BULLETIN DE L'ACADÉMIE
POLONAISE DES SCIENCES
Cl. III — Vol. III, No. 3, 1955

CHEMISTRY

On some properties of tetrahydro-1,5-oxazines deriving from 1-nitrobutane or 1-nitro(iso)butane

by

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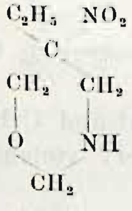
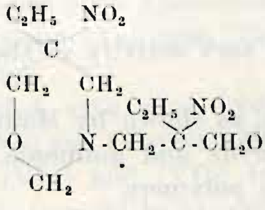
Communicated by T. URBAŃSKI at the meeting of December 13, 1954

It has been shown by E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochyński, A. T. Thomas and T. Urbański [1], that 1-nitropropane can react with formaldehyde and ammonia yielding three new ring compounds. Two of them (I and II) are derivatives of tetrahydro-1,3-oxazine, and one is a derivative of 1-oxa-3-azacyclooctane (III) The compounds which contain these two rings belong to ones which are relatively little known.


I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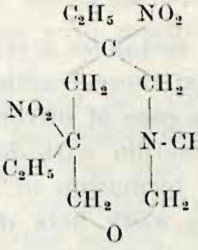
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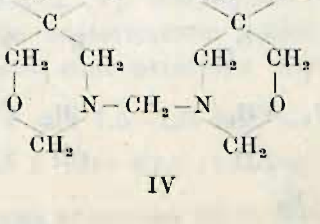
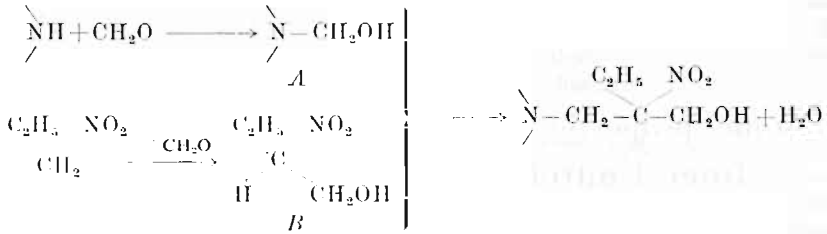
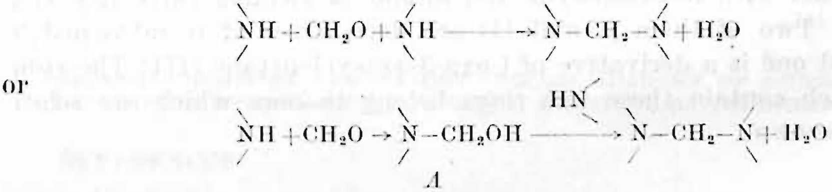

IV

According to T. Urbański and E. Lipska [2], a new compound (IV) with two tetrahydro-1,3-oxazine rings is formed as a result of the reaction of nitroethane formaldehyde and ammonia.

Compound (II) is an N-derivative of (I). The former can be obtained by the action on (I) of 1-nitropropane and two mols of formaldehyde. The reaction giving rise to (I) may occur through the formation of the intermediates (*A*) and (*B*), according to the following diagram:



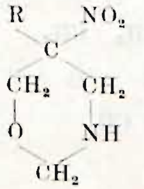
In the case also of a 1-oxa-3-azacyclooctane derivative, the activity of N-hydrogen produced the N-hydroxymethyl compound (III). Finally, in the instance of nitroethane, two tetrahydro-1,3-oxazine rings combined together through a molecule of formaldehyde, probably as shown in the following diagram:



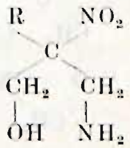
In all instances a relatively high activity of the N-hydrogens is responsible for these reactions.

In the case of nitromethane, as shown by Malinowski and Urbański [3], the reaction with formaldehyde and ammonia is very violent and leads to a formation of resinous polymers.

