STRUCTURE AND AMBIPHILIC REACTIVITY OF INDOLYSINES. 4. DINITROINDOLYSINES*

S. I. Bobrovskii, E. Y. Babaev, and Yu. G. Bundel

Vestnik Moskovskogo Universiteta. Khimiya,
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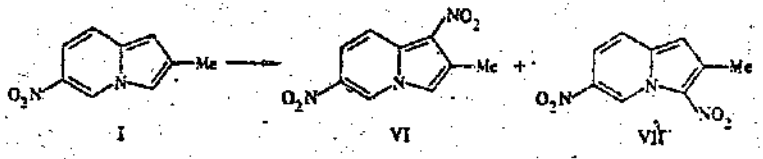
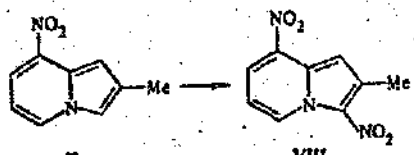
In previous reports [1,2] we described synthesis of accessible 7-methyl homologs of 6- and 8-NI (here and hereinafter NI - nitroindolysines) and their behavior under the conditions of isomerization recyclization. To continue our studies of reactivity of substituted indolysines in the present study we investigated nitration of 2-methyl-6- and 8-NI (I, II) and the behavior of the obtained diNI in an alkaline medium, including the conditions of isomerization recyclization.

It is previously found that reaction of 2-methylindolysine (III) with a mixture of HNO_3-Ac_2O at -70° leads to formation of 2-methyl-3-NI (IV) as sole product [3], whereas during nitration of (III) in an H_2SO_4 mostly 2-methyl-1-NI (V) (as well as 1.5% of IV) [4]. It turned out that nitration of I in acetic anhydride leads to a mixture of almost equal amounts of 2-methyl-1,6- and 3,6-diNI (VI, III):



I VI VII

Thus, on the example of nitration of I we were able to detect a rare example in the chemistry of indolysines of the appearance of ambident properties in s_EAr reactions during introduction of the substituent. (The previously described formation of 1- and 3-isomers during electrophilic substitution of 2,5-dimethylindolysine [5], in all likelihood, stemmed from steric factors.) Nitration of II in a medium of acetic anhydride at -70° leads to the formation of 2-methyl-3,8-diNI (VIII) as sole reaction product:



II VIII

*Report 3 [1].

Table 1

PMR Spectral Data on Indolysines I-VIII (in $CDCl_3$; Internal Standard - TMS)

Compound	N-1	C-Me	N-3	N-5	N-6	N-7	N-8
I	6.35	2.35	7.25	8.90	—	7.40	7.15
II	7.05	2.35	7.20	8.05	6.45	7.25	—
III	6.15	2.25	6.75	7.40	6.10	6.35	7.25
IV [3]	6.44	2.65	—	9.66	6.8—7.7		
V	—	2.50	7.00	8.30	6.65—7.35		8.00
VI*	—	2.35	7.2	9.15	—	7.4	7.4
VII	6.9	2.65	—	10.4	—	8.15	8.15
VIII	7.35	2.75	—	9.9	7.05	8.35	—

*In a $(CD_3)_2CO$ solution.

In the given case formation of isomeric 2-methyl-1,8-diNI is not observed, the peri-positioned nitro group apparently preventing attack of the electrophile on position 1.

