234. *Quaternary Ammonium Nitrates. Part I. Preparation from Alkyl Nitrates and from αω-Polymethylene Dinitrates.*

By E. S. Lane.

Good yields of quaternary ammonium nitrates are produced by quaternisation of tertiary bases with alkyl nitrates. The reaction has been extended to the production of polymethylenebis(quaternary ammonium nitrates) and of one polymethylenebis(thiuronium nitrate). General features of the reaction are discussed and the pharmacological activity of one compound as a neuromuscular blocking agent is reported.

Since the preparation of quaternary ammonium nitrates by metathesis from the corresponding halides is often tedious, it was decided to investigate their formation by direct quaternisation of tertiary bases with alkyl nitrates. Reference has been made to hexamine metho- and etho-nitrates, obtained by reaction of hexamine with the corresponding alkyl nitrate (Hahn and Walter, *Ber.*, 1921, **54**, 153; see also Foss *et al.*, *J.*, 1950, 624), and to the preparation of long-chain quaternary ammonium nitrates by reaction of the higher alkyl nitrates with tertiary bases (B.P. 605,402, Baldwin, Statham, and Imperial Chemical Industries Limited). The latter procedure has now been found to give high yields of the authentic quaternary ammonium nitrates. The reaction has been extended to the production of polymethylenebis(quaternary ammonium nitrates) and of a polymethylenebis (thiuronium nitrate).

Quaternisation of tertiary bases with alkyl nitrates was carried out by refluxing the ester with an excess of tertiary amine, with or without a solvent. Alkyl nitrates are thermally much less stable than the corresponding halides and this leads to some coloration of the quaternised base, but after purification the quaternary ammonium nitrates are obtained (in most cases) as colourless or pale cream-coloured crystals which are soluble in cold water and alcohols but sparingly soluble in cold acetone, ether, and low-boiling light petroleum. The products were characterised by readily crystallised picrates and, in one case, by a crystalline perchlorate. In view of the thermal instability of nitric esters, they were not distilled before quaternisation. Purification of the higher alkyl nitrates was effected by washing them with methanol in which they are only very sparingly soluble. This purification facilitated a high yield of solid higher alkyl quaternary ammonium nitrates.*

Reaction of αω-polymethylene dinitrates with tertiary bases was carried out by the same general procedure. This reaction appears to be general with esters of primary alcohols or glycols, but secondary and tertiary esters show wide differences in behaviour. Simple compounds, *e.g.*, *sec.*-butyl nitrate, reacted normally, but the trinitrate of tristearin-11 : 11′ : 11″-triol (hydrogenated castor oil) yielded no trace of a water-soluble quaternary salt on continued refluxing with several tertiary bases. Similar failure occurred with the nitrate from amyl lactate. With tertiary esters, extensive decomposition occurs, apparently with loss of the elements of nitric acid; for instance, *cyclo*hexyl nitrate reacted with pyridine to yield *cyclo*hexene and polymeric material, whilst 1 : 1 : 3-trimethyltrimethylene dinitrate and pyridine gave an almost quantitative yield of pyridine nitrate together with unidentified polymeric product. *tert.*-Butyl nitrate and pyridine gave a good yield of butylene: no quaternary salt was isolated.

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* See also B.P. Appln. 489/1951, assigned to National Research Development Corporation.

The only examples so far encountered of primary nitric ester groups failing to quaternise tertiary bases have been with nitrates of alcohols containing a *neo*pentyl-type of structure, *e.g.*, pentaerythritol, 2 : 2-diethylpropane-1 : 3-diol, and 2-hydroxymethyl-2-methylpropane-1 : 3-diol, where the non-reactivity is almost certainly due to steric hindrance (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 187).

The majority of the nitric esters examined reacted readily with pyridine or trimethylamine, but scarcely at all with higher tertiary amines, *e.g.*, 2-hexylpyridine, tri-*n*-amylamine, even in solvents (*e.g.*, acetonitrile) known to promote quaternisation. Another example of unexplained non-reactivity was observed in the reaction of pentamethylene dinitrate and hexamine, only 5′-nitratopentylhexamine nitrate being obtained.

Pentamethylene dinitrate reacted readily with thiourea, forming pentamethylenebis-(thiuronium nitrate) in almost theoretical yield (compare Taylor, *J.*, 1917, **111**, 650).

