Tetrahedron Vol. 27, pp. 1461 to 1464. Pergamon Press 1971. Printed in Great Britain

N-NITROSATION OF N-CYCLOHEXYLSULPHAMIC ACID

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(*Received in the UK* 15 *November* 1970; *Accepted for publication* 27 *November* 1970)

Abstract—The action of nitrous acid on cyclamic acid (N-cyclohexylsulphamic acid) has been investigated and the organic products formed in the reaction have been identified. Using strong nitrosating conditions, cyclohexyl nitrite is formed (76%) together with cyclohexene (23%). The effect of reaction conditions on the yield of these products has been studied using GLC. The evidence suggests that in strong nitrosating conditions cyclohexanol, formed by N-nitrosation, is quantitatively converted to cyclohexyl nitrite.

THE reaction of cyclamic acid and its salts with nitrous acid is one of the main reactions for the determination of these compounds. The reaction may be written as follows (1).

$$NO^+ + C_6H_{11}NHSO_3H \rightarrow H_2SO_4 + N_2 + C_6H_{11}^+ \qquad (1)$$

Published methods of determining cyclamate based on this reaction depend on determination of either the nitrite consumed in the reaction,[1] the sulphuric acid produced,[2] or the organic products formed.[3, 4] Whilst the latter methods should be the most specific, little experimental work has been reported establishing the nature and the yield of the organic products. Cyclohexene and cyclohexanol are generally listed as the main reaction products and cyclohexanone and certain substituted cyclic compounds have also been reported.[4] Cyclohexene is formed in about 24% yield[5] and the authors have shown that in strong nitrosating conditions cyclohexyl nitrite is formed in 76% yield.[6] In the present study the nature and the yields of the organic products formed have been investigated using the technique described by Rees[3] for the extraction of the organic product from the reaction medium prior to GLC analysis.

RESULTS AND DISCUSSION

Cyclamate reacts quantitatively under the conditions of nitrosation used and cyclohexene, cyclohexanol and cyclohexyl nitrite are extracted quantitatively by a single stage extraction from the reaction medium. Analysis shows that under strong nitrosating conditions, cyclohexene and cyclohexyl nitrite are the principal reaction products, whilst in weakly nitrosating conditions mainly cyclohexene and cyclohexanol are formed. The identity of cyclohexyl nitrite as a reaction product is confirmed by comparison with authentic cyclohexyl nitrite synthesised by esterification of cyclohexanol.[6] Cyclohexanone, reported by Richardson and Luton[4] as a reaction product, cannot be formed via N-nitrosation, but may possibly be produced by photolysis of cyclohexyl nitrite. The yields of cyclohexene and of cyclohexyl nitrite produced under various reaction conditions are listed in Table 1. Over a wide range of nitrosating conditions the yield of cyclohexyl nitrite varies from 3 to 76 %, whilst the yield of cyclohexene changes only slightly from 23 to 27 % (Table 1a). For a specific excess of nitrite the yields of cyclohexene and of cyclohexyl nitrite remain practically constant over the cyclamate range 1·25–5 μM/ml (Table 1b, c, d) and over the acidity range 1·0–2·5 N H_2SO_4 (Table 1e, f); under these conditions the reaction is stoichiometric. At sulphuric acid concentrations greater than 2·5 N or less than 1·0 N (Table 1e, f) the anomalous yields of cyclohexyl nitrite relative to cyclohexene indicate changes in the nature or concentration of the nitrosating species. The carbonium ion produced by N-nitrosation is stabilised either by losing a proton to form cyclohexene or by reacting with other anions such as OH^- or NO_2^- to form cyclohexanol or cyclohexyl nitrite. A second reaction is then possible, viz. esterification of cyclohexanol. This is dependent on the concentration of the nitrosating species present and hence on the acidity of the medium. Disproportionate yields are also noted over the temperature range 0–20° (Table 1g, h) indicating that the esterification process is temperature dependent. The present work has shown that when strong nitrosating conditions are used, cyclohexyl nitrite is formed from cyclamate in maximum yield and under the same conditions cyclohexanol is also esterified quantitatively to cyclohexyl nitrite. Thus any cyclohexanol formed initially at the deamination stage would be subsequently esterified to cyclohexyl nitrite. The extent to which deamination occurs, as indicated by the % yield of cyclohexene, is related to the pK value of the acid. For the various acids used (Table 1) the following % yields at acidities of 1·0 N were found; boric acid pK $6{\cdot}4 \times 10^{-10}$, 0%; oxalic acid pK $1{\cdot}77 \times 10^{-4}$, 0%; citric acid pK 8×10^{-4}, 10%; sulphuric acid pK 2×10^{-2}, 26%. No reaction occurs when acids with pK values below $4{\cdot}65 \times 10^{-4}$ (nitrous acid) are used, indicating that the effective nitrosating species is derived from free nitrous acid; this is further indicated by the similarity in the yields obtained when silver nitrite and sodium nitrite are used in equivalent concentration (Table Ia, j).

