342. *On the Structure of Knudsen's Base and of Related Compounds. Part II.*

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Further evidence is adduced for the identity of the corresponding salts of Knudsen's base, of the base obtained by treating hexamine dinitrate with hot solvents, and of the 1-methyl-hexamine ammonium cation, from the study of dinitro- and nitrosonitro-derivatives and of dipicrates. The mechanism of the production of the methylhexamine cage is considered.

The work described in Part I (*J.*, 1950, 624) establishes with reasonable certainty the three-fold identity among the corresponding salts of (1) Knudsen's base, (2) the base *A* obtained by treating hexamine dinitrate with hot solvents, and (3) the methylhexamine cation, but some further evidence along three lines is described below.

(1) *Dinitro-derivatives.*—Knudsen's nitrate and authentic hexamine methonitrate were treated with cold nitric acid (98%), a reaction which with the authentic methonitrate has been shown by workers in the University of Pennsylvania to give 3 : 7-dinitro-1-methylpenta-methylenetetramine 1-nitrate (IV), m. p. 143° (private communication from Professor Marvin Carmack). According as Knudsen's nitrate has structure (III) or (II) of Part I, it should give either (IV) or 3 : 7-dinitro-1 : 5-dimethyl-1 : 3 : 5 : 7-tetra-aza*cyclo*octane 1-nitrate (V).

(IV.)   (V.)
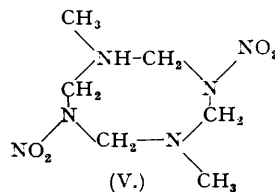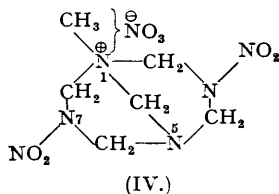
Both products had m. p. 142° alone or mixed, and both gave positive Thiele–Lachmann tests for *N*-nitro-groups and negative Liebermann tests for *N*-nitroso-groups. The analytical data (see table), especially the values for *N*-Me and CH$_2$, confirm the structure (IV) for the products and thus structure (III; X = NO$_3$, of Part I) for Knudsen's nitrate. The corresponding picrates were also prepared and similarly found to be identical, and to be derived from structure (IV).

(2) *Nitrosonitro-derivatives.*—Knudsen's picrate and authentic hexamine methopicrate were treated with a mixture of nitric acid (98%) and dinitrogen tetroxide. Hexamine metho-nitrate under these conditions yields 3-nitroso-7-nitro-1-methylpentamethylenetetramine 1-nitrate (VI; X = NO$_3$) (private communication from Dr. A. Carruthers, then of Bristol University). Hexamine methopicrate would be expected, therefore, to yield (VI; X = picrate), and Knudsen's picrate either (VI; X = picrate) or 3-nitroso-7-nitro-1 : 5-dimethyl-1 : 3 : 5 : 7-tetra-aza*cyclo*octane 1-picrate (VII; X = picrate).

(VI.)   (VII.)
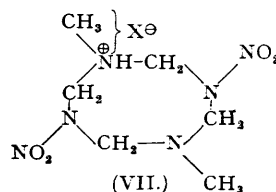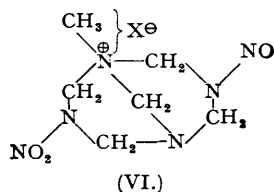
Both the products have m. p. 128—129° alone or mixed, and both give positive Thiele–Lachmann and positive Liebermann tests. This and analyses (see table) indicate that they are identical nitrosonitro-compounds of structure (VI; X = picrate) and confirm the structure (III) for Knudsen's base salts.

