

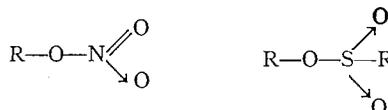
ORGANIC NITRATES AS SYNTHETIC INTERMEDIATES
PREPARATIONS OF NITRATES AND SOME REPRESENTATIVE REACTIONS¹

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ABSTRACT

It has been shown that the carbon-oxygen bond of nitrate esters is susceptible to cleavage by certain representative nucleophilic reagents, of which sodium iodide, sodium cyanide, and potassium thiocyanate have received particular attention. Allyl, 3-hydroxypropyl, 4-fluorobutyl, hexyl, and benzyl nitrate were examined in order to determine the effect if any of functional groups on the ease and efficiency of cleavage.

Alkyl and aralkyl sulphonates are well known as synthetic intermediates, undergoing most of the replacement and elimination reactions characteristic of the alkyl halides. However, their preparation, while frequently occurring in very high yield, is time consuming, and the products often have very high boiling points, making purification inconvenient. Accordingly, attention was directed to esters of other inorganic oxy-acids; these it was hoped would undergo the same reactions, due to oxygen-alkyl fission. From a superficial consideration of structure, nitrates were selected for study:



The chemistry of nitrate esters has been reviewed recently (3). Several alkylation reactions have been reported: benzyl nitrate has been used successfully in benzylating malonic and acetoacetic esters (15); methyl nitrate has been converted to the corresponding isothiuronium nitrate using thiourea (21); diphenylmethyl nitrate has been converted to N-diphenylmethylacetamide on treatment with acetamide (6); trialkylsulphonium nitrates have been formed from dialkyl sulphides and alkyl nitrates (18); amines have been alkylated using alkyl and aralkyl nitrates (9, 12, 19); and the action of sodium ethoxide on nitrates has produced ethyl ethers (4, 5). The reactions of nitrates have received most attention in the field of carbohydrates, and in at least one instance the nitrate grouping has been replaced by iodide using sodium iodide in acetone (11). No reference has been made to the replacement reactions of the nitrate grouping as a simple alternative to the use of alkyl halides in preparative organic chemistry.

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Nitrates may be prepared by direct esterification of alcohols with nitric acid, or by reaction of a suitable alkyl halide with silver nitrate. However, only the first of these is of practical importance in this work, since the halides required for the second method could themselves be used directly in the replacement reactions. The direct esterification method has been reported to be very simple and to give high yields, but the conditions are sometimes critical; the halide method gives consistently good results. For convenience, both methods were employed to obtain the nitrate esters used in this work. Results are shown in Table I.

TABLE I
NITRATES: PREPARATION, PHYSICAL CONSTANTS, AND ANALYTICAL RESULTS

R in RONO ₂	Method of preparation ^a	Yield, %	Boiling point		n_D^{25}	C, %		H, %	
			°C.	mm.		Calc.	Found	Calc.	Found
CH ₂ :CHCH ₂ - ^b	I	33	102-105		1.4112				
	II	49	104-106		1.4120				
HO(CH ₂) ₃ -	I	49	103-104	16	1.4378	29.75	29.83	5.84	5.90
	III	76	123-125	42	1.4372				
CH ₃ (CH ₂) ₃ - ^c	II	54	130-131		1.4031				
	III	61	130-133		1.4030				
	IV	74	130-132		1.4036				
F(CH ₂) ₄ -	II	68	74-77	19	1.4060	35.03	34.82	5.89	5.88
	III	75	65	12	1.4070				
Cl(CH ₂) ₄ -	III	64	92-93	11	1.4541	31.28	30.93	5.26	4.92
CH ₃ (CH ₂) ₅ - ^d	II	83	66-70	12	1.4174				
	III	77	66	11	1.4180				
	IV	73	67-69	12	1.4182				
F(CH ₂) ₆ -	II	28 ^h	112	28	1.4179	43.62	43.82	7.34	7.35
C ₆ H ₅ CH ₂ - ^e	I	70	101-104	12	1.5179				
CH ₃ (CH ₂) ₉ - ^f	IV	59	127-128	12	1.4328				
CH ₃ (CH ₂) ₁₁ - ^g	IV	67	143-144	5	1.4380				

^aMethods of preparation—I: chloride + silver nitrate; II: bromide + silver nitrate; III: iodide + silver nitrate; IV: alcohol + HNO₃ and H₂SO₄.

