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REARRANGEMENTS IN THE 6-NITRO-2,9-DIOXA-1-

AZABICYCLO[4.3.0]NONANE SERIES

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An unusual rearrangement of several 8-substituted 6-nitro-2,9-dioxa-l-azabicyclo[4.3.0] nonanes (I) has previously been reported [1]. In this communication we shall present detailed data on this rearrangement.

The heating of Ia-Ic in dry DMFA at 60-90°C results in the splitting off of  $HNO_2$  and the formation of derivatives of spiro[isoxazoline-5,2'-tetrahydrofuran] (IIa-IIc). In the case of Id the reaction product is a derivative of isoxazole (III):



 $R = COOCH_3$  (a), CN (b),  $COCH_3$  (c), Ph (d)

These reactions take place over the course of a longer time even at  ${\sim}20$  °C.

The IR spectra of IIa-IIc do not show absorption bands of a nitro group and have absorption bands of the corresponding functional substituents. The PMR spectra (Table 1) are consistent with structures IIa-IIc. The relative constancy of the <sup>13</sup>C chemical shifts of the analogous carbon atoms in all the compounds is characteristic (Table 2). Only the chemical shifts of the C<sup>3</sup> signals vary as a function of the nature of R in accordance with the proposed structure. The strong diamagnetic shift of the C<sup>3</sup> signal of compound IIb is attributed to the influence of the nitrile group [2]. The mass spectra of IIa-IIc are also consistent with the proposed structures. The fragmentation of IIa-IIc under electron bombardment is represented in Scheme 1. The most interesting ion in the mass spectra of all three compounds is the ion with m/e 84, which forms as a result of the splitting off of an R-CNO fragment from the molecular ion (M<sup>+</sup>).

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TABLE 1. Data from the PMR Spectra of IIa-IId ( $\delta$ , ppm relative to HMDS in CDCl<sub>3</sub>)

Com- pound	CH <sub>2</sub> C=	CH <sub>2</sub> O	2CH2	R
IIa	3,06 s	3,91 m	1,7-2,35m	OCH <sub>3</sub> 3,64 s
IIb	3,09 s	3,98 m	1,78-2,42m	CH <sub>3</sub> 2,44 s
IIc	3,09 s	3,98 m	~2,19 m	Ph~7,54(2H)
IId <sup>*</sup>	3,2 s	3,93 m	1,8-2,4 m	~7,26(3H)

\*Spectrum in CC14.



Scheme 1

Along with the spectral characteristics, structure III is confirmed by the back synthesis

$$C_{s}H_{s}C \equiv N \rightarrow O + CH \equiv C - (CH_{s})_{s}OH \rightarrow (III)$$

The rearrangement of Id was studied in various solvents. In dry DMSO the yield of III was reduced slightly, and in dry hempa it decreased by a factor of  $\sim$ 15. Compound IV, whose elemental analysis corresponds to the product of the formation addition of a molecule of H<sub>2</sub>O to III, was isolated as the main product. The IR spectrum of IV showed a broad band at 3300 cm<sup>-1</sup>. The <sup>13</sup>C NMR spectrum ( $\delta$ , ppm relative to TMS in DMFA-d<sub>7</sub>) of IV had signals corresponding to the carbons of a phenyl ring (131.9 s, 131.1, 130.1, 127.6), as well as to carbons of C=N (158.3 s), O-C-O (110.3 s), and CH<sub>2</sub>O (62.0 t) groups. According to the value of the chemical shift, the CH<sub>2</sub>O group is located in the aliphatic chain rather than in the ring. In addition, the spectrum contained signals of three more CH<sub>2</sub> groups (44.5 t, 36.0 t, 28.5 t). On the basis of these data we can propose the following structure for IV:



The PMR spectrum\* ( $\delta$ , ppm relative to HMDS in DMFA-d<sub>7</sub>) of IV had the signals of an AB

<sup>\*</sup>The spectrum was obtained following the addition of  $CF_3COOH$  to the ampul in order to eliminate the signals of the OH protons, which hide the triplet with  $\delta$  3.53 ppm. No changes were observed in the remaining signals.

system of protons (3.38 d and 3.13 d,  $J_{AB} = 18.5$  Hz), as well as signals at 7.65 (m, 2H, Ph), 7.33 (m, 3H, Ph), 3.53 (t, CH<sub>2</sub>O), and 1.45-2.11 (m, 2CH<sub>2</sub>).

Most of the peaks in the mass spectrum of IV can be explained, if we assume that under electron bombardment  $H_2O$  splits off from  $M^+$  to form isoxazole III.\* However, in the mass spectrum of IV there were intense peaks with m/e 87 and 135, which were not present in the mass spectrum of III. It may be postulated that the reversible transitions  $IV \rightleftharpoons V$  take place at the temperature of the recording of the mass spectrum (130°C), and the ions with m/e 87 and 135 form from V:



The fragmentation of IV under electron bombardment is represented in Scheme 2.