TABLE 1. YIELDS OF CYCLOHEXENE AND OF CYCLOHEXYL NITRITE

		Composition of reaction mixture			% Yield	
Parameter varied	t°	Nitrite μM/ml	Cyclamate μM/ml	Acidity (Normality)	Cyclohexene	Cyclohexyl nitrite
(a) Nitrite	18	200	5	1·0	23	76
Nitrite	18	150	5	1·0	23	76
Nitrite	18	100	5	1·0	23	70
Nitrite	18	50	5	1·0	24	57
Nitrite	18	25	5	1·0	26	40
Nitrite	18	12·5	5	1·0	26	18
Nitrite	18	6·25	5	1·0	27	3
(b) Cyclamate	18	25	5·0	1·0	26	40
Cyclamate	18	25	3·75	1·0	26	40
Cyclamate	18	25	2·5	1·0	26	40
Cyclamate	18	25	1·25	1·0	26	39

		Composition of reaction mixture			% Yield	
Parameter varied	t°	Nitrite µM/ml	Cyclamate µM/ml	Acidity (Normality)	Cyclohexene	Cyclohexyl nitrite
(c) Cyclamate	18	50	5·0	1·0	24	57
Cyclamate	18	50	3·75	1·0	24	57
Cyclamate	18	50	2·5	1·0	24	57
Cyclamate	18	50	1·25	1·0	25	57
(d) Cyclamate	18	150	5·0	1·0	23	76
Cyclamate	18	150	3·75	1·0	23	76
Cyclamate	18	150	2·5	1·0	23	76
Cyclamate	18	150	1·25	1·0	23	75
(e) Acidity (H_2SO_4)	18	25	5	9·0	0·5	19
Acidity (H_2SO_4)	18	25	5	4·5	17	47
Acidity (H_2SO_4)	18	25	5	3·75	21	47
Acidity (H_2SO_4)	18	25	5	2·5	26	40
Acidity (H_2SO_4)	18	25	5	2·0	26	40
Acidity (H_2SO_4)	18	25	5	1·5	26	40
Acidity (H_2SO_4)	18	25	5	1·0	26	40
Acidity (H_2SO_4)	18	25	5	0·5	26	37
Acidity (H_2SO_4)	18	25	5	0·25	26	29
(f) Acidity (H_2SO_4)	18	150	5	9·0	0·5	48
Acidity (H_2SO_4)	18	150	5	4·5	16	65
Acidity (H_2SO_4)	18	150	5	3·75	20	75
Acidity (H_2SO_4)	18	150	5	2·5	23	76
Acidity (H_2SO_4)	18	150	5	2·0	23	76
Acidity (H_2SO_4)	18	150	5	1·5	23	76
Acidity (H_2SO_4)	18	150	5	1·0	23	76
Acidity (H_2SO_4)	18	150	5	0·5	23	74
Acidity (H_2SO_4)	18	150	5	0·25	23	58
(g) Temp	20	25	5	1·0	26	41
Temp	18	25	5	1·0	26	40
Temp	15	25	5	1·0	26	39
Temp	10	25	5	1·0	26	35
Temp	5	25	5	1·0	25	29
Temp	0	25	5	1·0	24	20
(h) Temp	20	150	5	1·0	23	76
Temp	18	150	5	1·0	23	76
Temp	15	150	5	1·0	23	75
Temp	10	150	5	1·0	23	68
Temp	5	150	5	1·0	22	58
Temp	0	150	5	1·0	22	45
(i) Acidity (Citric)	18	25	5	2·5	17	4
Acidity (Citric)	18	25	5	1·5	13	3
Acidity (Citric)	18	25	5	1·0	10	1
Acidity (Citric)	18	25	5	0·5	3	Nil
(j) Nitrosating Agent ($AgNO_2$)	18	12·5	5	1·0	26	20
Nitrosating Agent ($AgNO_2$)	18	6·25	5	1·0	26	3