Polymethylenebis(quaternary ammonium) salts are known to possess considerable neuromuscular blocking activity (Paton and Zaimis, *Brit. J. Pharmacol.*, 1949, **4**, 381; Walker, *J.*, 1950, 193; Taylor, *J.*, 1951, 1150, etc.). Dr. E. J. Zaimis kindly tested some of the compounds described in this paper and reported: " From experiments using the tibialis anterior muscle in the cat, the gastrocnemius muscle in the adult fowl, and the whole chick, it appears that decamethylenebis(pyridinium nitrate) [LD_{50} (intravenously in mice), 7·2 mg. per kg.] is the only one showing an interesting activity at the neuromuscular junction. It possesses considerable anticholinesterase activity (40 times less potent than prostigmine) but at the same time exhibits a direct action causing depolarisation of the motor end plate. To produce a depolarising block comparable with that resulting from decamethonium a dose of about 200 times greater is required. The anticholinesterase activity was tested *in vitro* also. It is proposed to make a more detailed pharmacological study of this compound in the near future."

The pharmacological activity of decamethylenebis(pyridinium bromide) in mice has been reported in less detail by Collier and Taylor (*Nature*, 1949, **164**, 491).

EXPERIMENTAL

Microanalyses are by Drs. Weiler and Strauss, of Oxford.

Cetylpyridinium Nitrate.—Fuming nitric acid (25·4 ml., 0·5 mol.) was added dropwise to acetic anhydride (56·4 ml., 0·5 mol.), cooled and stirred in an ice-bath. The internal temperature being kept at 10°, powdered cetyl alcohol (91 g., 0·375 mol.) was added portionwise (2 hours), and the temperature then allowed to rise to 20°; the mixture was diluted with water (300 ml.), and the aqueous layer removed. The organic layer was purified by shaking it with methanol (3 × 100 ml.), which was only sparingly soluble in the ester. The methanol-washed cetyl nitrate (108 g.) and pyridine (100 ml.) were refluxed for 24 hours, then cooled to 30° and mixed with acetone (to 500 ml. bulk). This solution was cooled in ice, and the precipitated cetylpyridinium nitrate filtered off, recrystallised from acetone (twice), and dried *in vacuo*; the yield of salt, m. p. 62—64°, was 70 g. (Found: C, 68·9; H, 10·4; N, 7·9. Calc. for $C_{21}H_{38}O_3N_2$: C, 68·8; H, 10·4; N, 7·7%). Evers and Klaus (*J. Amer. Chem. Soc.*, 1948, **70**, 3051) give m. p. 58—59°.

Dodecylpyridinium Nitrate.—Dodecyl nitrate (100 g.; from commercial " Lorol ") and pyridine (52 g.) were refluxed for 24 hours, the mixture then being completely water-soluble. Excess of pyridine was removed by steam-distillation, and the still residue diluted with water, boiled with charcoal, and filtered. The colourless filtrate was then evaporated to dryness under reduced pressure. Dodecylpyridinium nitrate was obtained as a straw-coloured wax (98 g.). The *perchlorate* melted at 76·5° (Found: N, 3·75; Cl, 10·2. $C_{17}H_{30}O_4NCl$ requires N, 4·0; Cl, 10·2%).

1-sec.-*Butylpyridinium Nitrate.*—*sec.*-Butyl nitrate (12 g.) and pyridine (20 g.) were refluxed for 8 hours, and the mixture worked up as in the previous example, yielding *sec.*-butylpyridinium nitrate as a water-soluble, golden-yellow, viscous liquid. The corresponding picrate was a yellow oil. Neither compound crystallised.

Preparation of Polymethylene Dinitrates.—Fuming nitric acid (25·4 ml., 0·5 mol.) was added dropwise to acetic anhydride (56·4 ml., 0·5 mol.), cooled and stirred in an ice-bath. The internal temperature being kept below 10°, the polymethylene glycol (0·2 mole) was added portionwise. When the addition was complete the mixture was allowed to warm to room temperature, then poured into ice–water (500 g.). The oily layer was run off, washed with sodium hydrogen carbonate solution and with water, and dried (Na_2SO_4).

*Preparation of Polymethylenebis(quaternary Ammonium Nitrates).**—The polymethylene dinitrate was refluxed with a two-fold excess of the appropriate tertiary amine. One example is given in detail below; the properties of the quaternary salts are listed in the Table. The reaction involving trimethylamine was carried out in a sealed tube at 100°.

Tetramethylenebis(pyridinium nitrate). Tetramethylene dinitrate (20·7 g.) and pyridine (20 g.) were refluxed for 2 hours. On cooling, the mixture solidified, the solid was filtered off and dissolved in water, and the solution decolorised (charcoal), filtered, and evaporated to dryness (27·4 g.). Recrystallised from methanol, *tetramethylenebis(pyridinium nitrate)* formed pale cream-coloured crystals, m. p. 163—164° (Found: C, 49·6; H, 5·3; N, 16·6. $C_{14}H_{18}O_6N_4$ requires C, 49·7; H, 5·3; N, 16·6%).

Polymethylenebis(quaternary ammonium nitrates and picrates).