It should be noted that at the temperature of the recording of the NMR spectra the IV  $\rightleftharpoons$  V equilibrium either does not exist or is strongly shifted in the direction of IV, since only the signals of IV were observed in the <sup>13</sup>C NMR and <sup>1</sup>H NMR spectra.

Compound IV remained unchanged upon heating in DMFA at 70-90°C for 8 h. However, IV underwent reactions with acids, one of which produced spiro[3-phenylisoxazoline-5,2'-tetrahydrofuran] (IId):

$$(III) \stackrel{HNO_2}{\leftarrow} (IV) \stackrel{Et_2O \cdot BF_3}{\longrightarrow} (III) + (IId)$$

The structure of IId was proved with the aid of the spectral data (see Tables 1 and 2 and Scheme 1). Since neither IId nor III was converted into IV upon heating in aqueous DMFA,

\*All these peaks were present in the mass spectrum of a known sample of III.

Com- pound	C3 .	C4	Cs	с <sup>5</sup> '	C <sub>3</sub> ,	C <sup>4′</sup>	R
IIa	150,1 s	38,5 t *	116,3 s	67,1 t	<b>3</b> 2,5 t	<b>22,3</b> t	C=O 159,9 s OCH <sub>3</sub> 51,2 q
IIb	<b>132,9</b> s	39,7 t	116,7s	67,9t	<b>32,4</b> t	22,2 t	C=N 109,2 s
IIc	<b>158,1</b> s	<b>38,4</b> t	118,2 s	<b>68,6</b> t	<b>34,1</b> t	23,9 t	C=O 192,5 s CH <sub>3</sub> 25,6 q
IId <sup>†</sup>	155,5 s	41,2t	114,8 s	<b>67,1</b> t	33,4 t	<b>23,</b> 8 t	Ph. 129,5 Ph 128,9 127,8 125,7

TABLE 2. Data from the <sup>13</sup>C NMR Spectra of IIa-IId ( $\delta$ , ppm relative to TMS in CHCl<sub>3</sub>)

\*The assignment was made with the aid of selective monochromatic decoupling from the protons of the CH<sub>2</sub> group of the isoxazoline ring (306 Hz relative to HMDS in the PMR spectrum). +In CCl<sub>4</sub>.

it may be postulated that IV is the primary product of the rearrangment of Id. This hypothesis is supported by the investigation of the rearrangement of Id in aqueous DMFA, DMSO, and hempa in the presence of urea for the binding of the  $HNO_2$  formed. Compound IV was isolated in all cases, its yield being >70% in hempa. Under these conditions it was possible to also isolate IId, whose formation is clearly promoted by the addition of H<sub>2</sub>O, in all the solvents. For example, while in dry DMFA the formation of IId could not be detected at all, in aqueous DMFA this product was obtained with a 15-20% yield.

The data presented show that the rearrangement of Id first results in the formation of IV, which is then converted under the influence of the  $HNO_2$  produced in the reaction into IId and III. It is still unclear whether III is obtained directly from IV or through the preliminary formation of IId.\*

The influence of additions of water and urea to DMFA has also been investigated for Ia-Ic. In this case, it was not possible to isolate compounds of type IV. Therefore, it cannot be asserted that the compounds of this type are intermediates in the formation of IIa-IIc, although such an hypothesis seems very likely, since in the presence of urea the yields of IIa-IIc were always reduced. The addition of water, as in the case of Id, promotes the formation of the spiro compounds in the cases of Ia and Ic, but has a negative effect on the yield of the final product in the case of Ib.

Polar solvents are clearly better for carrying out the rearrangement. However, this reaction also takes place in several other solvents. For example, in dry acetone Id was converted into III (15.4% yield), and in aqueous acetone the yield of III increased to 49%.

## EXPERIMENTAL

The <sup>13</sup>C NMR spectra were obtained on a JEOL PFT-100 instrument at 25.15 MHz, the PMR spectra were obtained on a Perkin-Elmer R-12 instrument, and the mass spectra were obtained on a Varian CH-6 instrument with direct introduction of the sample into the ion source, an energy of the ionizing electrons equal to 70 eV, an accelerating voltage of 1.75 kV, and an emission current of 100  $\mu$ A.

Silica gel LSL 5/40 with a luminescent indicator was used for the preparative TLC (the eluent was a 1:1 chloroform-ether mixture).

Compounds Ia-Id were obtained by adding N-hydroxy-3-nitro-4,5-dihydro-6H-1,2-oxazine (V) to the respective olefins [3]. The syntheses of Ia and Id have been described in [3].