	C, %.	H, %.	N, %.	N-CH$_3$, %.	CH$_2$, %.	Anion X⊖, %.
Dinitro-nitrate.						
Found { From Knudsen's nitrate	24·7	4·6	33·1	4·0	24·1	21·5 ⎤
{ From hexamine methonitrate	24·5	4·5	33·6	4·2	23·6	21·1 ⎥ nitrate
Calc. { For C$_{16}$H$_{13}$O$_7$N$_7$ (IV)	24·4	4·4	33·2	5·1	23·8	21·0 ⎥
{ For C$_6$H$_{15}$O$_7$N$_7$ (V)	24·2	5·0	33·0	10·1	18·8	20·9 ⎦
Nitrosonitro-picrate.						
Found { From Knudsen's picrate	32·2	3·3	29·7	3·1	15·6	51·2 ⎤
{ From hexamine methopicrate	32·6	3·5	27·6	4·5	14·9	50·9 ⎥
Calc. { For C$_{12}$H$_{15}$O$_{10}$N$_9$ (VI; X = picrate)	32·4	3·4	28·4	6·5	15·8	51·3 ⎥
{ For C$_{12}$H$_{17}$O$_{10}$N$_9$ (VII; X = picrate)	32·3	3·8	28·2	13·0	12·5	51·1 ⎥
Dipicrate.						⎥ picrate
Found { From Knudsen's picrate	38·6	3·6	22·8	6·2	13·1	71·4 ⎥
{ From hexamine methopicrate	38·5	3·7	22·7	6·4	13·0	71·2 ⎥
{ Authentic dimethylhexamine dipicrate	38·4	3·8	22·9	6·4	13·4	72·4 ⎥
Calc. { For C$_{20}$H$_{22}$O$_{14}$N$_{10}$ (VIII; X = picrate)	38·4	3·6	22·4	9·3	13·4	72·8 ⎥
{ For C$_{20}$H$_{24}$O$_{14}$N$_{10}$ (IX; X = picrate)	38·2	3·8	22·4	13·8	11·2	72·6 ⎦

(3) *Dipicrates.*—The elements of methyl picrate were added to Knudsen's picrate and authentic hexamine methopicrate and the product, in each case, was identified with dimethylhexamine dipicrate, m. p. 212° (VIII; X = picrate), prepared independently *via* the dinitrate in McGill University (private communication from Professor Carl Winkler) from hexamine and methylammonium nitrate and in Bristol University (private communication from Dr. A. Carruthers) from 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane, formaldehyde, ammonium nitrate, and nitric acid.
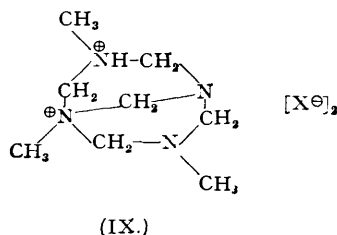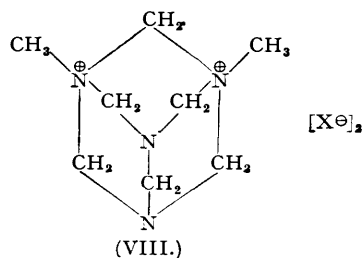

(VIII.)   (IX.)

Had Knudsen's picrate had structure (II; X = picrate) of Part I, the product of the addition of methyl picrate would probably have been (IX; X = picrate), differing widely from (VIII) in the significant *N*-methyl and methylene contents. Analytical results are given in the table.

The dipicrates from Knudsen's picrate, and authentic hexamine methopicrate melted at 195—196° alone or mixed. The melting point of dimethylhexamine dipicrate was reported from McGill and Bristol as 212°. Authentic specimens of the dipicrate from Bristol (m. p. 212° in Bristol) with the dipicrate from either Knudsen's picrate or authentic hexamine methopicrate gave mixed m. p. 195—200°, and all specimens of the dipicrate prepared in Manchester by the Bristol and McGill methods and a specimen of the dipicrate which had m. p. 212° in Bristol have similarly shown m. p. 195—196° in Manchester. The position is closely similar to that found with hexamine methopicrate itself. It is more disquieting that mixtures of authentic hexamine methopicrate and of authentic dimethylhexamine dipicrate also melt at 195—200°. However, the analytical results leave no doubt that the product from both Knudsen's picrate and hexamine methopicrate is indeed dimethylhexamine dipicrate, and the rather anomalous melting points act as a further caution against relying too much on these rather high decomposition points.

