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5-BROMO-5-NITROTETRAHYDRO-1,3-OXAZINES *

5-BROMO-5-NITROTETRAHYDRO-1,3-OKSAZYNY

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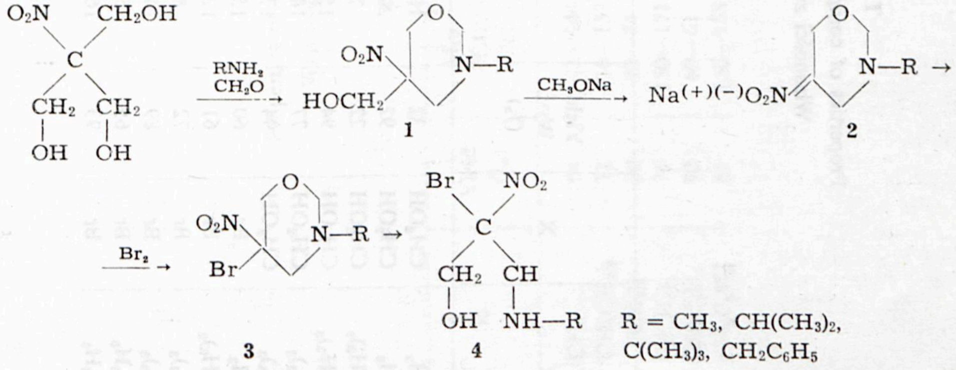
Continuing our experiments on formation of tetrahydro-1,3-oxazine derivatives with the nitro group in position 5, we have prepared now 3-alkyl-5-bromo-5-nitrotetrahydro-1,3-oxazines (3). Compounds of this structure have shown interesting biological properties [1,2]. Our attempts to obtain 3 in reaction of 2-bromo-2-nitropropanediol-1,3 with 1,3,5-trialkylhexahydro-*s*-triazines failed. The decomposition of the starting materials occurred, and no product could be isolated from the reaction mixture. The synthesis of 3 was accomplished starting from corresponding 3-alkyl-5-hydroxymethyl-5-nitrotetrahydro-1,3-oxazines (1). Compounds **1** ($R{=}CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$) were prepared by the method described previously for **1**, $R{=}CH_2C_6H_5$ [3] from 2-hydroxymethyl-2-nitropropandiol-1,3, formaldehyde and the corresponding amine.



$R = CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$

Compounds **1** were treated with sodium methoxide to split off formaldehyde, and to convert **1** into sodium salt of the corresponding 3-alkyl-5-nitrotetrahydro-1,3-oxazine (**2**). Sodium salts **2** were then reacted with equimolar amount of bromine to produce **3**, $R{=}CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$, in good yields. When R was benzyl or *tert*-butyl products **3** were crystalline solids. With other R (methyl, isopropyl) the products were liquid, and were isolated as solid hydrochlorides.

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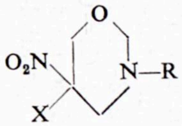
* Part CVIII on Chemistry of Nitroparaffins. Part CVII: Piotrowska H., *Roczniki Chem.*, **46**, 2357 (1972).

Table 1 — Tablica 1

Properties of compounds **1** and **3** and of their hydrochlorides

Własności związków **1** i **3** i ich chlorowodorków

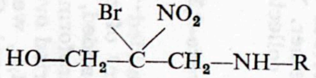


No Nr	Compound No Nr związku	R	X	Yield Wyd. (%)	M. p. T. t. °C	Empirical formula Wzór sumaryczny	Analysis — Analiza, % Calcd. — obliczono C	H	N	Found — otrzymano C	H	N
1	**1**	CH_3	CH_2OH	32	102—103	$C_6H_{12}O_4N_2$	40.9	6.9	15.9	41.1	7.0	15.9
2	**1**.HCl	CH_3	CH_2OH	92	209—210(d)	$C_6H_{13}O_4N_2Cl$	—	—	13.1	—	—	13.3
3	**1**	$CH(CH_3)_2$	CH_2OH	22	74—75	$C_8H_{16}O_4N_2$	47.1	7.9	13.7	47.2	7.9	14.0
4	**1**.HCl	$CH(CH_3)_2$	CH_2OH	94	152—153(d)	$C_8H_{18}O_4N_2Cl$	—	—	11.6	—	—	11.5
5	**1**	$C(CH_3)_3$	CH_2OH	77	147—148	$C_9H_{18}O_4N_2$	49.5	8.3	12.8	49.7	8.4	12.9
6	**1**.HCl	$C(CH_3)_3$	CH_2OH	94	178—179(d)	$C_9H_{19}O_4N_2Cl$	—	—	11.0	—	—	11.1
7	**3**.HCl	CH_3	Br	60	154—155(d)	$C_5H_{10}O_3N_2ClBr$	22.9	3.8	10.7	23.1	3.9	10.6
8	**3**.HCl	$CH(CH_3)_2$	Br	61	124—125(d)	$C_7H_{14}O_3N_2ClBr$	29.4	4.8	9.7	29.6	5.0	9.5
9	**3**	$C(CH_3)_3$	Br	72	87—88	$C_8H_{15}O_3N_2Br$	36.0	5.7	10.5	36.2	5.8	10.7
10	**3**.HCl	$C(CH_3)_3$	Br	89	149—150(d)	$C_8H_{16}O_3N_2ClBr$	—	—	9.2	—	—	9.4
11	**3**	$CH_2C_6H_5$	Br	65	51—52	$C_{11}H_{13}O_3N_2Br$	43,9	4.4	9.3	44.0	4.5	9.4
12	**3**.HCl	$CH_2C_6H_5$	Br	93	165—166(d)	$C_{11}H_{14}O_3N_2ClBr$	—	—	8.3	—	—	8.5