Synthesis of Ib, First, 3 g of V were added portionwise to 5 ml of acrylonitrile at 5°C, the mixture was stirred for 30 min, 10-15 ml of ether were added, and the flask was

\*Compound IId was smoothly converted into III following treatment with HNO2 in DMFA.

cooled by dry ice. The crystals formed were filtered and washed with 20 ml of cooled ether. This yielded 3.23 g (79%) of Ib, mp 64-66°C (with decomposition). Found: N 20.91%. Cal-culated for  $C_7H_9N_3O_4$ : N 21.16%. IR spectrum (v, cm<sup>-1</sup>): 1365, 1570 (NO<sub>2</sub>), 2260 (C=N).

Synthesis of Ic. First, 2 g of V were added portionwise to 2 ml of freshly redistilled methyl vinyl ketone in 6 ml of hexane at 0-5°C, the mixture was stirred for 30 min, and the flask was cooled by dry ice. The crystals precipitated were filtered and washed with 10 ml of cold ether. This yielded 2.72 g (92%) of Ic, mp 61-62°C (with decomposition). Found: N 12.77%. Calculated for  $C_8H_{12}N_2O_5$ : N 12.96%. IR spectrum (v, cm<sup>-1</sup>): 1365, 1570 (NO<sub>2</sub>), 1730 (C=0).

Synthesis of IIa. A 0.5-g portion of Ia was heated in 15 ml of DMFA (8 h) at 70-80°C, the mixture was poured into  $H_2O$  saturated with NaCl and extracted by ethyl acetate, and the extract was washed with an aqueous solution of NaCl and dried with MgSO<sub>4</sub>. After the solvent was driven off, preparative TLC yielded 0.24 g (60%) of IIa, mp 29-30°C (from hexane),  $R_f$  0.68. Found: C 51.87; H 5.93; N 7.78%. Calculated for  $C_8H_{11}NO_4$ : C 51.89; H 5.94; N 7.57%. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1590 (C=N), 1735 (C=O).

In aqueous DMFA (DMFA: $H_20 = 5:1$  by volume) under similar conditions the yield of IIa was 75%, and with the addition of 0.25 g of urea it was 40%.

Synthesis of IIb. A 0.55-g portion of Ib was heated in 15 ml of DMFA for 8 h at 70-80°C, the mixture was poured into H<sub>2</sub>O saturated with NaCl and extracted by ethyl acetate, and the extract was washed with an aqueous NaCl solution and dried with MgSO<sub>4</sub>. After the solvent was driven off, preparative TLC yielded 0.23 g (55%) of IIb, mp 36-37°C (from hexane), R<sub>f</sub> 0.7. Found: C 55.28; H 5.33; N 18.65%. Calculated for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C 55.26; H 5.26; N 18.42%. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1565 (C=N), 2245 (C=N).

In a DMFA-H<sub>2</sub>O mixture (5:1 by volume) under similar conditions the yield of IIb was 31%, and with the addition of 0.32 g of urea it was 15%.

Synthesis of IIc. A 0.65-g portion of Ic was heated in 15 ml of DMFA for 8 h at 70-80°C, the mixture was poured into water saturated with NaCl and extracted with ethyl acetate, and the extract was washed with an aqueous solution of NaCl and dried with MgSO<sub>4</sub>. After the solvent was driven off, preparative TLC yielded 0.28 g (55%) of IIc, mp 29-30°C (from hexane), Rf 0.71. Found: C 56.41; H 6.55; N 8.15%. Calculated for C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub>: C 56.80; H 6.51; N 8.28%. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1590 (C=N), 1715 (C=O).

In a DMFA- $H_2O$  mixture (5:1 by volume) under similar conditions the yield of IIc was 60.5%, and with the addition of 0.37 g of urea it was 41.5%.

<u>Rearrangement of Id.</u> a. A 0.5-g portion of Id was heated in 15 ml of DMFA for 8 h at 70-80°C, the mixture was poured into  $H_2O$  saturated with NaCl and extracted with ethyl acetate, and the extract was washed with an aqueous solution of NaCl and dried with MgSO<sub>4</sub>. After the solvent was driven off, preparative TLC yielded 0.32 g (79%) of III, mp 53-55°C (from 1:1 hexane-benzene),  $R_f 0.4O$ . The Id obtained did not produce any melting-point depression with the product of a back synthesis.

In a DMFA-H<sub>2</sub>O mixture (5:1 by volume) under similar conditions the yield of III was 61.5%. In addition, IId was isolated with a 16.5% yield, mp 63-65°C,  $R_f$  0.73. Found: C 70.77; H 6.65; N 7.04%. Calculated for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>: C 70.93; H 6.40; N 6.98%.