The final test was made by Professor F. J. Llewellyn who, in *X*-ray powder photographs of the dipicrate from Knudsen's picrate (m. p. 195—196°) and authentic dipicrate (m. p. 212° in Bristol, 195—196° in Manchester), found identical patterns (see Plate).

The results from these three lines of work thus confirm the threefold identity and structure (III of Part I) for the Knudsen base salts.

X-Ray powder diagrams for dimethylhexamine dipicrate (north and south quadrants) and the methyl dipicrate from Knudsen's base (east and west quadrants).
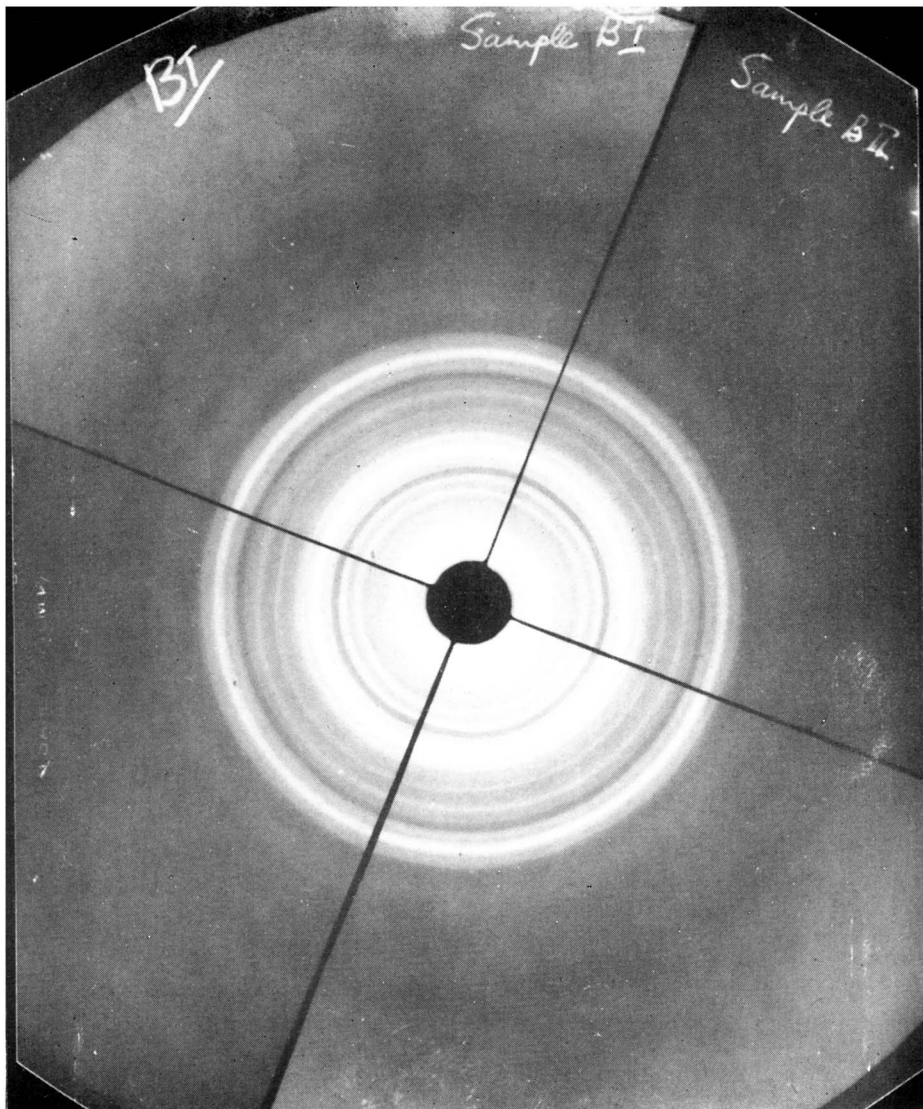
A Consideration of the Production of Tetra-alkylammonium Derivatives of Hexamine.—Apart from the normal direct alkylation process by alkyl halides and esters, the methylhexamine cation arises, somewhat unexpectedly, in at least two other reactions : (1) Knudsen's reaction, between formaldehyde and ammonium sulphate and (2) the action of hot solvents on hexamine dinitrate. In both, the methylating agent must be formaldehyde. *N*-Methylation by formaldehyde has long been recognised. Thus Plöchl (*Ber.*, 1888, **21**, 2117), Brochet and Cambrier (*Compt. rend.*, 1895, **120**, 449, 557; *Bull. Soc. chim.*, 1895, [iii], **13**, 392), Eschweiler (*Ber.*, 1905, **38**, 880), Köppen (*ibid.*, p. 882), and especially Werner (*J.*, 1917, **111**, 844) have demonstrated the formation of mono-, di-, and tri-methylamine from aqueous formaldehyde and ammonium chloride. It seems certain that *N*-methylation in biological syntheses is due to formaldehyde (Robinson, *ibid.*, p. 876), probably by the reactions :