Parameter varied	t°	Composition of reaction mixture Nitrite μM/ml	Cyclamate μM/ml	Acidity (Normality)	% Yield Cyclohexene	Cyclohexyl nitrite
(k) Nature of Acid:						
Boric	18	25	5	1·0	Nil	Nil
Oxalic	18	25	5	1·0	Nil	Nil
HCl	18	25	5	1·0	25	40

Acidifying agent = H_2SO_4 unless otherwise indicated
Nitrosating agent = $NaNO_2$ unless otherwise indicated

EXPERIMENTAL

Apparatus. A Griffin and George gas chromatograph with a flame ionisation detector was used. This was fitted with either a "PEG Adipate" column (5 ft × 0·25 in, 12·3% polyethylene glycol adipate on embacel 85 to 100 mesh, operating at 50°), or with a "Carbowax" column (5 ft × 0·25 in, 15% carbowax 20M on celite HMDS, operating at 100°).

Materials. Redistilled cyclohexene, b.p. 82–83°. Cyclohexanol and cyclohexanone free from traces of cyclohexanone and cyclohexanol respectively. Cyclohexyl nitrite (b.p. 32–35°/10 mm) prepared by the dropwise additon of H_2SO_4 (5·6 ml, 9 N) to a mixture containing cyclohexanol (10·0 g), $NaNO_2$ (7·0 g) in water (15 ml) over a period of 30 min, whilst maintaining the solution below 0°. The upper yellow organic layer was washed with water (2 × 10 ml), dried over $CaCl_2$, distilled under reduced pressure and stored in the dark. Light petroleum (b.p. 30–40°). This was used as supplied unless GLC analysis revealed the presence of peaks corresponding to cyclohexene; in this case the reagent was distilled and the fraction boiling at 30–35° was used. n-Decane and n-pentadecane, used as internal standards were supplied by Koch Light Ltd.

Procedure. Organic products formed in the nitrosation were extracted from the reaction medium with light petroleum and determined by GLC analysis as follows. A light petroleum soln containing an appropriate internal standard was added to the aqueous reaction medium containing cyclamate and acid. After shaking, the solvent extract was analysed by GLC. Cyclohexene, cyclohexanol and cyclohexyl nitrite were identified as products of the reaction. Cyclohexanone previously reported as a reaction product,[4] was not detected. The following retention times (min) were observed, on Peg Adipate column, cyclohexene 1·8; cyclohexyl nitrite 11·0; n-decane (internal standard) 6·4: on Carbowax column, cyclohexanol 8·2; n-pentadecane 14·5; cyclohexanone 5·2.

Acknowledgement—We thank J. Lyons & Co. Ltd., for the opportunity given (to AJS) to carry out this work and for helpful advice from colleagues.

REFERENCES

[1] M. L. Richardson and P. E. Luton, *Analyst* **91**, 522 (1966)
[2] J. B. Wilson, *J. Assoc. Offic. Agric. Chemists* **38**, 559 (1955)
[3] D. I. Rees, *Analyst* **90**, 568 (1965)
[4] M. L. Richardson and P. E. Luton, *Ibid.* **91**, 520 (1966)
[5] D. I. Rees, Private communication
[6] A. J. Shenton and R. M. Johnson, *Chem. & Ind.* 364 (1967)