	M. p.	Formula	Found: N, %	Req.: N, %
		Nitrates		
Tetramethylenebispyridinium	[See above]			
Pentamethylenebispyridinium	106°	$C_{15}H_{20}O_6N_4$	15·7	15·9
Pentamethylenebis-2-hydroxyethyldimethylammonium	123—124	$C_{13}H_{32}O_8N_4$	15·05	15·2
Hexamethylenebispyridinium	194—195	$C_{16}H_{22}O_6N_4$	15·2	15·3
Decamethylenebispyridinium	150—151	$C_{20}H_{30}O_6N_4$	13·1	13·29
Decamethylenebistrimethylammonium	196—198	$C_{16}H_{38}O_6N_4$	13·8	14·0
Decamethylenebisbenzyldimethylammonium	159	$C_{28}H_{46}O_6N_4$	10·6	10·5
		Picrates		
Tetramethylenebispyridinium	203 *	—	—	—
Pentamethylenebispyridinium	112—113	$C_{27}H_{24}O_{20}N_{10}$	16·5	16·4
Pentamethylenebis-2-hydroxyethyldimethylammonium	239—240	$C_{25}H_{36}O_{22}N_{10}$	16·1	15·9
Hexamethylenebispyridinium	184—185·5	$C_{28}H_{26}O_{20}N_{10}$	15·8	16·05
Decamethylenebispyridinium	101—102·5	$C_{32}H_{34}O_{20}N_{10}$	14·9	14·9
Decamethylenebistrimethylammonium	146—147 †	—	—	—
Decamethylenebisbenzyldimethylammonium	138·5—139·5	$C_{40}H_{40}O_{20}N_{10}$	12·5	12·9

* Gautier and Renault (*Compt. rend.*, 1947, **225**, 682) give m. p. 207°.
† Zaimis (*Brit. J. Pharmacol*, 1950, **5**, 424) gives m. p. 145—146°.

Polymethylenebis(quaternary ammonium picrates). Analyses are listed in the Table. *Reaction of Pyridine with* 1 : 1 : 3-*Trimethyltrimethylene Dinitrate.*—The dinitrate (20·8 g.), pyridine (16 ml., 2 mol.), and methanol (100 ml.) were refluxed for 8 hours and cooled. The resulting crystalline mass (13 g.) was filtered off, recrystallised from benzene and methanol, and identified as pyridine nitrate, m. p. 114—116° (Found: C, 42·6; H, 4·2; N, 19·1. Calc. for $C_5H_6O_3N_2$: C, 42·3; H, 4·2; N, 19·7%). On evaporation of the filtrate a dark brown, viscous, water-insoluble liquid was obtained which could not be worked up.

Reaction of Pyridine with tert.-*Butyl Nitrate.*—*tert.*-Butyl nitrate (16 g.) and pyridine (16 g.) were refluxed, and the uncondensed vapours from the top of the condenser led into a trap, cooled in solid carbon dioxide. After 1 hour, butylene (6·5 g.; b. p. 1—4°) was recovered from the trap.

Reaction of Pyridine with cyclo*Hexyl Nitrate.*—*cyclo*Hexyl nitrate (15 g.) and pyridine (15 g.) were refluxed for 4 hours. The reaction mixture, which was not water-soluble, was fractionated. The fraction, b. p. 80—84°, was unsaturated, giving an oily dibromide. *cyclo*Hexene boils at 83°.

5′-*Nitratopentylhexamine Nitrate.*—Pentamethylene dinitrate (5·8 g.) was refluxed for 8 hours with hexamine (9 g.) in ethyl alcohol (50 ml.). The water-soluble reaction mixture was cooled, filtered, and evaporated to dryness, redissolved in water, decolorised (charcoal), filtered, and evaporated *in vacuo*. The pale straw-coloured viscous *nitrate* could not be crystallised (Found: N, 25·2. $C_{11}H_{22}O_6N_6$ requires N, 25·15%). The *picrate* had m. p. 100—102° (Found: N, 21·8. $C_{17}H_{25}O_{10}N_8$ requires 22·4%).

Pentamethylene-1 : 5-*dithiuronium Dinitrate.*—Pentamethylene dinitrate (26 g.), thiourea (21 g., 2 mol.), and "Cellosolve" (150 ml.) were refluxed for 24 hours. Solvent was then removed under reduced pressure, and the residue recrystallised twice from methanol–ether (1 : 1), giving microcrystalline *pentamethylene*-1 : 5-*dithiuronium dinitrate* (12 g.), m. p. 118—119° (Found: N, 23·8; S, 18·4. $C_7H_{18}O_6N_6S_2$ requires N, 24·2; S, 18·5%). The corresponding

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* See also B.P. Appln. 13,749/1951, assigned to National Research Development Corporation.

dipicrate melted at 230—231° (Found: N, 21·2; S, 9·5. $C_{19}H_{24}O_{20}N_{12}S_2$ requires N, 20·6; S, 9·4%).

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