THE ACTION OF PYRIDINE ON THE DINITRATE ESTERS OF 1,4;3,6-DIANHYDROHEXITOLS[1]

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ABSTRACT

In contrast to the rapid and selective replacement of a secondary *O*-nitro group by hydrogen in the hexitol hexanitrates at 25–50° C, the dinitrate esters of the 1,4;3,6-dianhydrides of D-mannitol, D-glucitol, and L-iditol (*cis*-isohexides) reacted slowly in anhydrous pyridine at 87–115° C. The chief products were a polymer, nitrogen oxides, and pyridinium nitrate; the yield of mononitrates did not exceed 10% and none of the parent diols were formed.

The relative rates of the first-order decomposition of the nitroxy groups in the isomeric dinitrates were in reverse order to that for S_N2 reaction at carbon in these compounds. Activation energies and frequency factors were determined and water was shown to have a retarding effect.

Thermal decomposition of the dinitrates in solution in nitrobenzene, *m*-xylene, or *sym*-tetrachloroethane was much slower than the pyridine reaction at the same temperature and was independent of the polarity of the solvent and the conformation of the ester.

INTRODUCTION

Dulcitol and D-mannitol hexanitrates have been shown to react selectively with pyridine to yield the corresponding 1,2,4,5,6-pentanitrates (1, 2). The rate of reaction was different for the two hexitol derivatives and the resulting pentanitrates were essentially stable to pyridine under the same conditions. Sorbitol hexanitrate reacted similarly with pyridine but the pentanitrate was not fully characterized (3). The reaction was inconveniently fast for kinetic studies even at 25° C and the multiplicity of nitroxy groups and molecular conformations further complicated the problem of sorting out the reaction mechanism.

The three known isomeric 1,4;3,6-dianhydrohexitols (the *cis*-isohexides) and their derivatives have been shown to behave characteristically in certain types of reactions due to differences in their restricted conformations (4, 5). In an attempt to determine the mechanism of the pyridine – nitrate ester reaction the dinitrates of the isohexides (I–III, Fig. 1) were selected for study since observation of similar steric effects in their reactions with pyridine would aid in diagnosis of the type of mechanism involved. The presence of only two, non-vicinal, secondary, nitroxy groups in these isomers was also expected to simplify analysis of the results.

RESULTS AND DISCUSSION

The three isohexide dinitrates (Fig. 1) were prepared in crystalline form and characterized through their nitrogen contents, infrared spectra, and nearly quantitative conversion to the parent diols. The physical constants and nitrogen contents of the isomers are shown in Table I. The dinitrates dissolved readily in pyridine and the colorless solutions were stable over several weeks at room temperature. No vigorous reaction occurred on heating under reflux; however, slow decomposition, accompanied by a red coloration of the solution and evolution of oxides of nitrogen, began at temperatures above 50° C.

At 115° C 0.424 *M* solutions of the isohexide dinitrates in anhydrous pyridine decomposed according to an apparent first-order rate law for loss of nitroxy groups (Fig. 2). Since pyridine, as solvent, was present in constant excess, it was likely that the reaction actually involved a second-order process which appeared to be first order because of this

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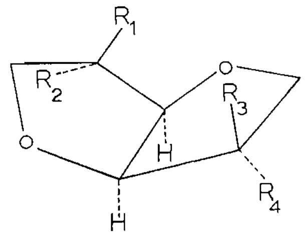


FIG. 1. 2,5-Dinitrates of 1,4;3,6-dianhydrohexitols.

I $R_1 = ONO_2$, $R_2 = H$, $R_3 = ONO_2$, $R_4 = H$: isomannide dinitrate
II $R_1 = ONO_2$, $R_2 = H$, $R_3 = H$, $R_4 = ONO_2$: isosorbide dinitrate
III $R_1 = H$, $R_2 = ONO_2$, $R_3 = H$, $R_4 = ONO_2$: isoidide dinitrate

TABLE I
1,4;3,6-Dianhydrohexitol dinitrates

	Isomannide dinitrate (I)	Isosorbide dinitrate (II)	Isoidide dinitrate (III)	Ref.
Melting point, ° C				
Found	64.5–65.5	50.5–51.5	68–69	
Reported	65.5	70	—	(6)
		71		(7)
		52		(8)
$[\alpha]_D$				
Found	+335	+141	+72.9	
Reported	—	+134	—	(8)
Nitrogen content (%)				
Found	11.8[a]	11.9[a]	11.8[a,b]	
Required	11.87	11.87	11.87	

[a] Modified micro-Kjeldahl method.

