4,5,6H-OXAZINE-1,2 N-OXIDES IN THE 1,3-CYCLOADDITION REACTION

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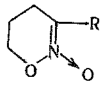
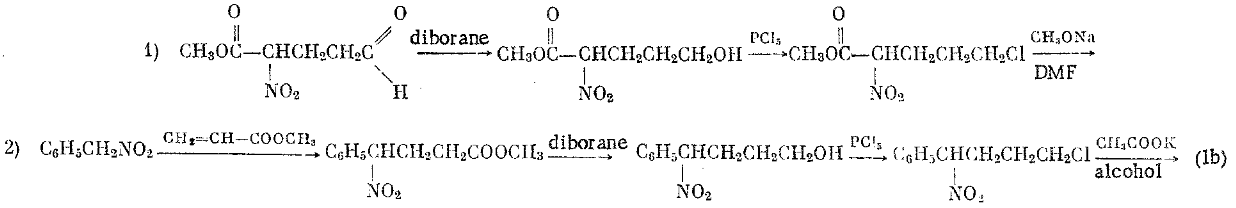
We showed earlier on the example of isoxazoline N-oxides that five-membered cyclic nitron esters possess decreased reactivity in the 1,3-cycloaddition reaction in comparison with linear nitron esters containing analogous substituents at the carbon atom of the 1,3-dipole [1]. To study the effect of the size of the nitron ester ring on its reactivity we synthesized six-membered nitron esters of the general formula


(I)

$R=COOCH_3(a);\ C_6H_5(b);\ NO_2(c)$

and investigated their behavior in the 1,3-cycloaddition reaction with compounds containing a C = C bond.

The principle of intramolecular cyclization of anions of halonitro compounds, which was known earlier for γ-halonitro derivatives [2], was used to prepare (I). We extended this reaction to δ-halonitro compounds and showed that in this case intramolecular O-alkylation also occurs with formation of 4,5,6H-oxazine-1,2 N-oxides.



$$1)\ CH_3O\overset{\overset{O}{\|}}{C}-\underset{\underset{NO_2}{|}}{C}HCH_2CH_2C\overset{O}{\underset{H}{\diagup\!\!\diagdown}} \xrightarrow{\text{diborane}} CH_3O\overset{\overset{O}{\|}}{C}-\underset{\underset{NO_2}{|}}{C}HCH_2CH_2CH_2OH \xrightarrow{PCl_5} CH_3O\overset{\overset{O}{\|}}{C}-\underset{\underset{NO_2}{|}}{C}HCH_2CH_2CH_2Cl \xrightarrow[\text{DMF}]{CH_3ONa}$$

$$2)\ C_6H_5CH_2NO_2 \xrightarrow{CH_2=CH-COOCH_3} C_6H_5\underset{\underset{NO_2}{|}}{C}HCH_2CH_2COOCH_3 \xrightarrow{\text{diborane}} C_6H_5\underset{\underset{NO_2}{|}}{C}HCH_2CH_2CH_2OH \xrightarrow{PCl_5} C_6H_5\underset{\underset{NO_2}{|}}{C}HCH_2CH_2CH_2Cl \xrightarrow[\text{alcohol}]{CH_3COOK} (Ib),$$

$$3)\ (O_2N)_3CCH_2CH_2CH_2OH \xrightarrow{PBr_3} (O_2N)_3CCH_2CH_2CH_2Br \xrightarrow{KOH+NH_2OH} KC(NO_2)_2CH_2CH_2CH_2Br \rightarrow (Ic)$$

The structure of (I) was confirmed by their chemical transformations and analysis of IR spectra. In the IR spectra the shift of the C = N absorption band by 25-50 cm^{-1} in the direction of lower frequencies in comparison with the corresponding isoxazoline N-oxides [1, 3] attracts attention. Compounds (I) were found to be significantly more active in the 1,3-cycloaddition reaction than their five-membered analogs. Thus, (Ia) reacts in 4-5 h with methyl acrylate and in 3 days with styrene,* while for 3-carbmethoxyisoxazoline N-oxide this time amounts to 13 days and ~2 months, respectively [1]. In the case of (Ib) the reaction with methyl acrylate and styrene is over in 7 and 11 days, respectively, while 3-phenylisoxazoline N-oxide does not react with styrene in general at room temperature and the reaction with methyl acrylate is complete in 1.5 months [1]. In contrast to the corresponding isoxazoline N-oxides, (Ia, b) also react with nonactivated olefins at room temperature: we could obtain adducts with allyl chloride for both compounds. Compound (Ic) is the most reactive of the N-oxides studied by us: its reaction with methyl