^bHenry (10) reports b.p. 106°.

^cCowley and Partington (7) report b.p. 135.7° at 770 mm. and n_D^{20} 1.4063.

^dSoffer, Parrotta, and Di Domenico (20) report b.p. 46° at 1 mm. and $n_D^{24.5}$ 1.4180.

^eLucas and Hammett (13) report b.p. 72.5-73.5° at 4-5 mm. and n_D^{25} 1.5180.

^fMedard and Alquier (14) report b.p. 88-89° at 1-2 mm.

^gMedard and Alquier (14) report b.p. 99-100° at 1-1.5 mm.

^hLow yield due to accidental loss.

The cleavage of nitrates is significant in the main as a method of replacing -OH by different functional groups, that is, as an alternative to the use of halides or sulphonates. Some representative cleavages are shown in Table II. In addition to those listed, benzyl nitrate was treated (a) with sodium bromide

to form benzyl bromide in 64% yield, and (b) with thiourea followed by hydrolysis to form benzyl mercaptan in 32% yield. Analytical results and physical constants of new compounds are listed in Table III. The boiling points of some of the products were very similar to those of the parent nitrates, making purification difficult.

TABLE II
CLEAVAGE OF NITRATES: YIELDS (%)

Reaction	R =				
	CH ₂ :CHCH ₂ -	HO(CH ₂) ₅ -	F(CH ₂) ₄ -	CH ₃ (CH ₂) ₅ -	C ₆ H ₅ CH ₂ -
RONO ₂ + NaI → RI + NaNO ₃	62	60	63	84	76
RONO ₂ + NaCN → RCN + NaNO ₃	31 ^a	—	45 ^a	77 ^b	68 ^a ; 66 ^b
RONO ₂ + KSCN → RSCN + KNO ₃	33 ^c	35	57	86	86

^a80% Ethanol as solvent.

^bEthylene glycol as solvent.

^cAllyl isothiocyanate.

TABLE III
PRODUCTS OF CLEAVAGE: PHYSICAL CONSTANTS AND
ANALYTICAL RESULTS OF NEW COMPOUNDS

	Boiling point		<i>n</i> _D ²⁵	C, %		H, %		Other, %	
	°C.	mm.		Calc.	Found	Calc.	Found	Calc.	Found
HO(CH ₂) ₅ I	99-100	20	1.5480	19.37	19.65	3.80	3.81	I, 68.23	I, 68.10
HO(CH ₂) ₅ SCN	143-144	14	1.4688	41.00	40.97	6.03	6.10	N, 11.96	N, 11.66
F(CH ₂) ₄ I	53-54	13	1.4940					I, 63.78	I, 64.08
F(CH ₂) ₄ CN	72	10	1.3963					F, 18.81	F, 18.6
F(CH ₂) ₄ SCN	100-101	13	1.4611	45.11	44.96	6.01	5.90	N, 10.52	N, 10.35

In view of the ready conversion of halides and sulphonates to fluorides by potassium fluoride (16, 17), a representative nitrate was examined under conditions similar to those reported. On heating hexyl nitrate at 110° for eight hours with potassium fluoride in diethylene glycol, low yields (10-15%) of hexyl fluoride were obtained. From this preliminary observation, it seems unlikely that nitrates will be used extensively in the preparation of aliphatic fluorides.