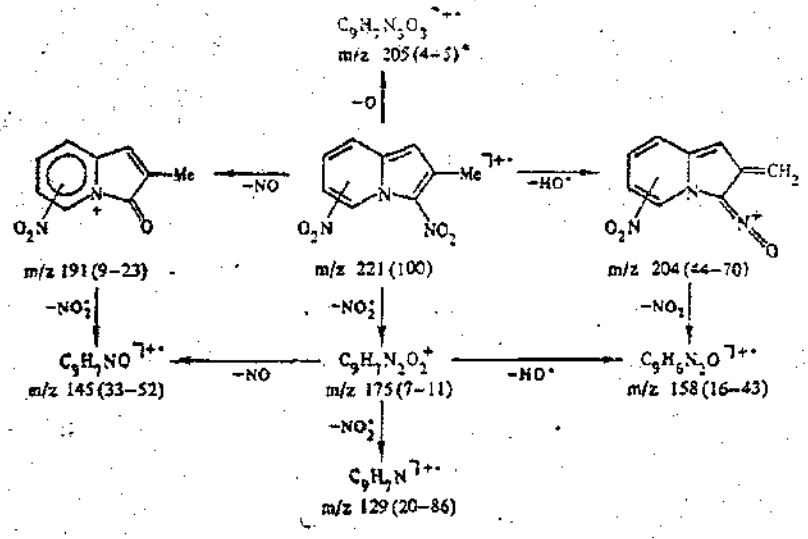
Nitration of I in a medium of H_2SO_4 led to the formation of small amount (9%) of the same product, i.e., VI and VII (about 1:1) whereas II under the same conditions almost fully resinified. Formation of V from III in a mixture HNO_3-H_2SO_4 was explained by participation in nitration (at position I) of the 3H-indolysinium cation formed in an acid medium [4]. In the case of 6(8)-NI, much less basic than indolysines that do not contain the O_2N group [6], the percentage of nonprotonated forms is lower. Considering that the reactivity of the nitroindolysinium cations [2] should be reduced (in comparison with indolysiniums not containing the O_2N group) we can assume that even in an H_2SO_4 medium the nonprotonated 6(8)-NI was subject to nitration. The low yields of diNI during nitration of I and the absence of products of nitration of II are explained in this case by the low equilibrium concentration of the neutral form I (II).

The obtained isometric diNI VI, VII were separated and VI-VIII were purified using column chromatography. For unequivocal determination of the structure of these compounds comparative analysis of the PMR spectra of I-V and diNI VI-VIII proved adequate (Table 1). A significant down-field shift of the resonance signal of the H-5 proton (in comparison with III, I and II respectively) under the influence of the magnetically anisotropic nitro group in the peri-position is observed in compounds IV, VII and VIII, whereas the resonance signal of the H-8 proton found in the periposition to the NO_2 group is shifted downfield in compounds V and VI (compare with III and I). Since the H-5 proton and the somewhat more shielded H-8 proton remain the most downfield signals in all the investigated compounds, their position in the PMR spectrum is diagnostic for determining the structure of the products of nitration of I and II.

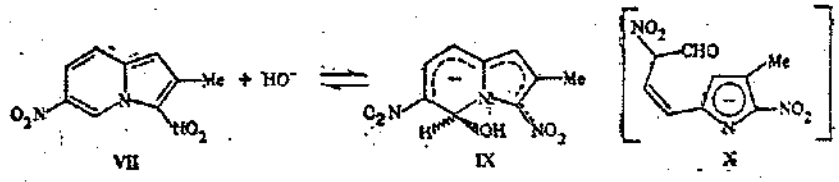
In the present study we obtained and analyzed the mass spectra of diNI VI-VIII.* Introduction of the second NO_2 group (cf. fragmentation of monoNI, II, IV, V [7-9]) does not lead overall to a reduction in stability of the molecular

*Allowing for an isotope correction.

ion, but the selectivity of the mass spectrum declines. The principal directions of primary fragmentation of VI-VIII, as in the case of monoNI IV, V, are elimination of HO· as a result of the ortho effect and for VII, VIII nitro-nitrite rearrangement, whereas elimination of the NO_2 group characteristic of I and II and cleavage of the oxygen atom are less significant. The intense ions with m/z 158, 145 and 129 are formed as a result of fragmentation of the primary fragmented ions (m/z 191, 175, 158), which confirms the presence of two nitro groups in compounds VI-VIII; the ions m/z 128, 130 are probably the result of elimination of NO and CO molecules from the ion m/z 158. Below we show the proposed general scheme of fragmentation, including possible directions of breakdown of the molecular ion and the primary fragmented ions (on the example of VII, VIII; in parenthesis we have shown the ranges of the ratios of intensities of the fragmented ions and the molecular in %).



In studying the behavior of diNI in an alkaline medium we found that in an alcohol solution of alkali the yellow color of VI-VIII changes sharply to crimson or light blue (Table 2) as a result of formation of anionic complexes, for example



which allows us to recommend diNI VI-VIII (especially 1,6-diNI VI, which forms a stable anionic complex) as akaline indicators. It was previously demonstrated that similar anionic σ-complexes that form from monoNI I and II have a yellow color. The deeper color of adducts of type IX probably stems from the presence of a larger conjugation chain, including two nitro groups. From this viewpoint we can also explain the deeper color of the anionic complex IX from VII in comparison with the similar complexes from VI or VIII.