T a b l e 2 — T a b l i c a 2

Properties of compounds **4** and of their hydrochlorides

Własności związków **4** i ich chlorowodorków



$$HO{-}CH_2{-}\overset{Br\quad NO_2}{C}{-}CH_2{-}NH{-}R$$

No Nr	Compound No Nr związku	R	Yield (%)	M.p. T.t. °C	Empirical formula Wzór sumaryczny	Analysis — Analiza, %					
						Calcd. — obliczono			Found—otrzymano		
						C	H	N	C	H	N
1	4·HCl	CH_3	64	143—144	$C_4H_{10}O_3N_2ClBr$	19.2	4.0	11.2	19.3	4.2	11.1
2	4·HCl	$CH(CH_3)_2$	72	136—137	$C_6H_{14}O_3N_2ClBr$	25.9	5.0	10.0	26.1	5.2	10.1
3	4	$C(CH_3)_3$	80	73—74	$C_7H_{15}O_3N_2Br$	—	—	11.0	—	—	10.8
4	4·HCl	$C(CH_3)_3$	76	150—151	$C_7H_{16}O_3N_2ClBr$	28.8	5.5	9.6	29.0	5.7	9.7
5	4	$CH_2C_6H_5$	92	60—61	$C_{10}H_{13}O_3N_2Br$	—	—	9.7	—	—	9.6
6	4·HCl	$CH_2C_6H_5$	81	156—158	$C_{10}H_{14}O_3N_2ClBr$	36.9	4.3	8.6	37.0	4.4	8.8

Hydrochlorides of **3** are readily subject to ring opening, yielding hydrochlorides of 2-bromo-2-nitro-3-N-alkylaminopropanol (**4**). Two free bases **4**, R=$C(CH_3)_3$, $CH_2C_6H_5$, were found to be crystalline. They were unstable in an alkaline medium and also decomposed on standing. When warmed with formaldehyde in ethanol they cyclized to tetrahydro-1,3-oxazines **3**.

EXPERIMENTAL

3-Alkyl-5-hydroxymethyl-5-nitrotetrahydro-1,3-oxazines (1)

20 g (0.128 mole) of 2-hydroxymethyl-2-nitropropanediol-1,3, 32 g (0.4 mole) of 30% formalin and 2 g $NaHCO_3$ were stirred at 15°C to dissolve the triol. Then 0.128 mole of the suitable primary amine was added slowly with stirring. The temperature rose to 40—45°C. When the exothermic reaction ceased the mixture was warmed at 60°C for 3 hrs. The oily layer was separated, washed with water, treated with small amount of ethanol and left in refrigerator. The crystalline products were crystallized three times from ethanol. Hydrochlorides of **1** were prepared by adding ethereal hydrogen chloride to solution of **1** in ether. Yields and properties of compounds **1** and those of their hydrochlorides are collected in Table 1.

3-Alkyl-5-bromo-5-nitrotetrahydro-1,3-oxazines (3)

0.1 mole of corresponding oxazine **1** was added to sodium methoxide solution obtained from 2.3 g (0.1 mole) of Na and 20 cm^3 of methanol and warmed to 40°C for 30 min. Then 120 cm^3 of chloroform was added, the whole cooled to 0°C and 0.1 mole of bromine dissolved in 20 cm^3 of chloroform added dropwise. The reaction mixture was washed with 5% $NaHCO_3$, water, dried over anh. $MgSO_4$, and the solvent evaporated. Compounds **3**, R = CH_3 and $CH(CH_3)_2$, were isolated in the form of hydrochlorides which were crystallized from ethanol. Compounds **3**, R = $C(CH_3)_3$ and $CH_2C_6H_5$, were crystallized from ethanol. Yields and properties of compounds **3** are collected in Table 1.

2-Bromo-2-nitro-3-N-alkylaminopropanols (4)

2 g of corresponding 3-alkyl-5-bromo-5-nitrotetrahydro-1,3-oxazine (**3**) or its hydrochloride was refluxed for 2 hrs in 100 cm^3 of 80% ethanol and 4 cm^3 conc. HCl. The solvents were removed in vacuo, and the residue crystallized from ethanol yielding hydrochloride of **4**.

Free solid bases **4**, R = $C(CH_3)_3$, $CH_2C_6H_5$ were obtained from hydrochlorides by cautious neutralization with 5% $NaHCO_3$. They crystallized from ethanol. Yields and properties of compounds **4** and those of their hydrochlorides are collected in Table 2.

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3. Urbański T., Gürne D., *Roczniki Chem.*, **28**, 175 (1954).

STRESZCZENIE

3-Alkilo-5-bromo-5-nitrotetrahydro-1,3-oksazyny (**3**, R = CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$) otrzymano z odpowiednich 3-alkilo-5-hydroksymetylo-5-nitrotetrahydro-1,3-oksazyn (**1**) działaniem metoksylanem sodu i bromowaniem powstałych w tej reakcji soli sodowych 3-alkilo-5-nitrotetrahydro-1,3-oksazyn (**2**).

Związki **3**, R = CH_3, $CH(CH_3)_3$ wydzielono jako krystaliczne chlorowodorki. Bromonitrooksazyny **3** ulegają łatwo otwarciu pierścienia w środowisku kwaśnym z utworzeniem chlorowodorków 2-bromo-2-nitro-3-N-alkiloaminopropanoli (**4**). Własności otrzymanych związków zebrano w tablicach 1 i 2.

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