In compounds containing both sulphonate and halogen groups, the former have been shown to be preferentially replaced relative to the latter (17), as for example in the conversion of 4-chlorobutyl methanesulphonate by potassium thiocyanate to 4-chlorobutyl thiocyanate in 67% yield. This was not possible with ω -haloalkyl nitrates; under the conditions necessary to replace the nitrate grouping, the halogen was also replaced.

From limited observations, alkyl nitrites proved to be useless as alternatives to nitrates in the replacement reactions described above. Under conditions similar to those used for converting hexyl nitrate to hexyl iodide, hexyl nitrite formed *n*-hexanol.

The preliminary results presented in this paper indicate that alkyl nitrates are of potential value as synthetic intermediates, while not offering any particular advantages over the well-known alkyl halides and sulphonates. It is hoped to examine the cleavage of nitrates in more complex molecules in order to assess the versatility and scope of the reaction.

EXPERIMENTAL³

(a) Preparation of Intermediates

Trimethylene iodohydrin.—Trimethylene chlorohydrin (20 gm., 0.21 mole), sodium iodide (63 gm., 0.42 mole), and anhydrous acetone (200 ml.) were heated under reflux for 13 hr. Most of the acetone was removed by distillation. After the mixture had been cooled and diluted with water, the product was extracted with ether. The extract was dried over anhydrous sodium sulphate. The ether was removed, and the residue on fractional distillation from freshly prepared silver crystals yielded trimethylene iodohydrin (19.7 gm., 50%) of b.p. 105° at 25 mm. and n_D^{25} 1.5480.

4-Fluorobutyl bromide, 4-fluorobutyl iodide, and 6-fluorohexyl bromide have been described elsewhere (16).

4-Chlorobutyl iodide was prepared from 1,4-dichlorobutane using sodium iodide in acetone (1).

(b) Preparation of Nitrates

The four methods summarized in Table I are represented by the following examples.

Method I: Benzyl nitrate.—Benzyl chloride (80 gm., 0.63 mole) was added over a period of 10 min. to silver nitrate (130 gm., 0.76 mole) in anhydrous acetonitrile (150 ml.). The mixture was then heated under reflux for 50 min. The silver chloride was removed by filtration and washed with a small quantity of acetonitrile. After removal of the acetonitrile at a temperature of less than 90°, the residue on distillation yielded benzyl nitrate (68.4 gm., 70%).

Method II: n-Hexyl nitrate.—*n*-Hexyl bromide (84.5 gm., 0.51 mole) was slowly added to a solution of silver nitrate (116 gm., 0.68 mole) in anhydrous acetonitrile (110 ml.) and the resultant mixture was allowed to stand at room temperature for 15 hr. After removal of the silver bromide by filtration, the mixture was heated under reflux for one hour. The solution was cooled and filtered, and then diluted with water (250 ml.). The crude nitrate was extracted with ether and the extract dried over anhydrous sodium sulphate. After removal of the ether, *n*-hexyl nitrate (62.5 gm., 83%) was obtained as a colorless liquid.

Method III: 4-Fluorobutyl nitrate.—4-Fluorobutyl iodide (47.0 gm., 0.23 mole) was slowly added to silver nitrate (42.5 gm., 0.25 mole) in anhydrous acetonitrile (60 ml.) with external cooling provided by an ice bath. The mixture was allowed to stand at room temperature for 19 hr., was filtered, and then the solvent removed. The residue on distillation yielded 4-fluorobutyl nitrate (23.8 gm., 75%).

³Physical constants and analytical data are listed in Tables I and III.

Method IV: n-Butyl nitrate.—Concentrated sulphuric acid (76.8 ml., specific gravity 1.84, 95% by weight) was slowly added at a temperature of less than 10° to a mixture of urea (2.5 gm.) and concentrated nitric acid (76.8 ml., 1.2 moles, specific gravity 1.42, 70% by weight). The resultant solution was cooled to 0° in an ice-HCl bath, and *n*-butyl alcohol (44.4 gm., 0.60 mole) was added with vigorous stirring at the rate of about 1 ml. per min. When the addition was complete, the mixture was stirred for a further 15 min. and then diluted with water. The nitrate layer was washed three times with 10% aqueous potassium carbonate and then with water. After it was dried over anhydrous sodium sulphate, distillation yielded *n*-butyl nitrate (52.8 gm., 74%) as a colorless, pleasant-smelling liquid.