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* The end of reaction was judged by the disappearance of the initial N-oxide in the reaction mixture (chromatography on Al_2O_3).

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TABLE 1

Product	Reaction time	Yield, %	mp, °C	Found, %			Calculated, %		
				C	H	N	C	H	N
(IIa)	3 days	72	75 *	63,69 63,71	6,67 6,63	5,55 5,26	63,87	6,46	5,32
(IIb)	5 h	76	74—79 *	48,95 48,73	6,43 6,51	5,33 5,30	48,98	6,12	5,71
(IIc)	3 days	70,5	75—87 *	45,70 45,96	5,93 6,16	6,26 6,30	45,86	5,94	5,94
(IIIa)	11 days	80	80—82 *	77,00 77,06	6,82 7,04	5,24 5,36	76,95	6,76	4,98
(IIIb)		71	98—100 *	64,01 64,04	6,66 6,73	5,55 5,54	63,88	6,46	5,32
(IIIc)	7 days	8	175—176 †	63,87 63,94	6,60 6,43	5,05	63,88	6,46	5,32
(IIId)	11 days	46	74—77 *	61,69 61,29	6,28 6,50	6,02 6,04	61,53	6,31	5,52
(IVa)	10 min	Quant.	92—93 ‡	57,76 57,83	5,72 5,89	10,99 11,03	57,60	5,60	11,20
(IVb)	5 min	"	73,5—74,5 **	41,29 41,39	5,52 5,60	11,54 11,76	41,38	5,17	12,07

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* From hexane.

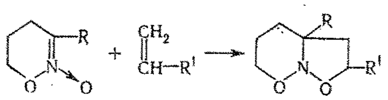
† From a 1:1 benzene–hexane mixture.

‡ From a 3:2 hexane–chloroform mixture.

** From CCl_4.

acrylate and styrene is over in several minutes, while several hours are necessary for completion of the reaction of these compounds with 3-nitroisoxazoline N-oxide under these conditions [4]. At the same time, it should be noted that the same order of activating effect of substituents in position 3 is also maintained for the series of six-membered nitronic esters that was observed for isoxazoline N-oxides: $NO_2 > COOCH_3 > C_6H_5$ [1].

The reaction products of (I) with olefins are derivatives of a new heterocyclic system, (4,3,0)-dioxa-2,9-aza-1-nonane



(II) $R = COOCH_3$ $R' = C_6H_5$ (a); $COOCH_3$ (b); CH_2Cl (c)
(III) $R = C_6H_5$ $R' = C_6H_5$ (a); $COOCH_3$ (b, c); CH_2Cl (d)
(IV) $R = NO_2$ $R' = C_6H_5$ (a); $COOCH_3$ (b)

IR spectra of (II)-(IV) contain bands characteristic for the O–N–O grouping (1040-1060 cm^{-1}) and functional substituents. The position of R' is assigned on the basis of data obtained earlier on the strict structural course of the 1,3-cycloaddition reaction of nitronic esters* [5].

The cycloaddition reaction was carried out by maintaining the oxazine-1,2 N-oxide for a certain time with a three-fivefold excess of the dipolarophile at room temperature; the excess unsaturated compound was distilled and the product was recrystallized. Experimental conditions are presented in Table 1. In a series of cases the obtained materials do not have a sharp melting point. This evidently indicates that they are mixtures of cis-trans isomers (occurring at the position of R' in relation to R). An analogous picture is also observed in reactions of 3-nitroisoxazoline N-oxides with the corresponding dipolarophiles [4]. In the case of reaction of (Ib) with methyl acrylate we could separate isomers (IIIb) and (IIIc) by recrystallization from hexane. Both of these materials have identical R_f (chromatography on Al_2O_3) and identical IR spectra, which makes the hypothesis that these compounds are structural isomers (R' in position 5 or 4 of the ring) not very likely and, on the other hand, is easily explained if they are cis-trans isomers. It is seen from Table 1 that adducts having a sharp melting point are always obtained upon reaction of (I) with styrene. It is probable that in this case the reaction leads to only one of the possible isomers.