[b] Determined by Mr. I. G. Csizmadia. Found: C, 30.9; H, 3.95%. Calc. for $C_6H_8N_2O_8$: C, 30.5; H, 3.41%.

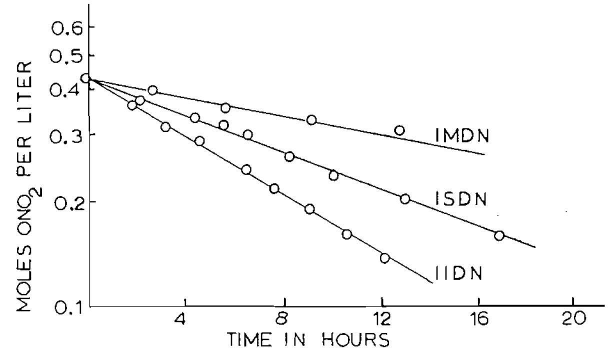


FIG. 2. Rate plots of isohexide dinitrate – pyridine reaction at 115° C. IMDN, isomannide dinitrate; ISDN, isosorbide dinitrate; IIDN, isoidide dinitrate.

limitation (9). The course of the reaction was followed by colorimetric determination of unreacted nitrate ester in aliquots of the reaction mixture. The rates were confirmed by quantitative isolation of the unreacted material followed by complete characterization. The rate of nitroxy group decomposition was also determined at 100° C and 87° C

TABLE II

Rates of decomposition of the isohexide dinitrates in pyridine

Conditions		Rate constants, $\text{sec}^{-1}\times10^{-6}$		
Temperature, ° C	Moles water per mole nitroxy group	Isoidide dinitrate	Isosorbide dinitrate	Isomannide dinitrate
87	0	3.20	1.15	0.13
100	0	8.58	2.29	0.74
115	0	25.4	15.2	8.07
115	0.5	18.8	12.7	3.3
115	1.0	13.5	10.0	3.6
115	2.0	10.3	7.9	3.1

(Table II). From these results Arrhenius activation energies of 21, 24, and 41 kcal and log frequency factors of 7.6, 8.9, and 18.3 were found for isoidide, isosorbide, and isomannide dinitrates respectively.

None of the parent diols could be detected in the reaction products by chromatography. Isohexide mononitrates were isolated and characterized but accounted for a maximum of 10% of the decomposed dinitrate in runs with aqueous pyridine; with anhydrous pyridine only traces of mononitrate could be detected. Most of the weight of the reaction products was brown-black, polymeric material. In addition to pyridinium nitrate a small amount of an unidentified, optically active oil was also isolated.

For comparison with the pyridine reaction the rate of thermal decomposition of the dinitrates was determined in four solvents with boiling points above 115° C and dipole moments ranging from 0.37 to 3.98 Debye units. The slow decomposition of isosorbide dinitrate at 100° and 115° C in these solvents is shown in Table III. The other two isomers decomposed at the same rate in *sym*-tetrachloroethane but were not tested in the other solvents.