$$\text{>NH} \xrightarrow{\text{CH}_2\text{O}} \text{>N·CH}_2\text{·OH} \xrightarrow{\text{2H}} \text{>N·CH}_3$$
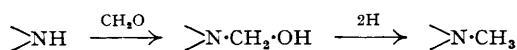
The first of these stages undoubtedly occurs (see, *e.g.*, Robinson, *J.*, 1936, 1079) and the overall process is well established.

The reducing agent needed for the second stage may be formaldehyde itself. Thus formaldehyde undergoes the Cannizzaro reaction in alkaline solution Lieben (*Monatsh.*, 1901, **22**, 289) :

$$2\text{CH}_2\text{O} + \text{H}_2\text{O} \longrightarrow \text{CH}_3\text{·OH} + \text{H·CO}_2\text{H}$$

while from the formaldehyde–ammonium chloride methylation reaction (acid conditions) Werner (*loc cit.*) has isolated methyl formate. The formic acid produced can, itself, act as a reducing agent : $\text{H·CO}_2\text{H} \longrightarrow (2\text{H}) + \text{CO}_2$. In all these reactions carbon dioxide is evolved, especially at high temperatures (*ca.* 70°). If some other reducing system is present, *e.g.*, >CH·OH, it may be used. Thus Hess (*Ber.*, 1913, **46**, 4104) has shown that the following process occurs in the hygrine series :

not isolated
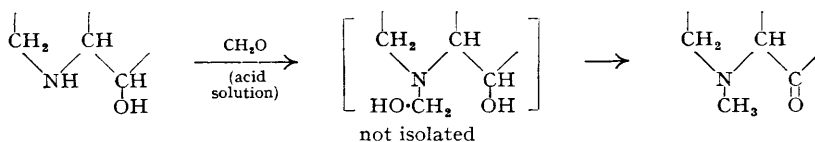
Werner (*loc. cit.*) advances the view that the stage N·CH$_2$·OH $\longrightarrow$ N·CH$_3$ of the process goes by the steps NHR·CH$_2$·OH $\longrightarrow$ NR:CH$_2$ + H$_2$O $\xrightarrow{\text{CH}_2\text{O}}$ NHR·CH$_3$ + H·CO$_2$H.

