393. *Quaternary Ammonium Nitrates. Part II.* Reactions of Nitratoalkyl Ethers, Amines, Amides, and Urethanes with Tertiary Amines and Related Compounds.*

By E. S. Lane.

The normal reaction of alkyl nitrates with tertiary amines to form quaternary ammonium nitrates has been shown to occur when the alkyl group contains various substituent groups. The preparation and properties of some new substituted alkyl nitrates and the direct quaternisation of a tertiary phosphine with an alkyl nitrate are also described.

In Part I* it was shown that alkyl nitrates and polymethylene dinitrates reacted with tertiary bases to form the corresponding quaternary ammonium nitrates. The effect of substitution in the alkyl chain on this reaction has now been further investigated. Butoxyethyl nitrate and triethylene glycol dinitrate both reacted readily with tertiary amines to form the expected quaternary ammonium nitrates, and this method can be used to supplement those already described[1,2] for the synthesis of these physiologically active compounds.

The nitric esters of mono-, di-, and tri-ethanolamine and of *N*-methyldiethanolamine also quaternised readily with tertiary amines. With more reactive bases, *e.g.*, pyridine and benzyldimethylamine, the violence of this reaction necessitated dilution with inert solvent. This reaction supplements and extends those of Marxer and Miescher[3,4] for the synthesis of ganglion-blocking agents related to "Pendiomide." An interesting feature of these amino-substituted quaternary ammonium nitrates is their very low solubility in ethanol and methanol.

N-2-Hydroxyethylstearamide was esterified readily in acetic anhydride–fuming nitric acid, in quantitative yield. *NN'*-Di-(2-hydroxyethyl)oxamide and higher homologues reacted similarly with this reagent; *NN'*-di-(2-hydroxyethyl)-maleamide and -diglycollamide were exceptional and decomposed during nitration into unidentified products. When the alkyl chain in the *N*-substituent was lengthened, as, for example, in *N*-3-hydroxypropylstearamide, or branched, as in *NN'*-di-(3-nitratobutyl)oxamide, esterification still occurred as expected. If, however, the 2-hydroxyethyl substituent was attached to a urea residue, as in *N*-2-hydroxyethylurea, this reaction was accompanied by complete hydrolysis, with evolution of carbon dioxide. Except for *NN'*-di-(2-nitratoethyl)oxamide,[5] these amides form a new class of substituted nitric ester, and are characterised by water-insolubility, stability, and ready crystallisation. They react with tertiary bases forming the corresponding quaternary ammonium nitrates. The halogen analogues of some of these salts are of technological importance, particularly the long-chain acylaminoalkyltrialkylammonium halides.[6-8] *NN'*-Di-(2-nitratoethyl)oxamide with methanolic potassium hydroxide gave di-(Δ^2-1 : 3-oxazolin-2-yl) (I), prepared similarly by Wenker[9] from *NN'*-di-(2-chloroethyl)oxamide. Normally an alkyl nitrate with alcoholic alkali gives the mixed ether but a further example of the use of a nitric ester, albeit a highly substituted one, to form a Δ^2-oxazoline ring on hydrolysis has been noted recently.[10]

The products from *NN'*-di-(2-hydroxyethoxycarbonyl)ethylenediamine (II) depended on the reagents. Acetic anhydride–fuming nitric acid gave *NN'*-di-(2-nitratoethoxycarbonyl)-*NN'*-dinitroethylenediamine (III), whilst fuming nitric acid alone is believed

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* Part I, *J.*, 1953, 1172.

[1] Hazard, Cheymol, Chabrier, Corteggiani, Muller, and Gay, *Bull, Soc. chim. France*, 1953, 270.

[2] Fakstorp, Christiansen, and Pedersen, *Acta Chem. Scand.*, 1953, **7**, 134.

[3] Marxer and Miescher, *Helv. Chim. Acta*, 1951, **113**, 925.

[4] U.S.P., 2,654,776; B.P. 719,610.

[5] Stuart and Wright, *Canad. J. Res.*, 1948, **26**, 13, 401.

[6] U.S.P. 2,459,088.

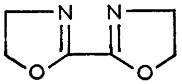
[7] U.S.P. 2,459,062, 2,626,876.

[8] B.P. 688,048.