It should be noted that (IVa, b) are unstable in solution and all operations with them should be carried out as rapidly as possible. Compounds (IVa, b) are stable in a solid state and can be stored for a long time, particularly at reduced temperature. All of the remaining adducts are completely stable.

EXPERIMENTAL

Methyl Ester of 1-Nitro-4-hydroxyvaleric Acid (V). To 6.32 g of the methyl ester of 5-oxo-2-nitrovaleric acid [6] in 20 ml of abs. tetrahydrofuran (THF) at 15°C was added dropwise 35 ml of a solution (1.55 N) of diborane in THF; the mixture was stirred for 15 min at 20° and decomposed with abs. CH_3OH until gas evolution ceased. Then an additional 30 ml of abs. CH_3OH was added, the mixture was boiled for 3 h, and the solvents were distilled. We obtained 3.98 g (62%) of (V); bp 100-101° (0.35 mm); n_D^{20} 1.4550; d_4^{20} 1.2426. Found: C 41.39; 41.13; H 6.61; 6.59%; MR 38.69. $C_6H_{11}NO_5$. Calculated: C 40.69; H 6.21%; MR 38.67.

Methyl Ester of 2-Nitro-5-chlorovaleric Acid (VI). To 8.83 g of PCl_5 in 15 ml of abs. benzene at 10-12° was added dropwise a solution of 6.91 g of (V) in 10 ml of abs. benzene and the mixture was stirred for 2.5 h at 50°. The reaction mixture was poured into 300 ml of water, the benzene layer was separated, and the aqueous layer was extracted with ether. The ether–benzene extract was washed two times with water, dried over $MgSO_4$, and the solvents were distilled. We obtained 3.99 g (52.5%) of (VI), bp 88-91° (0.5 mm), n_D^{20} 1.4611. Found: N 7.5; 7.48%. $C_6H_{10}NO_2Cl$. Calculated: N 7.16%. The material darkens upon standing.

Preparation of (Ia). We left 1.61 g of (VI) and Na methoxide in CH_3OH (from 0.19 g of Na) for 20 min, evaporated the alcohol, and dissolved the remaining crystals of the Na salt of (VI) in dimethylformamide (DMF). After 2 h the DMF was distilled and the residue was extracted with boiling hexane. The hexane

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*At the present time we strictly demonstrated this position of R' on the basis of analysis of PMR spectra.

yielded 1.06 g (81%) of (Ia), mp 62-63° (from hexane). Found: C 45.30; 45.36; H 5.63; 5.66; N 8.51; 8.53%. $C_6H_9NO_4$. Calculated: C 45.28; H 5.66; N 8.80%. IR spectrum (ν, cm^{-1}): 1570 ($C = N \rightarrow O$), 1740 ($C = O$).

Methyl Ester of 4-Phenyl-4-nitrobutyric Acid (VII). To 29.3 g of $C_6H_5CH_2NO_2$ simultaneously were added dropwise with stirring 9.25 g of methyl acrylate and 7.4 ml of $(C_2H_5)_3N$, maintaining a temperature of 5-10°. The reaction mixture was stirred at this temperature for 3-5 h and held at 20° for 15 h. Distillation yielded 18.7 g (78%) of (VII); bp 123° (0.5 mm); n_D^{20} 1.5195; d_4^{20} 1.1777. Found: N 6.16; 6.37%; MR 56.85. $C_{11}H_{13}NO_4$. Calculated: N 6.28%; MR 56.84.