In view of the extreme ease of hydrolysis of the aldimines (see, *e.g.*, Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford, 1947, p. 65) the existence of NR:CH$_2$ in appreciable amount in dilute acid solution is most unlikely. Moreover, Werner's view forces him to propose a most artificial mechanism to account for the production of trimethylamine.
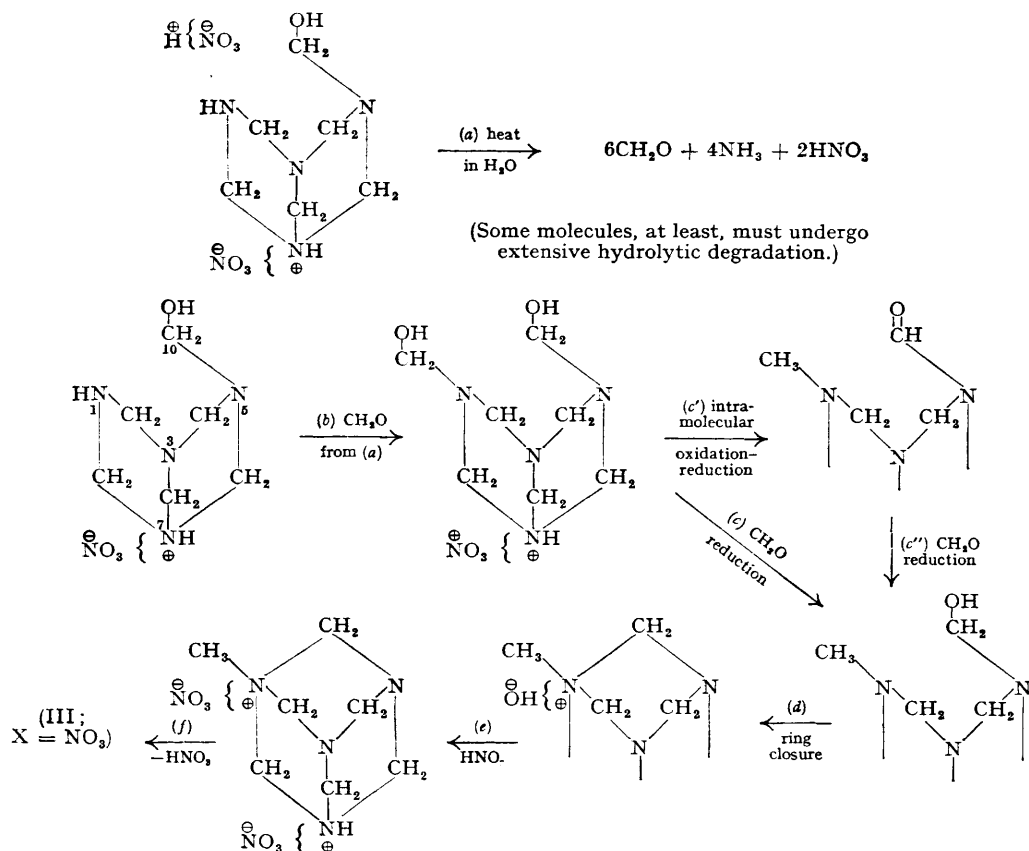
The less involved hypothesis of direct reduction of N·CH$_2$·OH seems preferable. It may well be that, once the initial *N*-methylation has occurred, the N·CH$_3$ system is "stored" in the form of methylbishydroxymethylamine or 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane. Werner claims that the absence of "condensation products," including 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane, from the milder low-temperature reactions of formaldehyde with ammonium chloride is proved by the non-appearance of a precipitate on the addition of picric acid. This evidence is not conclusive since pre-formed 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*-hexane is not thus precipitated. It *is* possible, however, that the compound is not stable in acid solution.

Outside the hexamine field it does not appear that formaldehyde can effect the final stage in the complete methylation of an amine, *i.e.*, the production of the quaternary tetra-alkyl ammonium salt :
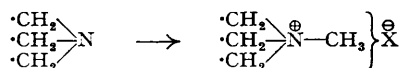
Indeed, it seems likely that so mild a reagent acting through so labile an intermediate as the N·CH$_2$·OH system would be unable to achieve the drastic final stage in which the nitrogen atom is constrained permanently to the quadricovalent ammonium state, but would more readily replace hydrogen atoms attached to nitrogen in the tercovalent electrostatically-neutral state.