In aqueous DMFA in the presence of 0.6 g of urea under similar conditions the yields were 20.5% of III, 8% of IId, and 30.2% of IV, mp 125-127°C (from ethyl acetate),  $R_f$  0.11. Found: C 65.11; H 7.02; N 6.62%. Calculated for  $C_{12}H_{15}NO_3$ : C 65.16; H 6.78; N 6.33%. IR spectrum (v, cm<sup>-1</sup>): 3300 (OH).

b. Similarly, in dry DMSO the yield was 69% of III, in aqueous DMSO it was 57.6% of III, and in aqueous DMSO in the presence of urea the yields were 37% of III, 12.3% of IId, and 13.6% of IV.

c. A mixture of 0.5 g of Id, 15 ml of hempa, 3 ml of H<sub>2</sub>O, and 0.24 g of urea was heated for 8 h at 70-80°C, poured into water saturated with NaCl, and extracted with ethyl acetate. The extract was washed with an aqueous solution of NaCl and dried with MgSO<sub>4</sub>. The crystalline product obtained after the solvent was driven off was washed on a filter with a 1:1 chloroform-ether mixture. This yielded 0.28 g of IV. From the filtrate 0.05 g (12.5%) of III, 0.02 g (5%) of IId, and 0.03 g of IV were obtained by TLC. The total yield of IV was 70.5%. Under similar conditions in the absence of urea the yields were 41% of III, 8.2% of IId, and 26.4% of IV. In dry hempa the yields were 5% of III and 40.7% of IV.

<u>Reaction of IV and IId with  $Et_20 \cdot BF_3$  and  $HNO_2$ .</u> a. Six drops of  $Et_20 \cdot BF_3$  were added to a suspension of 0.2 g of IV in 20 ml of ethyl acetate, and the mixture was held at  $\sim 20^{\circ}C$  for 30 min, washed with a solution of NaHCO<sub>3</sub> and water, and dried with MgSO<sub>4</sub>. After the solvent was driven off, 0.06 g (32.6%) of III and 0.09 g (49%) of IId were isolated by preparative TLC. Under similar conditions III was obtained with an 89% yield from IId.

b. A solution of 0.0316 ml of conc. HCl in 1.5 ml of DMFA was added to a cooled suspension of 0.025 g of NaNO<sub>2</sub> in 2 ml of DMFA, the mixture was stirred for 10 min, and 0.08 g of IV was added. After heating for 7 h at 70°C and the usual treatment, 0.07 g (95%) of III was obtained.

Compound III was obtained with a 91.5% yield from IId under similar conditions.

Synthesis of III (Back Synthesis). A solution of 0.81 ml of Et<sub>3</sub>N in 1 ml of absolute benzene was added dropwise with stirring at 15°C to 0.5 g of chlorobenzaldoxime and 0.55 g of 1-pentyn-5-ol in 9 ml of absolute benzene. The precipitate formed was filtered off, and the filtrate was washed with water and dried with MgSO<sub>4</sub>. After the benzene was distilled off, 0.49 g (75%) of III with mp 53-55°C (from a 1:1 hexane-benzene mixture) was obtained. Found: C 71.25; H 6.54; N 6.91%. Calculated for  $C_{12}H_{13}NO_2$ : C 70.93; H 6.40; N 6.89%. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1615 (aromatic C=C), 3280 (OH). PMR spectrum ( $\delta$ , ppm relative to HMDS in CDCl<sub>3</sub>): 6.28 (s, CH), 2.04 (s, OH), 3.66 (t, CH<sub>2</sub>O), 2.84 (t, CH<sub>2</sub>C=), 1.94 (m, CCH<sub>2</sub>C). <sup>13</sup>C NMR spectrum ( $\delta$ , ppm relative to TMS in CHCl<sub>3</sub>): 170.3 (s, C<sup>5</sup>), 158.9 (s, C<sup>3</sup>), 95.7 (d, C<sup>4</sup>), 57.6 (t, CH<sub>2</sub>O), 26.8 (t) and 19.7 (t, 2 CH<sub>2</sub>), 125.4 (s), 123.5, 125.3, 126.3 (Ph).

## CONCLUSIONS

1. 8-Substituted 6-nitro-2,9-dioxa-1-azabicyclo[4.3.0]nonanes have been rearranged to form 3-substituted spiro[isoxazoline-5,2'-tetrahydrofurans].

2. 8-Phenyl-6-nitro-2,9-dioxa-1-azabicyclo[4.3.0]nonane has been rearranged to form 3phenyl-5-hydroxy-5-(γ-hydroxypropyl)isoxazoline, which is converted under the action of nitrous acid into 3-phenyl-5-(γ-hydroxypropyl)isoxazole and spiro[3-phenylisoxazoline-5,2'tetrahydrofuran].

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