutidine (Ia) took place in methyl ethyl ketone solution at room temperature with the formation of the phenacylate (IIa);

*For communication 2, see [1].

**Deceased.

Table 1

Characteristics of the Compounds Obtained

Compound	Yield, %	T. mp., °C (solvent)	Found, %* C	H	N	λ_{max}	ε	M	$[M-OH]^+/M$
IIIa	99	188 (heptane)	71,38	4,95	—	250 320 пл. 450	$3,96 \cdot 10^4$ $3,12 \cdot 10^4$ $7,79 \cdot 10^3$	252	0,91
IIIb	98	115—117 (hexane)	70,85	5,19	—	253 354 пл. 450	$7,43 \cdot 10^4$ $1,32 \cdot 10^4$ $1,89 \cdot 10^3$	252	0,32
IV	26	208—210 (heptane)	71,83	5,15	11,06	216 272 328	$2,21 \cdot 10^4$ $1,34 \cdot 10^4$ $1,11 \cdot 10^3$	252	1,22

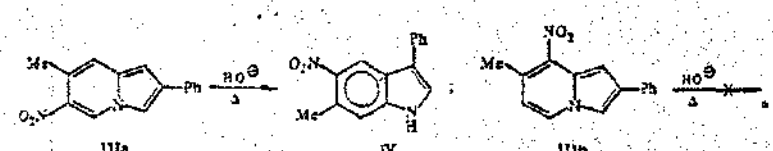
*Calculated, %: C 71.43; H 4.76; N 11.00.

the production of the isomer (IIb) required the boiling of the reaction mixture. The cyclocondensation of the salts (II), taking place spontaneously even in the cold in 20% aqueous ethanolic solution, led to high yields of the nitroindolizines (IIa, b) when the reaction mixture was treated with sodium bicarbonate. Column chromatography was used to purify compounds (IIa, b). The nitroindolizines obtained were colored substances comparatively sparingly soluble in nonpolar solvents and in chloroform. The characteristics of compounds III are given in Table 1.

Spectral characteristics confirmed the structures of the nitroindolizines obtained. The electronic absorption spectra of indolizines (IIa, b) were close to those of lower homologues. A short-wave band in the 250-253 nm region was observed both in the case of the 6- and the 8-nitro-2-phenylindolizines and in the spectrum of 2-phenylindolizine [1]. To distinguish isomers it is possible to use the second absorption band, which is located in the region of longer wavelengths for the 8-nitroindolizines than for the 6-nitro isomers [1,3]. The long-wave absorption band appears in the spectrum in the form of a broad shoulder.

The mass spectra of compounds (III) were monotypical and, on the whole, similar to the spectra of their lower homologues [3,6]. An important new fragmentation pathway was the elimination of HO· as a consequence of the ortho positioning of CH_3 and NO_2 groups (the "ortho effect" [7]). Here the ortho effect was more pronounced for indolizine (IIIa) (Table 1) than for the isomeric (IIIb). We found a similar relationship in the case of the 2,7-dimethyl-6- and -8-nitroindolizines [4,8].

The nitroindolizines (IIIa, b) were subjected to the isomerizing recyclization reaction. In this reaction, (IIIa) was converted with a yield of 26% into the nitroindole (IV), which has not yet been described previously. Under the same conditions, the isomeric (IIIb) did not lead to the formation of the corresponding indole but the initial compound could not be regenerated:



IIIa IV IIIb

The structure of the indole obtained was confirmed by the totality of its spectral characteristics. Thus, the UV spectrum of this compound practically reproduced the spectrum of a lower homologue - 5-nitro-3-phenylindole (V) [9]. In the mass spectrum of indole (IV) which was, on the whole, similar to that of (V) [6], the $[M - OH]^+$ peak due to the ortho effect was also observed, as in the case of the nitroindolizines (IIIa, b).

In our opinion, one of the possible reasons for the different behaviors of the nitroindolizines (IIIa, b) in the isomerizing recyclization reaction is the different acidities of the 7-CH_3 groups in these compounds. Because of the substantially polyenic nature of the $C_5{=}C_6{=}C_7{=}C_8$ fragment of the nucleus of the nitroindolizines [10], the 7-CH_2 carbanion formed on the deprotonation of (IIIb) must be stabilized by conjugation with the 8-NO_2 group. Similar reactions with the participation of such an anion competing with the recyclization process may be the cause of the observed resinification of the reaction mixture. In the case of the indolizine (IIIa), the formation of the analogous 7-CH_2 carbanion is less favorable because of the absence of conjugation with the 6-NO_2 group.