It is suggested, therefore, that the production of hexamine methonitrate from hexamine dinitrate proceeds through the " cage-opened " structure as follows :

$$\xrightarrow[\text{in } H_2O]{(a)\ \text{heat}} \quad 6CH_2O + 4NH_3 + 2HNO_3$$

(Some molecules, at least, must undergo extensive hydrolytic degradation.)

$$\xrightarrow[\text{from } (a)]{(b)\ CH_2O}$$

$$\xrightarrow[\substack{\text{oxidation-}\\\text{reduction}}]{\substack{(c')\ \text{intra-}\\\text{molecular}}}$$

(c) CH₂O reduction

(c″) CH₂O reduction

(III ; X = NO₃)

$$\xleftarrow[-HNO_3]{(f)}$$

$$\xleftarrow[HNO_·]{(e)}$$

$$\xleftarrow[\substack{\text{ring}\\\text{closure}}]{(d)}$$

This scheme is necessarily more clear-cut and formalised than the actual process is likely to be. With the exception of the reduction (c) and the ring closure (d) * all the steps involved are reversible. Each $>N\cdot CH_2\cdot OH$ system exhibits the tautomerism, $>N\cdot CH_2\cdot OH \rightleftharpoons$ $>NH + CH_2O \rightleftharpoons >\overset{\oplus}{N}\{CH_2\}OH^{\ominus}$ (cf. the tautomerism of cotarnine). It is not certain in what order the earlier steps occur. Thus the reduction of $N\cdot CH_2\cdot OH$ to $N\cdot CH_3$ may occur quite early at N—$CH_2\cdot OH$. Similarly the exchange of OH for NO_3, placed above at (e), may occur earlier by $>N\cdot CH_2\cdot OH \longrightarrow >N\cdot CH_2\cdot O\cdot NO_2$. It may well be that the critical reduction proceeds by processes (c') and (c″) rather than by the direct process (c). The process (c') is to be expected from the results of Hess (*loc. cit.*).

The fact that dimethylpentamethylenetetramine derivatives do not arise can be correlated with the probable properties of the methylhydroxymethylpentamethylenetetramine derivative produced after process (c) [or (c') and (c″)]; this might well undergo irreversible ring closure * by process (d), in preference to further reduction to a dimethylpentamethylenetetramine derivative.

In connection with the later stages of this scheme it is of considerable interest that the *primary* crude product of the action of water on hexamine dinitrate is a water-soluble material giving a strongly acid solution and very similar to, indeed probably identical with, the hexamine nitrate methonitrate, m. p. 150°, prepared by workers in the University of Pennsylvania (private communication from Professor Marvin Carmack). The relative instability of this

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* The ring closure (d) is likely to be irreversible because in the product $N_{(1)}$ is constrained to the quaternary tetra-alkylammonium state and $\overset{\oplus}{N}$–C bonds are stronger than N–C bonds.

substance and its tendency to lose nitric acid, giving hexamine methonitrate, fits in with the difficulty with which the hexamine molecule retains a double positive ionic charge.

The possibility that hexamine methonitrate arises from hexamine dinitrate by process (*a*), followed by the methylation of some of the ammonia to methylamine and resynthesis of the hexamine cage from formaldehyde and base incorporating the methylamine, rather than by direct methylation of pre-formed hexamine, is not ruled out by the experimental observations; indeed the later stages of some such process must occur in our preparation of hexamine methohydroxide from formaldehyde, ammonia, and methylamine, Knudsen's alternative preparation of his base from hexamine and methylammonium nitrate, and in the production of the dimethylhexamine cage by the Bristol and McGill reactions.