The presence of an acyl acceptor group in the third position of 5(8)-NI leads to a significant acceleration of isomerization recyclization; the products are the corresponding 2-acyl-5(7)-nitroindoles [11]. It turned out that in an aqueous-alcoholic solution of alkali diNI VII and VIII are unstable and fully resinify at room temperature in 1 to 2 days (or during 10 to 15 minutes of boil-

Table 2

Data of Electron Absorption Spectra of Dinitroindolysines VI-VIII and Their Anionic σ-Complexes

Compound	λ, nm (log ε), 96% ethanol	λ, nm (log ε) 2.5N KOH in 96% ethanol
VI	225(3.05); 285(3.10); 383(3.00)	m 230(3.78); 295—305(3.55); 390(3.67); 476(3.76)
VII	213(2.92); 287(3.10); 377(2.58); 422(2.81)	278(3.77); 328(3.69); 429(3.47); 504(3.33)
VIII	232(2.92); 313(3.12); 398(2.96)	231(3.54); 307(3.57); 395(3.48); 458(3.78)

ing). Compounds of the indole or indolysine series are not detected chromatographically. Apparently, the nitro group in position 3 (like the acyl groups) facilitates opening of the pyridine ring in the anionic σ-complex (IX), but in contrast to the acyl groups prevents cyclization (in subsequent formation of the benzene ring of indole) as a result of the reduced nucleophilicity of the nitropyrrolyl anion, which is a fragment of the opened form (X).

The data obtained in the present study, together with previously published data [1,6,10-12], allow us to outline the boundaries of applicability of Kost-Sagitullin rearrangement in the indolysine series.

Experimental part. The mass spectra were recorded on a Varian MAT-111 instrument (E-80 eV). The high-resolution mass spectra were recorded on a Varian MAT-212 instrument (E-70 eV); mass reference point - perfluorokerosene; the mass measurements were done manually. The electron spectra were recorded on a Specord M-40 instrument; the PMR spectra - on a BS-467 instrument (60 MHz), internal standard - TMS. The individuality of the obtained compounds was controlled chromatographically on Silufol UV-253 plates. Separation and purification of the obtained compounds were run by column chromatography on silica gel L 40/100. Compounds I, II [13], IV [3], V [4] were synthesized according to the described method.

Nitration of 2-methyl-6-nitroindolysine. 0.2 ml of HNO_3 (d 1.4) in 1 ml Ac_2O was added during mixing to a mixture of 0.30 g (1.7 mmol) of I and 10 ml of acetic anhydride at -70°. After 30 minutes the reaction mixture was poured into 20 ml of ice water, neutralized with an NaOH solution to pH 7; extracted with chloroform, and the extract was evaporated. After chromatography (eluent - chloroform) two fractions were obtained. From the first we isolated 0.08 g (21%) of yellow-brown crystals of 2-methyl-1,6-dinitroindolysine (VI), R_f 0.52, mp 185°. Found: M-221.0441 (high resolution mass spectrum). $C_9H_7N_3O_4$. Calculated: M-221.0437. Mass spectrum*: 222(12), 221(100), 205(11), 204(70), 191(9), 175(11), 159(3), 158(43), 146(6), 145(33), 129(20), 128(6), 117(10), 104(7), 103(11), 102(20), 90(14), 98(11), 78(13), 77(17), 76(20), 75(11), 64(6), 63(5), 52(14), 51(17), 50(11), W_M = 21.6; $S_{1/2}$ = 4. From the second fraction we isolated 0.09 g (24%) of a yellow powder of 2-methyl-3,6-dinitroindolysine (VII), R_f 0.38, mp 225°. Found, %° C 49.0; H 3.6; N 18.7. $C_9H_7N_3O_4$. Calculated, %:

*In parentheses we have shown the intensities of the ion peaks (in %) relative to the intensity of the molecular ion, whose peaks are maximal in the mass spectra of VI-VIII. Ions with an intensity of no less than 1% of the total ionic current were recalculated.

C 49.0; H 3.2; N 19.0. Mass spectrum: 222(10), 221(100), 205(9), 204(44), 191(18), 175(7), 158(16), 145(46), 130(17), 129(21), 128(17), 117(18), 116(8), 103(18), 102(26), 101(10), 90(26), 89(17), 78(18), 77(20), 76(13), 75(16), 74(9), 63(17), 57(8), 52(11), 51(20), 50(14). W_M = 13.7; $S_{1/2}$ = 3.