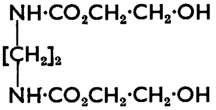
[9] Wenker, *J. Amer. Chem. Soc.*, 1938, **60**, 2152.

[10] B.P. 711,135.

to give *N*- rather than *O*-reaction, giving (V). *N*-Nitration of carbamic esters had been shown to occur by Curry and Mason.[11] Both compounds decomposed extensively on attempted reaction with pyridine.

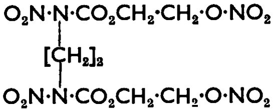


(I)



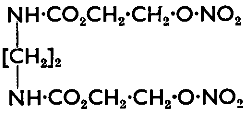
$$\begin{array}{l}\mathrm{NH\cdot CO_2CH_2\cdot CH_2\cdot OH}\\ |\\ \mathrm{[CH_2]_2}\\ |\\ \mathrm{NH\cdot CO_2CH_2\cdot CH_2\cdot OH}\end{array}$$

(II)



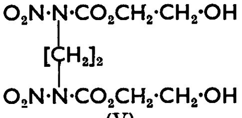
$$\begin{array}{l}\mathrm{O_2N\cdot N\cdot CO_2CH_2\cdot CH_2\cdot O\cdot NO_2}\\ \quad |\\ \mathrm{[CH_2]_2}\\ \quad |\\ \mathrm{O_2N\cdot N\cdot CO_2CH_2\cdot CH_2\cdot O\cdot NO_2}\end{array}$$

(III)



$$\begin{array}{l}\mathrm{NH\cdot CO_2CH_2\cdot CH_2\cdot O\cdot NO_2}\\ |\\ \mathrm{[CH_2]_2}\\ |\\ \mathrm{NH\cdot CO_2CH_2\cdot CH_2\cdot O\cdot NO_2}\end{array}$$

(IV)



$$\begin{array}{l}\mathrm{O_2N\cdot N\cdot CO_2CH_2\cdot CH_2\cdot OH}\\ \quad |\\ \mathrm{[CH_2]_2}\\ \quad |\\ \mathrm{O_2N\cdot N\cdot CO_2CH_2\cdot CH_2\cdot OH}\end{array}$$

(V)

The reaction of some substituted alkyl nitrates with thiourea to form thiuronium nitrates is detailed below. With *NN'*-di-(3-nitratobutyl)oxamide only one mol. of thiourea reacted under the conditions used. Similar non-reactivity of the second nitric ester group was observed in Part I.

For the first time the direct preparation of a phosphonium nitrate is reported: di-(*o*-methoxyphenyl)methylphosphine and ethyl nitrate, on prolonged refluxing in ethyl alcohol, forms ethyldi-(*o*-methoxyphenyl)methylphosphonium nitrate.

Generally, quaternary ammonium nitrates are more difficult to crystallise than the corresponding halide salts. This may be due, in part, to their almost invariably lower melting points. The characterisation of such compounds is best achieved *via* the corresponding picrates or perchlorates. The quantitative characterisation of quaternary ammonium nitrates by titration with perchloric acid in glacial acetic acid[12] may also be recommended in many cases.

EXPERIMENTAL

Determination of the Equivalent Weight of Quaternary Ammonium Salts.—Quaternary ammonium nitrates were titrated in glacial acetic acid with a freshly standardised solution of perchloric acid in glacial acetic acid, a high-frequency method[12] being used for the determination of end-point. This method gave unsatisfactory results with those polyfunctional compounds where perchlorate was precipitated during the titration with the production of a spurious end-point.

Quaternary ammonium picrates were determined titrimetrically by the visual end-point method due to Clark and Wang.[13]

2-*Butoxyethyltrimethylammonium Nitrate.*—2-Butoxyethyl nitrate[14] was heated with alcoholic trimethylamine for 2 hr. at 100°. Removal of the solvent left the *salt* as a colourless oil (Found: equiv., 224. $C_9H_{22}O_4N_2$ requires equiv., 222).

3-*Oxapentamethylenebis(pyridinium Nitrate).*—Diethylene glycol dinitrate was refluxed for 2 hr. with a ten-fold excess of pyridine. Excess of pyridine was removed from the lower, dark, viscous layer which was then treated with charcoal in aqueous solution and evaporated to dryness, yielding the *salt*, m. p. 45—46°, as cream-coloured cubes from acetone (Found: C, 44·4; H, 5·5; N, 14·7. $C_{14}H_{18}O_7N_4,H_2O$ requires C, 45·1; H, 5·4; N, 15·05%). The *dipicrate* melted at 110° (Found: C, 45·4; H, 3·2; N, 16·0%; equiv., 348. $C_{26}H_{22}O_{15}N_8$ requires C, 45·5; H, 3·5; N, 16·3%; equiv., 344).