(c) *Cleavages of Nitrates*

The following examples are representative of the cleavages of nitrates.

n-Hexyl iodide.—*n*-Hexyl nitrate (8.0 gm., 0.054 mole), sodium iodide (16.2 gm., 0.108 mole), and anhydrous acetone (40 ml.) were heated under reflux for 27 hr. The solvent was removed by distillation below 58°, and the residue was diluted with water (100 ml.) and extracted with ether. The extracts were washed successively with water, aqueous sodium thiosulphate, and water. They were then dried over anhydrous sodium sulphate and the ether was removed; the residue on distillation yielded *n*-hexyl iodide (9.7 gm., 84%), b.p. 60–63° at 12 mm., n_D^{25} 1.4894.

n-Heptanonitrile.—*n*-Hexyl nitrate (10.0 gm., 0.068 mole), sodium cyanide (3.4 gm., 0.070 mole), and ethylene glycol (20 ml.) were stirred at reflux temperature for two hours. The reddish-brown reaction mixture was diluted with water (200 ml.) and extracted with ether. The extracts were washed successively with 4 *N* hydrochloric acid (to remove traces of the isonitrile), aqueous sodium bicarbonate, and water, and dried over anhydrous magnesium sulphate. The ether was removed, and the residue on distillation yielded *n*-heptanonitrile (5.8 gm., 77%), b.p. 98° at 39 mm., n_D^{25} 1.4135.

4-Fluorobutyl thiocyanate.—4-Fluorobutyl nitrate (6.0 gm., 0.044 mole), potassium thiocyanate (12.8 gm., 0.132 mole), and 95% ethanol (50 ml.) were heated under reflux for 12 hr. The mixture was cooled, diluted with water (200 ml.), and extracted with ether. The extracts were washed with saturated calcium chloride and with water, and then dried over anhydrous sodium sulphate. After removal of the ether, the residue on distillation yielded 4-fluorobutyl thiocyanate (3.3 gm., 57%), a colorless, vile-smelling liquid.

Benzyl bromide.—A mixture of benzyl nitrate (6.0 gm., 0.039 mole), sodium bromide (12.1 gm., 0.117 mole), and anhydrous acetone (125 ml.) was heated under reflux with stirring for 26 hr. After the usual isolation procedure (removal of acetone, dilution with water, ether extraction, and drying), benzyl bromide (4.3 gm., 64%) was obtained as a colorless, lachrymatory liquid of b.p. 81–83° at 14 mm. and n_D^{25} 1.5690; Baker (2) reports b.p. 85° at 13 mm.

Benzyl mercaptan.—Benzyl nitrate (15.3 gm., 0.10 mole), thiourea (7.2 gm., 0.095 mole), and 95% ethanol (20 ml.) were heated under reflux for 4.5 hr. The cooled mixture was diluted with water (75 ml.) and the crude benzyl isothiuronium nitrate was collected by filtration. A small sample, recrystallized

from water, had m.p. 120–120.5°; Taylor (21) reports m.p. 118–119°. To the crude solid was added a solution of sodium hydroxide (8.0 gm., 0.20 mole) in water (80 ml.), and the mixture was heated under reflux for four hours. After it had been cooled and acidified with 3 *N* hydrochloric acid (75 ml.), the solution was extracted with ether. The extract was washed with aqueous sodium bicarbonate and with water, and dried over anhydrous sodium sulphate. After removal of the ether, the residue on distillation yielded benzyl mercaptan (3.8 gm., 32%) of b.p. 88–89° at 18 mm. and n_D^{25} 1.5723; Farlow and Signaigo (8) report b.p. 99° at 32 mm. and n_D^{25} 1.5729.

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