2-Methyl-3,8-dinitroindolysine. Prepared according to a similar method in an amount of 0.18 g (48%) from 0.30 g (1.7 mmol) of II. Yellow-brown powder, R_f 0.31 (benzene), mp 218-222°. Found: M = 221.0441 (high-resolution mass spectrum). $C_9H_7N_3O_4$. Calculated: M = 221.0437. Mass spectrum: 222(15), 221(100), 205(10), 204(50), 191(23), 186(12), 175(9), 158(18), 149(10), 145(52), 130(32), 129(86), 128(64), 118(7), 117(48), 104(18), 103(46), 102(100), 101(26), 91(18), 90(40), 89(92), 79(34), 78(26), 76(36), 75(48), 74(36), 64(16), 63(32), 62(20), 52(30), 51(48), 50(44). W_M = 8; $S_{1/2}$ = 9.

Nitration of 2-methyl-6-nitroindolysine in an H_2SO_4 medium. 0.30 g (1.7 mmol) of I was dissolved in 2 ml of 98% H_2SO_4 and 0.8 ml of HNO_3 (d 1.4) was added dropwise during mixing. After 5 minutes the reaction mixture was poured into 20 ml of ice water, neutralized with NaOH to pH 7, extracted with chloroform, and the extract evaporated. After chromatography we isolated 0.20 g (67%) of the original I, 0.014 g (4%) of VI and 0.018 g (5%) of VII.

During nitration of 0.30 g of II according to a similar method after chromatography of the strongly resinified mixture it was only possible to isolate 0.012 g (14%) of the original II.

Reaction of 2-methyl-3,6-dinitroindolysine with alkali. A solution of 0.08 g (0.36 mmol) of VII in 15 ml of 5 N KOH solution in 50% ethanol was heated to boiling. The crimson solution darkened markedly; after 15 minutes the original VII could not be detected chromatographically. After cooling the reaction mixture was neutralized with acetic acid and extracted with benzene. Compounds of the indolysine or indole series could not be detected chromatographically in the extract.

Reaction VIII runs in similar fashion with alkali; compounds of the indolysine or indole series could not be detected chromatographically in the resinified reaction mixture.

REFERENCES

1. S. I. Bobrovskii, E. V. Babaev, Yu. O. Vasil'ev, and Yu. G. Bundel, Vestn. Mosk. un-ta. Ser. 2, Khimiya [Moscow University Chemistry Bulletin], p. 28, 1987.
2. S. I. Bobrovskii, E. V. Babaev, and Yu. G. Bundel, KhGS, no. 2, p. 203, 1987.
3. E. T. Borrows, D. O. Holland, and J. Kenyon, J. Chem. Soc., no. 11, p. 1077, 1946.
4. J. A. Hickmann and C. W. Wibberley, J. Chem. Soc. Perkin II, no. 23, , p. 2954, 1972.
5. W. K. Gibson and D. Leaver, J. Chem. Soc. C, no. 3, p. 324, 1966.
6. E. V. Babaev, Author's abstract of candidate's dissertation, Moscow, 1987.
7. S. I. Bobrovskii, E. V. Babaev, and Yu. G. Bundel, Vestn. Mosk. un-ta. Ser. 2, Khimiya [Moscow University Chemistry Bulletin], p. 222, 1985.
8. P. B. Terent'ev, O. A. Solov'ev, R. A. Khmel'nitskii, S. P. Gromov, and R. S. Sagitullin, KhGS, no. 6, p. 765, 1982.

9. M. S. Bobyleva, N. S. Kulikov, and S. I. Bobrovskii, KhGS, no. 12, p. 1631, 1988.
10. A. N. Kost, R. S. Sagitullin, and S. P. Gromov, DAN SSSR, vol. 230, p. 1106, 1976.
11. S. I. Bobrovskii, E. V. Babaev, and Yu. G. Bundel, ZhOrKh, vol. 23, p. 240, 1987.
12. S. I. Bobrovskii, E. V. Babaev, S. P. Gromov, K. A. Paseshnichenko, and Yu. G. Bundel, KhGS, no. 2, p. 209, 1987.
13. A. N. Kost, R. S. Sagitullin, and S. P. Gromov, KhGS, no. 7, p. 922, 1976.

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