3 : 6-*Dioxaoctamethylenebis(pyridinium Nitrate).*—Triethylene glycol dinitrate and pyridine similarly gave the salt as an amber syrup, characterised as the *dipicrate*, m. p. 117—119° (Found: C, 46·0; H, 3·5; N, 15·7. $C_{28}H_{26}O_{16}N_8$ requires C, 46·0; H, 3·6; N, 15·35%).

Reaction of Tertiary Bases with the Nitric Esters of Mono-, Di-, and Tri-ethanolamine.—2-Nitratoethylammonium nitrate[15] (5 g.), ethanol (50 ml.), and pyridine (10 ml.) were refluxed together for 30 min. Removal of the solvent left an amber syrup which slowly crystallised.

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[11] Curry and Mason, *J. Amer. Chem. Soc.*, 1951, **73**, 5043.
[12] Lane, *Analyst*, 1955, **80**, 675.
[13] Clark and Wang, *Analyt. Chem.*, 1954, **26**, 1230.
[14] Desseigne, *Bull. Soc. chim. France*, 1946, 98.
[15] Barbière, *ibid.*, 1944, **11**, 470.

After recrystallisation from 90% ethanol, 2-*pyridiniumethylammonium dinitrate* formed colourless leaves, m. p. 114° (Found: C, 34·2; H, 5·2; N, 23·0%; equiv., 126. $C_7H_{12}O_6N_4$ requires C, 33·9; H, 4·8; N, 22·6%; equiv., 124). The dipicrate melted at 226° (decomp.) [lit.,[16] m. p. 225—226° (decomp.)]. By a similar procedure 2-quinoliniumethylammonium dipicrate was obtained, having m. p. 239° in agreement with Seshadri.[17]

Di-(2-nitratoethyl)ammonium nitrate [19] was similarly converted into *di*-(2-*pyridiniumethyl*)-*ammonium trinitrate*, colourless cubes, m. p. 146—147° (Found: C, 40·6; H, 5·1; N, 19·5. $C_{14}H_{20}O_9N_6$ requires C, 40·4; H, 4·8; N, 22·2%), *tripicrate*, m. p. 211—212° (decomp.) (Found: N, 17·9. $C_{32}H_{26}O_{21}N_{12}$ requires N, 18·4%), and *triperchlorate*. m. p. 176° (decomp.) (from acetic acid) (Found: N, 7·65. $C_{14}H_{22}O_{12}N_3Cl_3$ requires N, 7·9%).

Tri-(2-nitratoethyl)amine similarly [18] formed *tri*-(2-*pyridiniumethyl*)*amine trinitrate*, m. p. 100—103° (after shrinking at 80°) (deliquescent cubes), darkening in light (Found: C, 47·9; H, 5·4; N, 18·5. $C_{21}H_{27}O_9N_7$ requires C, 48·4; H, 5·2; N, 18·8%), and *tetraperchlorate* (explodes when heated) (Found: N, 8·6; Cl, 16·1. $C_{21}H_{28}O_{16}N_4Cl_4$ requires N, 8·8; Cl, 16·8%).

Tri-(2-nitratoethyl)ammonium nitrate, heated with alcoholic trimethylamine, formed *tri*-(2-*trimethylammoniumethyl*)*ammonium tetranitrate*, m. p. 143—146° (Found: C, 34·3; H, 8·1; N, 21·0. $C_{15}H_{40}O_{12}N_8$ requires C, 34·3; H, 7·6; N, 21·4%).

Methyl di-(2-nitratoethyl)amine with pyridine at 100° formed 3-methyl-3-azapentane-1 : 5-bis(pyridinium nitrate) characterised as the *tripicrate*, m. p. 160° (Found: N, 17·9. $C_{33}H_{28}O_{21}N_{12}$ requires N, 18·1%).