1-Phenyl-1-nitro-4-butanol (VIII). To 90 ml of a solution of diborane in THF (1.4 N) was added dropwise at 10-15° 18.7 g of (VII) in 30 ml of THF and the mixture was left for 15 h. The excess diborane was decomposed with abs. CH_3OH until gas evolution ceased, an additional 30 ml of abs. CH_3OH was added, the mixture was boiled for 3 h, and the solvents were distilled. We obtained 12.5 g (76.5%) of (VIII), bp 120° (0.45 mm), n_D^{20} 1.5340; d_4^{20} 1.1630. Found: N 7.61; 7.73%; MR 52.10. $C_{10}H_{13}NO_3$. Calculated: N 7.18%; MR 52.17.

1-Phenyl-1-nitro-4-chlorobutane (IX). To 5.3 g of PCl_5 in 15 ml of abs. benzene was added dropwise with stirring at 6-8° over 1 h a solution of 3.93 g of (VIII) in 15 ml of abs. benzene. The solution was stirred at this temperature for 2 h, poured into 200 ml of water, and extracted with benzene; the benzene extract was washed one time with a saturated soda solution, then two times with water, dried over $MgSO_4$, and distilled two times. We obtained 1.8 g (42%) of (IX), bp 115° (0.5 mm); n_D^{20} 1.5328; d_4^{20} 1.1992. Found: N 5.98; 6.18%; MR 55.24. $C_{10}H_{12}NO_2Cl$. Calculated: N 6.55%; MR 55.48. The material acquires a violet color upon standing.

Preparation of (Ib). We held 1.8 g of (IX) and 5 g of CH_3COOK in 30 ml of C_2H_5OH at 70° for 40 min, removed the alcohol, and extracted the residue with hot hexane. After removal of the hexane 1.28 g of oily crystals were obtained. Recrystallization from hexane yielded 0.88 g (59%) of (Ib); mp 80-81°. Found: C 68.24; 68.30; H 6.18; 6.31; N 7.64; 7.66%. $C_{10}H_{11}O_2$. Calculated: C 67.79; H 6.22; N 7.91%. IR spectrum (ν, cm^{-1}): 1570, 1590 ($C = N \rightarrow O$).

1,1,1-Trinitro-4-bromobutane (X). To 8.15 ml of PBr_3 in 20 ml of abs. benzene at 5-10° was added dropwise a solution of 18 g of 1,1,1-trinitrobutanol [7] in 10 ml of abs. benzene and the mixture was stirred at 60-70° for 2.5 h. The reaction mixture was poured into 100 ml of water and extracted with benzene; the benzene extract was washed with water and dried over $MgSO_4$, and the benzene was distilled. We obtained 11.4 g (49%) (X); bp 70° (0.35 mm); n_D^{20} 1.4977; d_4^{20} 1.7315. Found: N 15.72; 15.98%; MR 46.01. $C_4H_6BrN_3O_6$. Calculated: N 15.44%; MR 45.41.

Preparation of (Ic). To a solution of 1.75 g of (X) in 7 ml of CH_3OH at −10° was added a denitrating mixture prepared from 0.9 g of $NH_2OH \cdot HCl$ and 1.48 g of KOH in 15 ml of CH_3OH. The mixture was stirred for 1 h at this temperature and 1.45 g of the K salt was filtered. The obtained salt was dissolved in 15 ml of warm water and left for 15 h at ~20°; 0.55 of precipitated crystals of (Ic) were separated. Extraction of the aqueous solution with ethyl acetate yielded an additional 0.15 g of (Ic). Total yield of (Ic) was 0.7 g (87.5%, based on the salt); mp 77-79° (from alcohol). Found: C 33.24; 32.75; H 4.08; 4.08; N 18.94; 18.94%. $C_4H_6N_2O_4$. Calculated: C 32.88; H 4.11; N 19.18%. IR spectrum (ν, cm^{-1}): 1610 ($C = N \rightarrow O$); 1510; 1315 (NO_2).

CONCLUSIONS

1. A method of synthesis of N-oxides of 3-carbmethoxy-, 3-phenyl-, and 3-nitro-4,5,6H-oxazine-1,2 was developed.

2. Six-membered nitronic esters possess greater reactivity in the 1,3-cycloaddition reaction in comparison with their five-membered analogs.

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