Amine Oxidation. Part XI.[1] Oxidation of Some Substituted Tertiary Alkylamines and Some *NN*-Dimethylphenethylamines with Potassium Hexacyanoferrate(III)

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Kinetic studies on the oxidation of some diamines, amino-alcohols, amino-ethers, phenethylamines, and related tertiary amines by potassium hexacyanoferrate(III) give further information about the interactions that occur in the rate-determining step in these one-electron oxidations of tertiary amines. The over-riding influence in the acyclic diamines and aralkylamines is the electron-withdrawing inductive or field effect of the substituent which reduces the ease of oxidation. In general the closer the substituent is to the reaction centre the greater is the retardation. With the more constrained cyclic, bicyclic, and tricyclic polyamines the lone pair orbitals on the nitrogen atoms are in some instances held by the ring system in a favourable arrangement for through-bond or through-space coupling with the forming aminium radical. These interactions which are superimposed on the inductive and field effects lead to an increase in the ease of oxidation. The greater reactivity of the 1,2-amino-alcohols over their homomorphous amines is attributed to significant concentrations of the alkoxide ions in the alkaline reaction mixture. The difference in the reactivity of the amino-alcohols and their conjugate bases arises, in part from the difference in the inductive effects of the ionised and un-ionised substituents, and in part from through-bond and through-space effects.

THE initial and rate-determining step in the oxidation of trialkylamines with aqueous alkaline potassium hexacyanoferrate(III) has been shown to be a one-electron transfer to give an aminium radical [2] [reaction (1)]. Kinetic studies have given information on the influence of electronic and structural changes on the ease of loss of one electron and have revealed that the transition state for this process occurs late on the reaction co-ordinate.[2]

$$R_3N + Fe(CN)_6^{3-} \xrightarrow{k_1} R_3N^{+\bullet} + Fe(CN)_6^{4-} \quad (1)$$

This work has been extended to the oxidation of a selection of heteroatom substituted amines and some substituted *NN*-dimethylphenethylamines. The results throw further light on the influence of electronic effects on these one-electron oxidations.

RESULTS

Kinetic Studies.—The spectrophotometric method used to follow the disappearance of potassium hexacyanoferrate(III) has been described.[2b] The reactions obey the kinetic relationship $-d[Fe(CN)_6^{3-}]/dt = k_2'[\text{Amine}][Fe(CN)_6^{3-}]$. With a large excess of amine plots of the logarithm of the potassium hexacyanoferrate(III) concentration against time were linear. Each reaction was followed for at least three half-lives with the exception of those of the least reactive substrates which were studied for the following number of half lives, *trans*-1,5-dimethyldecahydronaphthyridine (2.0), *NN'N''*-trimethylhexahydro-*s*-triazine (1.5), 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (0.9), *N*-methylmorpholine (0.5), *NN'*-dimethylhexahydropyrimidine (0.4), 3-amino-1-azabicyclo[2.2.2]octane, *N*-methylthiomorpholine (0.3), and 1,5-diazabicyclo[3.2.1]octane (0.1).

All kinetic data were analysed by use of a least-mean-square program and the correlation coefficients were $\geqslant 0.99$.

TABLE 1

Second-order rate constants for the oxidation of some diaminoalkanes, amino-alcohols, and an amino-ether by potassium hexacyanoferrate(III) at 298.5 K; 1.84×10^{-3}M-$K_3Fe(CN)_6$, *ca.* 2×10^{-2}M-amine, 0.5M-KOH in 30% v/v aqueous methanol

Substrate $Me_2N[CH_2]_nR$		$10^2k_2'$/dm^3 mol^{-1} s^{-1} *	Rate relative to *NN*-dimethylaminopentane
n	R		
4	Me	1.77	1.00
1	NMe_2	0.459	0.26
2	NMe_2	0.621	0.35
	NHMe	0.631	0.36
	NH_2	0.409	0.23
3	NMe_2	0.545	0.31
	NHMe	0.575	0.33
	NH_2	0.598	0.34
4	NMe_2	0.860	0.49
5	NMe_2	1.24	0.70
6	NMe_2	2.19	1.24
7	NMe_2	1.46	0.83
8	NMe_2	2.03	1.15
9	NMe_2	1.03	0.58
2	OMe	0.145	0.08
	OH	3.78	2.14
3	OH	0.771	0.44
4	OH	1.11	0.63
5	OH	0.988	0.56

* All rate constants for ditertiary diamines are corrected to allow for the two sites of oxidation.

The second-order rate constants derived from the pseudo-first-order values are presented in Tables 1—3. The repro-

[1] Part X, J. R. Lindsay Smith and J. S. Sadd, *J.C.S. Perkin II*, 1976, 741.