NN'-*Di*(*hydroxyalkyl*)*diamides*.—Rauscher and Clark's method [20] using the appropriate diester (whenever available) and a slight excess of the hydroxyalkylamine was used; alternatively, the free acid was refluxed with a 50% excess of the hydroxyalkylamine for 4 hr. New *compounds* prepared by these methods are recorded in Table 1.

TABLE 1. NN'-*Di*(*hydroxyalkyl*)*diamides*.

	M. p.	Formula	Found, N (%)	Required, N (%)
NN'-Di-(3-hydroxypropyl)oxamide	122°	$C_8H_{16}O_4N_2$	18·0	17·7
NN'-Di-(3-hydroxybutyl)oxamide	112—112·5	$C_{10}H_{20}O_4N_2$	11·7	12·05
NN'-Di-(1-hydroxymethyl-(1-methylethyl)oxamide	185—186	$C_{10}H_{20}O_4N_2$	12·3	12·05
NN'-Di-(3-hydroxypropyl)succinamide	138—140	$C_{10}H_{20}O_4N_2$	12·4	12·05
NN'-Di-(2-hydroxyethyl)maleamide	99	$C_8H_{14}O_4N_2$	13·5	13·9
NN'-Di-(2-hydroxyethyl)decane-1 : 10-diamide	151—152	$C_{16}H_{32}O_4N_2$	8·95	8·9
NN'-Di-(2-hydroxyethyl)hexadecane-1 : 16-diamide	156	$C_{22}H_{44}O_4N_2$	6·95	7·0

N-3-*Hydroxypropylstearamide*, prepared from stearic acid and 3-aminopropanol, had m. p. 83—84° (Found: N, 4·15. $C_{21}H_{43}O_2N$ requires N, 4·1%).

2-*Stearamidoethyl Nitrate*.—Powdered *N*-2-hydroxyethylstearamide (16 g.) was added portionwise to a cooled, stirred mixture of acetic anhydride (14·1 ml.) and fuming nitric acid (6·5 ml.) at <5°. The mixture was cautiously heated to 30° to effect complete dissolution of the amide and then poured into cold water. The *ester* separated as a white solid, which was filtered off, washed with water, and dried in air. The yield is quantitative and the material can be used for quaternisation without further purification. The pure material melted at 68·5—69° (from ethanol) (Found: N, 7·55. $C_{30}H_{40}O_4N_2$ requires N, 7·5%).

3-*Stearamidopropyl nitrate*, similarly prepared, had m. p. 63—65° (Found: N, 7·3. $C_{21}H_{42}O_4N_2$ requires N, 7·3%).

Preparation of NN'-*Di*(*nitratoalkyl*)*diamides*.—These were prepared from the corresponding hydroxy-compounds by acetic anhydride–fuming nitric acid. One example is detailed; properties of the new *nitrates* prepared by this route are listed in Table 2.

NN'-*Di*-(3-*nitratobutyl*)*oxamide*. *NN'*-Di-(3-hydroxybutyl)oxamide (20 g.) was added portionwise to a stirred mixture of acetic anhydride (23 ml.) and fuming nitric acid (10 ml.) at <0°. Nitric acid (*d* 1·42) was then added to effect complete dissolution and the mixture was poured into cold water and neutralised with sodium carbonate. The solid separating was filtered off, and washed. The *ester* had m. p. 100·5° (from ethanol) (Found: N, 17·3. $C_{10}H_{18}O_8N_4$ requires N, 17·4%).

2-*Stearamidoethylpyridinium Nitrate*.—2-Stearamidoethyl nitrate (10 g.) and pyridine

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[16] Gabriel, *Ber.*, 1920, **53**, 1989.

[17] Seshadri, *J.*, 1929, 2952.

[18] Chute, Herring, Toombs, and Wright, *Canad. J. Res.*, 1948, **26**, *B*, 89.

[19] Dunn, Meen, and Wright, *J. Amer. Chem. Soc.*, 1952, **74**, 1344.

[20] Rausher and Clark, *ibid.*, 1948, **70**, 438.