Experimental Part. Mass spectra were taken on a Varian MAT-212 instrument (E - 70 eV); UV spectra on a Specord M-40 instrument; and PMR spectra on a BS-467 instrument (60 MHz) with TMS as internal standard. The individuality of the compounds obtained was checked chromatographically on Silufol plate. The compounds were purified by column chromatography on silica gel L 40/100.

2,4-Dimethyl-5-nitro-1-phenacylpyridinium bromide (IIa). A mixture of 4.95 g ($3.25 \cdot 10^{-2}$ mole) of (Ia) and 9.27 g ($4.66 \cdot 10^{-2}$ mole) of phenacyl bromide in 8 ml of methyl ethyle ketone was kept at room temperature for 4 days. The precipitate that had deposited was separated off and was washed with cold acetone, giving 6.52 g ($1.86 \cdot 10^{-2}$ mole, 57%) of the salt (Ia) with mp 223-224°C (decomp. from methanol). Found, %: C 50.46; H 4.68; N 7.86, $C_{15}H_{15}BrN_2O_3$. Calculated, %: C 51.28; H 4.27; N 7.86.

2,4-Dimethyl-3-nitro-1-phenacylpyriidinium bromide (IIb). A mixture of 3.08 g ($2.03 \cdot 10^{-2}$ mole) of (Ib) and 8.32 g ($4.18 \cdot 10^{-2}$ mole) of phenacyl bromide was boiled in 8 ml of methyl ethyl ketone for 18 hr. The precipitate was separated off and was washed with cold acetone to give 2.30 g ($6.55 \cdot 10^{-3}$ mole, 32%) of the salt (IIb), mp 214° (decomp. from methanol). Found, %: C 51.33; H 4.56. $C_{15}H_{15}BrN_2O_3$. Calculated, %: C 51.28; H 4.27.

7-Methyl-6-nitro-2-phenylindoline (IIIa). A solution of 2.15 g ($6.12 \cdot 10^{-3}$ mole) of the salt (IIa) was boiled in 200 ml of 25% aqueous ethanol for 30 min and was then neutralized with sodium bicarbonate to pH 8 and was boiled for another 1 hr. The solution, containing a precipitate, was cooled and extracted with chloroform, and the extract was dried with sodium sulfate. After the solvent had been driven off, the residue was chromatographed on a column (benzene, SiO_2). This gave 1.51 mg ($6.0 \cdot 10^{-3}$ mole, 98%) of an orange powder of (IIIa).

7-Methyl-8-nitro-2-phenylindolizine (IIIb). The salt (IIb) (0.35 g; $9.85 \cdot 10^{-4}$ mole) was treated in a similar manner to (IIa). After chromatography, 0.22 g ($8.65 \cdot 10^{-4}$ mole, 98%) of dark brown crystals of (IIIb) was isolated.

6-Methyl-5-intro-3-phenylindole (IV). In a current of argon, 3.336 g

$2.30 \cdot 10^{-3}$ mole) of (IIIa) was boiled in 30 ml of 85% ethanol containing 6 g of KOH for 3 hr. After cooling, the reaction mixture was poured onto ice and was neutralized with dilute HCl to pH 7. The solution was extracted with chloroform and the extract was evaporated. The residue was chromatographed (benzene, SiO_2) and a fraction with R_f 0.35 was collected. This gave 0.078 g ($3.10 \cdot 10^{-4}$ mole, 26%) of orange crystals of the indole (IV). PMR spectrum (DMSO-d_6), δ, ppm: 11.7 (br.s), 1-H; 8.4 (s), 4-H; 7.43 (m), 2-H, 7-H, 3-C_6H_5; 3.26 (s), 6-CH_3.

Reaction of (IIIb) with an Aqueous Ethanolic Solution of KOH. In a current of argon, 0.09 g of (IIIb) was boiled with 2 g of KOH in 20 ml of 85% ethanol. After the beginning of heating, the reaction mixture darkened appreciably. It was found by the TLC method (benzene, Silufol) that after heating for 2 hr the reaction mixture contained neither the initial indolizine nor a compound of the indole series. After the mixture was worked up in manner similar to that used in the isolation of (VI), it was impossible to detect an indole in the organic phase.

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10 December 1985

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