TABLE III

Thermal decomposition of isosorbide dinitrate in various solvents

		Decomposition, %			
		100° C		115° C	
Solvent	μ, Debyes	25 hours	50 hours	25 hours	50 hours
Nitrobenzene	3.98	2	5	18	37
m-Xylene	0.37	6	8	23	32
s-Tetrachloroethane	1.36	4	7	25	46
Diethylcarbinol	1.64	29	40	45	53

The rates of decomposition of the nitroxy groups were very similar in nitrobenzene, *m*-xylene, and *sym*-tetrachloroethane with first-order rate constants of 0.41×10^{-6} and 2.7×10^{-6} sec^{-1} at 100° C and 115° C respectively. The more rapid reaction in diethylcarbinol was probably due to incursion of a transnitration reaction:

$$\text{RONO}_2 + \text{R'OH} \rightleftharpoons \text{ROH} + \text{R'ONO}_2.$$

It is well established that the first and rate-determining step in the thermal decomposition of nitrate esters in the gaseous state is the fission of the oxygen–nitrogen bond, generating a free alkoxyl radical (10, 11). A similar mechanism for the first-order thermal decomposition of the esters in the condensed state seems probable (12). Thermal decomposition of the esters in solution, however, has not been previously investigated.

For the first-order decomposition of the isohexide nitrates in the non-hydroxylic solvents the activation energy of 37 kcal/mole and log frequency factor of 15 calculated from the data of Table III were in good agreement with the values quoted for gaseous and condensed nitrate esters (10, 11, 12). This suggested a free radical mechanism for this case also. Additional evidence of a free radical mechanism was the fact that the rates were independent of the polarity of the solvent (9). Since the rate of the thermal reaction was exceeded by a factor of 5.6 in the pyridine reaction with isosorbide dinitrate at both temperatures it was concluded that thermal decomposition did not play a major part in the pyridine reaction.

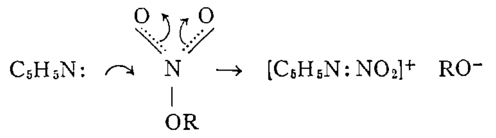
It was noted that the decomposition went faster with well-dried pyridine. To test the effect of water on the rate a series of runs was made with increasing amounts of water present. There was appreciable decrease in rate with increase in water content (Table II) but the nature of the products was not altered substantially. The rate law,

$$\text{rate} = \frac{k_1\,[\text{nitrate ester}]}{1+k_2[\text{H}_2\text{O}]},$$

was followed where k_1 was 2.54×10^{-5} and k_2 1.70 for isoidide dinitrate.

The S_N2 reactions at carbon of isohexide *O*-derivatives, such as the replacement of sulphonoxy group by iodine, had a characteristic order of rates due to steric hindrance at one face of the molecule (5). The *endo* group (as in isomannide) reacted several times faster than the *exo* group (as in isoidide). The order of the rates of the pyridine – nitrate ester reaction, however, was exactly the reverse and hence ruled out this mechanism.

On the other hand these results were consistent with nucleophilic attack by pyridine at the nitrogen of the nitroxy group resulting in heterolytic cleavage of the low energy O—NO$_2$ bond.



$$C_5H_5N: \curvearrowright \underset{\text{OR}}{\overset{\text{O}\quad\text{O}}{\text{N}}} \longrightarrow [C_5H_5N:NO_2]^+ \ \ RO^-$$

The approach of the bulky pyridine molecule to the *exo*-nitroxy group would be least hindered by the isohexide skeleton in this case. The unstable *N*-nitrated pyridine intermediate was recently synthesized by Oláh and co-workers by direct nitration of pyridine with nitronium tetrafluoroborate (13). This mechanism also agrees with retention of configuration at asymmetric carbons actually found with the hexitol hexanitrates. The subsequent reaction of the alkoxide ion led to polymer formation in the isohexide case. The failure to detect the parent diols was not due to their decomposition since they could be added to the reaction mixture and recovered quantitatively.

The nitroxy groups in the isohexide isomers were well separated on the carbon chain, and, except in the case of isomannide dinitrate (Fig. 1), were also well separated in space. These isolated groups reacted only slowly with pyridine. In the hexitol hexanitrates the secondary nitroxy groups were contiguous and closely packed; steric compression in the initial state was clearly indicated by the molecular models. The proximity of the α-nitroxy groups must therefore be of considerable importance in the activation of the center groups and in the lifetime of the alkoxide ion.