In the work here described, the authors found that 1-nitrobutane and 1-nitro-(iso)-butane can readily form tetrahydro-1,3-oxazine ring compounds of one simple type (V) only: 5-nitro-5-n-propyl (and 5-isopropyl)-tetrahydro-1,3-oxazines (Va) and (Vb) respectively



V



VI

(a) $R = n\text{-}C_3H_7$ (a) $R = n\text{-}C_3H_7$

(b) $R = i\text{-}C_3H_7$ (b) $R = i\text{-}C_3H_7$

and the open chain aminoalcohols:

2-nitro-2-hydroxymethylpentylamine (VIa)

and 2-nitro-2-hydroxymethyl-3-methylbutylamine (VIb).

All attempts to combine further products (V) with formaldehyde through the ring-nitrogen failed to produce any change in the compound.

This would suggest a relatively low activity of the N-hydrogens of both compounds (Va) and (Vb).

Both compounds were prepared either from 1-nitrobutanes or from the products of the addition of two mols of formaldehyde to the nitroparaffins, i. e. from 2-nitro-2-n-propyl-propanediol-1,3 and 2-nitro-2-isopropyl-propanediol-1,3. The preparation consisted in warming 1 mol of either nitrobutane with 3 mols of formaldehyde and 1 mol of ammonia, or 1 mol of either diol with 1 mol of formaldehyde and 1 mol of ammonia.

After several hours of heating on a steam-bath an oily product resulted. This was dried and dissolved in alcoholic hydrochloride. Crystalline hydrochlorides of (Va) or (Vb) precipitated. A higher yield (10–12% of the theoretical) was obtained when diols, instead of paraffins, were used as starting substances.

In addition to the products (V), aminoalcohols (VI) in the form of more soluble hydrochlorides were also obtained and separated from (V) by fractional crystallisation.

Both hydrochlorides (Va) and (Vb) yielded oily N-nitrosoderivatives,- which on being warmed with hydrochloric acid led to the initial hydrochlorides. The free bases (Va) and (Vb) reacted with methyl iodide to yield dimethyl iodides.

After being boiled with conc. hydrochloric acid for several hours, the hydrochlorides (Va) and (Vb) lost one mol of formaldehyde and formed the hydrochlorides (VIa) and (VIb) respectively. The free bases (VI), when warmed with formaldehyde underwent cyclisation, resulting in bases (V). More details will be given in two other papers [4].

The melting points of the compounds described in this paper are collected in the table on page 182.

According to S. Ślopek [4], tetrahydro-1,3-oxazine derivatives (I) and (V) show a definite bacteriostatic action *in vitro* against various *Mycobateria*. Bacteriostatic concentrations were found to be:

(I) (designated as *T* 41) 7.5–125 mg. %

(Va) (designated as *T* 176) 62.5–125 mg. %.

The product *T* 41 was examined by S. Ślopek *in vivo* against experimental tuberculosis in mice, and an action similar to that of streptomycine was observed [5].

TABLE

Products	m. p.
5-nitro-5-propyl-tetrahydro-1,3-oxazine hydrochlorides:	
(V a) R = n–C_3H_7	190–192°
(V b) R = i–C_3H_7	190°
N-dimethyl iodide of (V a)	199–200°
(V b)	201–202°
(VI a) R = n–C_3H_7	169–170°
(VI b) R = i–C_3H_7	165–167°
Picrate (V a)	163–164°
(V b)	167–168°
(VI b)	158–160°
O-N-dibenzoyl derivative of (VI a)	101–102°

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[1] E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochyński, A. T. Thomas, T. Urbański, J. Chem. Soc. (1947), 924.

[2] T. Urbański and E. Lipska, Roczniki Chemii **26** (1952), 182.

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[4] T. Urbański and H. Piotrowska, Roczniki Chemii (in the press). T. Urbański and J. Kolesińska, Roczniki Chemii (in the press).

[5] T. Urbański, Nature **168** (1951), 562.