[2] (*a*) C. A. Audeh and J. R. Lindsay Smith, *J. Chem. Soc.* (*B*), 1970, 128; (*b*) C. A. Audeh and J. R. Lindsay Smith, *ibid.*, 1971, 1741; (*c*) J. R. Lindsay Smith and L. A. V. Mead, *J.C.S. Perkin II*, 1973, 206.

ducibility of the second-order rate constants is within 4% for all the oxidations except those of 4-chloro-*NN*-dimethylphenethylamine (1.45 ± 0.07), 1,3,6,8-tetra-azatricyclo-[4.4.1.1^{3,8}]dodecane (2.84 ± 0.12), 1,5-diazabicyclo[3.2.1]-octane (0.108 ± 0.01), *NN'N''*-trimethylhexahydro-*s*-triazine (2.45 ± 0.25), 1-aza-3-oxobicyclo[2.2.2]octane (0.668 ± 0.068), 1,4-diazabicyclo[2.2.2]octane monomethoperchlorate (0.218 ± 0.07), and *NN'*-dimethylhexahydropyrimidine (0.405 ± 0.18). For comparative purposes the second-order rate constants for some unsubstituted aliphatic amines are also included.

TABLE 2

Second-order rate constants for the oxidation of some substituted *NN*-dimethylphenethylamines and 5-(3,4-dimethoxyphenyl)-*NN*-dimethylaminopentane by potassium hexacyanoferrate(III) at 298.5 K; 1.84 × 10^{-3}M-$K_3Fe(CN)_6$, *ca.* 2.0 × 10^{-2}M-amine, 0.5M-KOH in 30% v/v aqueous methanol

3-R^1-4-R^2-Ar[CH$_2$]$_n$NMe$_2$ R^1	R^2	*n*	$10^3k_2'$/dm^3 mol^{-1} s^{-1}	Rate relative to *NN*-dimethylaminopentane
H	H	2	2.95	0.17
H	OMe	2	3.98	0.24
OMe	H	2	2.45	0.14
OMe	OMe	2	3.65	0.21
H	Cl	2	1.49 *	0.08
OMe	OMe	5	15.1	0.85

* Due to the low solubility of this amine the reactant concentrations were, 0.538 × 10^{-3}M-$K_3Fe(CN)_6$ and 2.69 × 10^{-3}M-amine.

Hammett σ values of the substituents gives a ρ value of −0.56.

DISCUSSION

The presence of an oxygen or nitrogen atom or other electron-withdrawing group in an aliphatic tertiary amine would, by dint of its inductive or field effect, be expected to reduce the ease of formation of an aminium radical. Further the magnitude of this influence might be expected to decrease with increased separation of the substituent from the oxidation site; such a trend is indeed seen in the pK_a values of αω-primary diamines in aqueous solution.[3] In general the second-order rate constants for the oxidation of the diamines (Tables 1 and 3) agree with the above expectations. Thus almost all of the diamines are less reactive than their homomorphous monoamines and the greater the separation between the nitrogens the smaller is this difference in reactivity.

The Hammett ρ value of −0.56 from the oxidation of the ring-substituted *NN*-dimethylphenethylamines when compared with the value of −0.989 obtained from the oxidation of some ring-substituted *NN*-dimethylbenzylamines [2b] is entirely as expected. The reduction is due to the increased insulation of the substituted aromatic ring from the forming aminium radical. Interestingly the introduction of a methylene unit into substituted benzoic acids changes the ρ value for dissociation from 1.0 to 0.56 for phenylacetic acids.[4]

TABLE 3

Second-order rate constants for the oxidation of some heteroatom-substituted cyclic, bicyclic, and tricyclic amines by potassium hexacyanoferrate(III) at 298.5 K; 1.84 × 10^{-3}M-$K_3Fe(CN)_6$, *ca.* 2 × 10^{-2}M-amine, 0.5M-KOH in 30% v/v aqueous methanol