TABLE 2. NN'-*Di*(*nitratoalkyl*)*diamides.*

	M. p.	Formula	Found, N (%)	Required, N (%)
NN'-Di-(2-nitratoethyl)oxamide	148°	Stuart and Wright[8] cite m. p. 148·2°		
NN'-Di-(3-nitratopropyl)oxamide	122	$C_8H_{14}O_8N_4$	19·0	19·05
NN'-Di-(3-nitratobutyl)oxamide	100·5	$C_{10}H_{18}O_8N_4$	17·3	17·4
NN'-Di-(2-nitratoethyl)malonamide	101	$C_7H_{12}O_8N_4$	19·7	20·0
NN'-Di-(2-nitratoethyl)succinamide	98	$C_8H_{14}O_8N_4$	18·6	19·05
NN'-Di-(3-nitratopropyl)succinamide	101	$C_{10}H_{18}O_8N_4$	16·7	17·4
NN'-Di-(2-nitratoethyl)adipamide	89	$C_{10}H_{18}O_8N_4$	17·3	17·4
NN'-Di-(2-nitratoethyl)sebacamide	97·5	$C_{14}H_{26}O_8N_4$	14·7	14·8
NN'-Di-(2-nitratoethyl)decane-1 : 10-diamide	100	$C_{16}H_{30}O_8N_4$	14·2	13·8
NN'-Di-(2-nitratoethyl)hexadecane-1 : 16-diamide	110	$C_{22}H_{42}O_8N_4$	11·3	11·4

TABLE 3. *Quaternary ammonium salts derived from dicarboxylic acid bis*(*tertiary aminoalkylamides*).

	M. p.	Formula	Found (%)			Required (%)		
			C	H	N	C	H	N
NN'-Di-(2-pyridiniumethyl)oxamide dinitrate	210° *	$C_{16}H_{20}O_8N_6$	44·7	4·6	19·6	45·3	4·7	19·8
dipicrate	245 *	$C_{28}H_{24}O_{16}N_{10}$	—	—	18·4	—	—	18·5
NN'-Di-[2-(*cyclo*hexylmethylamino)-ethyl]oxamide dimethopicrate	161 *	$C_{34}H_{48}O_{16}N_{10}$	47·6	5·5	16·8	48·0	5·65	16·4
NN'-Di-(3-dimethylaminopropyl)-oxamide dimethonitrate	230 *	$C_{14}H_{32}O_8N_6$	40·7	7·85	19·7	40·8	7·8	20·4
dimethoperchlorate	282 *	$C_{14}H_{32}O_{10}N_4Cl_2$	14·85 †	—	11·7	14·6 †	—	11·5
NN'-Di-(2-pyridiniumethyl)succinamide dinitrate	—	$C_{18}H_{24}O_8N_6$	44·7	4·6	19·6	45·3	4·7	19·8
dipicrate	168	$C_{30}H_{28}O_{16}N_{10}$	—	—	18·3	—	—	17·9
NN'-Di-(2-pyridiniumethyl)adipamide dipicrate	114·5	$C_{32}H_{32}O_{16}N_{10}$	—	—	17·1	—	—	17·5
NN'-Di-(2-pyridiniumethyl)sebacamide dinitrate	114	$C_{24}H_{36}O_8N_6$	—	—	16·5	—	—	16·3
dipicrate	180	$C_{36}H_{40}O_{16}N_{10}$	49·6	4·75	16·0	49·6	4·8	16·1

* Decomp. † Cl.

(25 ml.) were heated together on a steam-bath for 8 hr. Removal of unchanged pyridine left a thick oil which was triturated with ether and dried *in vacuo*; the *salt* was obtained as a soft amber-coloured wax with no definite m. p. (Found : N, 8·75. $C_{25}H_{45}O_4N_3$ requires N, 9·3%). Similarly obtained were 3-*stearamidopropylpyridinium nitrate*, a yellow wax (Found : N, 8·7. $C_{26}H_{47}O_4N_3$ requires N, 9·0%), and *benzyldimethyl*-(3-*stearamidopropyl*)*ammonium nitrate*, an amber wax (Found : N, 7·8. $C_{30}H_{55}O_4N_3$ requires N, 8·1%). All these compounds gave foaming aqueous solutions.

Reaction of NN'-*Di*(*nitratoalkyl*)*diamides with Tertiary Amines.*—A similar procedure led to the *compounds* listed in Table 3. Where no m. p. is given the compound was a syrup. Failure to crystallise has been previously noted for other quaternary ammonium salts in this series.[21]

Di-(Δ^2-1 : 3-*oxazolin*-2-*yl*) (I).—*NN'*-Di-(2-nitratoethyl)oxamide (2·66 g.) was refluxed in methanol (30 ml.) containing potassium hydroxide (1·12 g.) for 1 hr., then filtered whilst hot from the inorganic precipitate. The filtrate, on evaporation to dryness, deposited the *base*, m. p. 211° (from toluene) (Found : equiv., 139. Calc. for $C_6H_8O_2N_2$: equiv., 140). Wenker[9] obtained m. p. 213°.