EXPERIMENTAL

1,4;3,6-Dianhydrohexitols (cis-Isohexides)

Isomannide and isosorbide were prepared from D-mannitol and sorbitol respectively by the method of Wiggins (14). Isoidide was most conveniently prepared, together with isosorbide, through hydrogenation of L-sorbose followed by dehydration.

L-Sorbose (50 g) in water (200 ml) was hydrogenated at 55 p.s.i. and 80° C for 4 hours with Raney nickel catalyst (from 10 ml of the alcoholic sludge). The catalyst and solvent were removed and the residue was dissolved in concentrated hydrochloric acid (300 ml). The solution was saturated with hydrogen chloride and refluxed for 24 hours. Hydrogen chloride was removed by repeated evaporation under reduced pressure alternated with addition of water, and the residual sirup was fractionally distilled under reduced pressure: fraction 1, b.p. 135–140° C at 0.18–0.20 mm, 8 g, crystallized (isosorbide); fraction 2, b.p. 140–143° C at 0.20–0.22 mm, 5 g, sirup (mixture); fraction 3, b.p. 143–155° C at 0.22–0.25 mm, 12 g, crystallized (isoidide). Fraction 3 after recrystallization from ethyl acetate had m.p. 44–46° C and specific rotation in water $[\alpha]_D^{23}$ +21.0° (*c*, 1.1). Cope and Shen (4) reported m.p. 43–45.5° C, $[\alpha]_D^{25}$ +18.7° (*c*, 2; water) for isoidide.

1,4;3,6-Dianhydrohexitol Dinitrates (I–III)

The nitrate esters were prepared from the isohexides by the method of Forman *et al.* (6) in a yield of about 50%; the yield was increased to 85–90% by nitration in acetic anhydride – nitric acid – acetic acid mixture.

Fuming nitric acid (sp. gr. 1.45, 5 ml) was slowly added to acetic acid – acetic anhydride (1:1, 15 ml) maintained at −2 to 5° C. The mixture was added dropwise, with stirring, to the isohexide (2 g) in acetic acid – acetic anhydride (2:1, 15 ml) maintained at 0° C. After standing for 2 hours at 5° C the mixture was poured into ice water (400 ml). Part of the nitrate ester (2.2 g) crystallized out on standing for 18 hours at 20° C and a further amount (0.6 g) was recovered by ether extraction of the mother liquor. The esters were recrystallized from methanol and analyzed for nitrate–nitrogen (Table I). The infrared spectra of the isomers (potassium bromide window) showed covalent nitrate group absorption at 1650, 1265, and 750 cm^{-1} and no hydroxyl or carbonyl peaks.

Hydrogenation of the nitrates in alcohol solution over palladium–charcoal (1) gave the parent diols in 90–98% yield.

Decomposition of Isohexide Dinitrates in Solution

(a) Solvents

Reagent grade pyridine was distilled and the middle fraction of 80% was collected and dried over calcium hydride for 48 hours, decanted, and redistilled immediately before use. Reagent grade nitrobenzene was dried over calcium chloride, distilled, redried over phosphorus pentoxide, and redistilled under reduced pressure. *m*-Xylene and *sym*-tetrachloroethane were dried over calcium chloride and distilled. Technical grade diethylcarbinol was dried over anhydrous sodium sulphate and distilled and the middle fraction was used.

(b) Decomposition in Pyridine

The reactions were conducted in glass bulbs (2.5-cm diameter) with long stems (30 cm) fitted with water jackets and closed by drying tubes containing Drierite. An initial concentration of 0.100 g of isohexide dinitrate in 2 ml pyridine was used (0.424 mole nitroxy group per liter). The bulbs were heated in an oil bath for reactions at 115° C (reflux temperature), in the vapor of boiling water (100° C), or in the vapor of a boiling two-layer mixture of 2-butanol and water (87° C).

Aliquots of the reaction mixture (0.100 or 0.200 ml) were removed at intervals, distilled water (2 ml) was added, and the mixture was extracted three times with 1-ml portions of ether. Tests with added amounts of the dinitrates showed that extraction was then complete. The combined ether extracts were made up to 10 ml and 1-ml samples were taken for colorimetric determination of nitrate ester (15, 16).