<div align="center">EXPERIMENTAL.</div>

<div align="center">(For additional analyses, see table, p. 1692).</div>

3 : 7-*Dinitro*-1-*methylpentamethylenetetramine* 1-*Nitrate.*—Authentic hexamine methonitrate was treated with nitric acid under the conditions used in the University of Pennsylvania. Hexamine methonitrate (10 g.) was added gradually with stirring to nitric acid (50 ml. of 98%) at $-10°$. The stirring was continued for $\frac{1}{2}$ hour, and the reaction mixture was then poured on crushed ice (500 g.). The mixture was kept for $\frac{1}{2}$ hour, and the precipitate was then collected, washed with water, alcohol, and ether, and dried; it had m. p. 142° (9 g.).

3 : 7-*Dinitro*-1-*methylpentamethylenetetramine* 1-*Picrate.*—(*a*) The corresponding nitrate was suspended in water (in which it is only sparingly soluble), and saturated aqueous picric acid was added. The *picrate* separated as yellow-orange needles and was washed with water, alcohol, and ether, and dried. It had m. p. 141° (yield 80%) (Found : C, 30·9; H, 3·4; N, 27·4; CH$_2$, 2·8; N-CH$_3$, 5·2; picrate ion, 49·3. C$_{12}$H$_{15}$O$_{11}$N$_9$ requires C, 31·1; H, 3·3; N, 27·4; CH$_2$, 3·0; N-CH$_3$, 6·3; picrate ion, 49·3%).

(*b*) Authentic hexamine methopicrate (4 g.) was dissolved in nitric acid (40 ml. of 98%) at 0°. The mixture was kept at 0° for $\frac{1}{2}$ hour and then poured gradually, with stirring, into ice–water (200 ml.). The product had m. p. 141° (3·4 g.).

(*c*) Knudsen's base picrate was treated with nitric acid as in (*b*) with identical results.

3-*Nitroso*-5-*nitro*-1-*methylpentamethylenetetramine* 1-*Picrate.*—(*a*) Authentic hexamine methopicrate (3 g.) was added with stirring at 0° during 4 minutes to nitric acid (25 ml. of 98%) containing dinitrogen tetroxide (9 g.). The reaction mixture was stirred at 0° for a further 2 minutes and then poured on crushed ice (200 g.). Golden-yellow crystals separated. After being washed with water, alcohol and ether, these had m. p. 129° (2·2 g.).

(*b*) A similar experiment with Knudsen's base picrate gave identical results.

1 : 5-*Dimethylhexamine* 1 : 5-*Dipicrate.*—(*a*) Following the University of Bristol procedure, 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane (0·33 mol.; prepared from methylamine and formaldehyde, following Henry, *Ber.*, 1893, **26**, *R*934) was added to paraformaldehyde (1 mol.) and ammonium nitrate (0·33 mol.), followed by nitric acid (6 mols. of 70%). The mixture was kept at 25° overnight. On the addition of methyl alcohol, 1 : 5-dimethylhexamine 1 : 5-dinitrate was precipitated. Purified by dissolution in nitric acid (70%) and re-precipitation with methyl alcohol, this had m. p. 193° (Dr. A. Carruthers reports m. p. 193°) (yield 30%). The dinitrate was dissolved in water and immediately treated with saturated aqueous picric acid. The precipitated dipicrate, after being washed with water, alcohol, and ether, and dried, had m. p. 195—196° (see, however, p. 1692) (yield, 80%).

(*b*) By a process analogous to the McGill University technique, authentic hexamine methopicrate (2 g.) and methylamine hydrochloride (1 g.) were heated at 50° in a mixture of acetic acid (25 ml.) and acetic anhydride (50 ml.) for 45 minutes. The solution was cooled and excess of saturated aqueous picric acid was added. The resulting orange crystalline precipitate, when washed with water, alcohol, and ether, and dried, had m. p. 195—196° (0·4 g.). A similar experiment with Knudsen's base picrate, gave an identical result.

A further experiment of this type was carried out using the crude mixture of Knudsen's base chloride and methylamine hydrochloride, together with acetic acid and acetic anhydride at 50°. The addition of picric acid precipitated the desired dipicrate, in low overall yield.