Nitration of NN'-*Di*-(2-*hydroxyethoxycarbonyl*)*ethylenediamine* (II).—The urethane[22] (15 g.) was added portionwise to a mixture of acetic anhydride (23 ml.) and fuming nitric acid (11 ml.) at <5°. Nitric acid (*d* 1·42; 15 ml.) was added to effect complete dissolution and the mixture was poured into cold water and neutralised with sodium carbonate. The precipitated NN'-*dinitro*-NN'-*di*-(2-*nitratoethoxycarbonyl*)*ethylenediamine* (III) had m. p. 80—81° (from methanol) (Found: C, 23·9; H, 2·8; N, 20·6. $C_8H_{12}O_{14}N_6$ requires C, 23·1; H, 2·9; N, 20·2%), and decomposed exothermically on reaction with pyridine, forming water-insoluble products.

NN'-Di-(2-hydroxyethoxycarbonyl)ethylenediamine (5 g.) was added portionwise to fuming nitric acid (12 ml.) at <5°; pouring the mixture into sodium carbonate solution gave a colourless oil which solidified (m. p. 91—92°) (Found : C, 30·1; H, 4·5; N, 17·4%). *NN'*-Di-(2-nitratoethoxycarbonyl)- (IV) and *NN'*-di-(2-hydroxyethoxycarbonyl)-*NN'*-dinitroethylenediamine (V) both have the molecular formula $C_8H_{14}O_{10}N_4$ (Required: C, 29·4; H, 4·3;

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[21] Phillips, *J. Amer. Chem. Soc.*, 1952, **74**, 4320.

[22] Chabrier, Delaby, and Najer, *Compt. rend.*, 1952, **235**, 376.

N, 17·2%). The *compound* obtained is believed to be the latter, as it decomposed in pyridine without formation of the expected quaternary nitrate.

Ethyldi-(o-*methoxyphenyl*)*methylphosphonium Nitrate.*—Di-(*o*-methoxyphenyl)methylphosphine[23] was refluxed for 8 hr. on a steam-bath with a 50% excess of ethyl nitrate in ethanol. Removal of solvent left the *salt*, m. p. 154—156° (from ethanol–acetone) (Found: C, 57·8; H, 6·5; N, 3·9%; equiv., 348. $C_{17}H_{22}O_5NP$ requires C, 58·2; H, 6·3; N, 4·0%; equiv., 351); the *picrate* had m. p. 136—137° (decomp.) (Found: N, 8·3%; equiv., 520. $C_{23}H_{29}O_9N_3P$ requires N, 8·1%; equiv., 517).

NN′-*Oxamidobis-*(3-*thiuroniumpropyl*) *Dinitrate.*—*NN′*-Di-(3-nitratopropyl)oxamide and two mols. of thiourea were refluxed together in toluene for 6 hr. On removal of solvent the *salt* was obtained as a yellow oil which slowly solidified. It formed cream cubes, m. p. 211° (decomp.), from ethanol (Found: N, 24·8; S, 14·2. $C_{10}H_{22}O_8N_8S_2$ requires N, 25·1; S, 14·85%); the *dipicrate*, insoluble in all common solvents, had m. p. 258° (decomp.) (Found: N, 21·6; S, 8·2. $C_{22}H_{26}O_{16}N_{12}S_2$ requires N, 21·6; S, 8·2%).

N-(3-*Nitratobutyl*)-N′-(3-*thiuroniumbutyl*)*oxamide Nitrate.*—*NN′*-Di-(3-nitratobutyl)oxamide (5 g.) and thiourea (2·4 g.) were refluxed together in 2-ethoxyethanol for 1 hr. The colourless oil remaining after removal of solvent did not crystallise but was characterised as the *picrate*, m. p. 229—230° (decomp., after shrinking at 200°) (Found: N, 19·9; S, 5·7. $C_{17}H_{24}O_{12}N_8S$ requires N, 19·9; S, 5·7%).

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[23] Kennedy, Lane, and Willans, unpublished work.