The nitrate sample, containing 10–80 μg nitrogen, was added to 15 ml of 70% (v/v) sulphuric acid in a 250-ml flask and 1 ml of a 1% solution of 3,4-dimethylphenol was added. After being mixed, the solution was let stand for 30–60 minutes at 30° C. Water (150 ml) was then added, boiling stones introduced, and the flask fitted with a U-shaped distilling tube leading into a 25-ml volumetric flask containing 2% sodium hydroxide solution (2.5 ml). Distillation was carried out with the volumetric flask cooled in ice water and 20 ml of distillate was collected. The distillate was made up to 25 ml and brought to 24.0±0.5° C before colorimetric estimation at 435 mμ in a Bausch and Lomb Spectronic 20 colorimeter. The nitrate–nitrogen content of the sample was given by O.D.×103 = μg nitrogen.

(c) *Thermal Decomposition in Solution*

The nitrate ester (50 mg) and solvent (1 ml) were placed in a reaction bulb as used in the pyridine studies and heated in the vapor of boiling diethylcarbinol (114–115° C). After the reaction period the contents of the bulb were transferred with ether to a 7.5 mm ×20 cm column of alumina (Alcoa Grade F-20, acid-washed, activated at 400° C for 4 hours). The column was eluated with ether followed by ether – ethyl acetate (9:1). Fractions of the eluate containing nitrate (diphenylamine test) were pooled and evaporated under reduced pressure. The residual sirupy dinitrates crystallized on seeding and were identified by their melting and mixed melting points.

(d) *Reaction Products*

Isohexide dinitrate (5 g) in pyridine (50 ml) was refluxed under anhydrous conditions until 50–90% decomposed. The mixture was poured into water (500 ml), extracted with ether (600 ml), and the solutions were filtered. The precipitate was a brown-black amorphous solid (product A, 0.5–1.5 g).

The ether solution was evaporated to dryness *in vacuo* to remove traces of pyridine and yielded a pale brown sirup (0.5–2.5 g). Samples of this sirup were chromatographed on paper in hexane–methanol solvent (17). Unreacted isohexide dinitrate and a faint nitrate-containing spot with lower R_f value were detected in the products from each reaction. Quantitative separation was obtained by chromatography on alumina columns developed with ether – ethyl acetate (9:1) followed by acetone–methanol (1:1). The ether – ethyl acetate fractions yielded unreacted isohexide dinitrate which was recrystallized and characterized by mixed melting point determinations.

The acetone–methanol fractions yielded a small amount of sirup which had R_f 0.05 on papergrams developed with hexane–methanol. The nitrate–nitrogen content was 5.6% (required for isohexide mononitrate, 7.3%). Complete nitration of the sirup gave a spot running parallel to isohexide dinitrate on papergrams.

The aqueous solution was evaporated *in vacuo* to a dark red sirup (0.5–1.5 g). Extraction of the sirup with hot ethanol (50 ml) left a brown, amorphous solid (product B, 0.5–1.0 g). A red-brown sirup (0.5–1.5 g) was recovered on evaporation of the ethanol solution. Celite column chromatography with 1-butanol – water as solvent (18) showed that this sirup contained no isohexide since the fractions had zero optical rotation. Isohexide added to the initial reaction mixture in some runs was recovered quantitatively from the Celite column by this technique.

The alcohol extract was subjected to ion-exchange and charcoal chromatography and pyridinium nitrate (0.2–0.8 g) was isolated together with a trace of an acidic, optically active oil.

Products A and B burned slowly in a Bunsen flame and were insoluble in organic solvents and water. Product A partially dissolved in 3 *N* sodium hydroxide solution and product B was soluble in aqueous pyridine and in 0.1 *N* sodium hydroxide solution. A brown-black solid was precipitated from the latter solution on acidification or addition of alcohol. Infrared spectra of the solid fractions thus obtained were very similar to each other and no functional groups could be identified. It was concluded that products A and B were polymers differing mainly in molecular weight.

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