Substrate	$10^4k_2'$/ dm^3 mol^{-1} s^{-1} *	Rate relative to unsubstituted analogue
3-Hydroxy-*N*-methylpiperidine	69.0	1.51 †
2-Hydroxymethyl-*N*-methylpiperidine	306	3.9 ‡
N-(2-Hydroxyethyl)piperidine	898	5.19 §
N-(2-Aminoethyl)piperidine	41.5	0.24 §
NN'-Dimethylhexahydropyrimidine	0.405	0.01 †
N-Methylpiperazine	135	2.95 †
NN'-Dimethylpiperazine	7.45	0.16 †
N-Methylmorpholine	0.993	0.02 †
N-Methylthiomorpholine	1.25	0.03 †
trans-1,5-Dimethyldecahydronaphthyridine	6.23	0.14 †
NN'N''-Trimethylhexahydro-*s*-triazine	2.48	0.05 †
NN'-Dimethyl-1,4-diazacycloheptane	552	0.03 ¶
NN'-Dimethyl-1,5-diazacyclo-octane	50 600 ‡‡	1.03 ‖
1,4-Diazabicyclo[2.2.2]octane	3.53	5.66 ††
1,4-Diazabicyclo[2.2.2]octane mono(methoperchlorate)	0.218	0.35 ††
1,5-Diazabicyclo[3.2.1]octane	0.108	0.17 ††
3-Amino-1-azabicyclo[2.2.2]octane	0.745	1.19 ††
1-Aza-3-hydroxybicyclo[2.2.2]octane	158	253 ††
1-Aza-3-hydroxybicyclo[2.2.2]octane	0.568 **	0.91 ††
1-Aza-3-oxobicyclo[2.2.2]octane	1 490	2 390 ††
1-Aza-3-oxobicyclo[2.2.2]octane	0.668 **	1.07 ††
Hexamethylenetetramine	0	0
1,3,6,8-Tetra-azatricyclo[4.4.1.1^{3,8}]dodecane	2.84	4.56 ††

* All rate constants for polytertiary polyamines are corrected for the number of sites of oxidation. † Relative to *N*-methylpiperidine, 4.57 × 10^{-3} dm^3 mol^{-1} s^{-1}. ‡ Relative to 1,2-dimethylpiperidine, 7.95 × 10^{-3} dm^3 mol^{-1} s^{-1}. § Relative to *N*-ethylpiperidine, 1.73 × 10^{-2} dm^3 mol^{-1} s^{-1}. ¶ Relative to *N*-methylhexamethyleneamine, 19 dm^3 mol^{-1} s^{-1}. ‖ Relative to *N*-methylheptamethyleneamine, 4.9 dm^3 mol^{-1} s^{-1}. †† Relative to 1-azabicyclo[2.2.2]octane, 6.24 × 10^{-5} dm^3 mol^{-1} s^{-1}. ‡‡ During this oxidation a transient red colour developed. ** 0.5M-KOH was replaced by 1 × 10^{-3}M-KOH and 0.499M-KCl in these oxidations.

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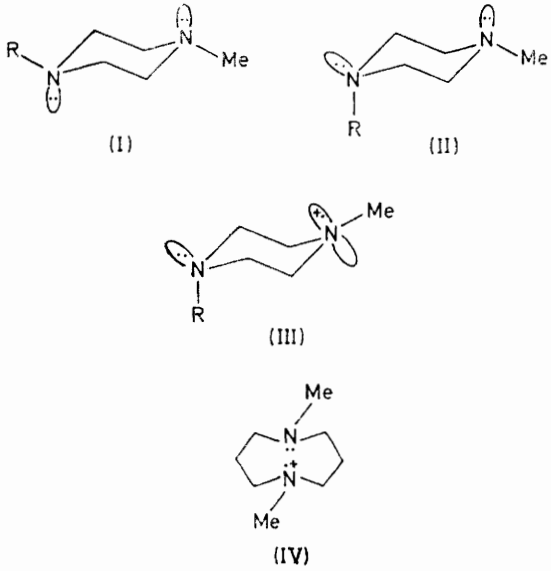
There is no evidence of anchimeric assistance in the oxidation of the αω-diamines or aralkylamines. Evidence has been obtained for the through-space stabilisation [5] of 3,4-dimethoxy-*NN*-dimethylphenethylaminium radical [6] and for the related internal hydrogen bridge stabilisation of the monoprotonated αω-primary diamines in the gas phase; [7] however, it is clear that in these oxidations any gain in the enthalpy of activation arising from an internal donor–acceptor interaction is more than outweighed by the loss in entropy.

The nitrogen atoms in the cyclic, bicyclic, and tricyclic amines being more constrained by the ring systems than the acyclic compounds are in some instances favourably disposed for intramolecular interactions. Thus 1,4-diazabicyclo[2.2.2]octane and 1,3,6,8-tetra-azatricyclo[4.4.1.1 ^{3,8}]dodecane are *ca.* 5 times more reactive than 1-azabicyclo[2.2.2]octane and over 13 times more reactive than 1,4-diazabicyclo[2.2.2]octane mono(methoperchlorate) and the tetramine is dramatically more reactive than the related hexamethylenetetramine. In agreement with these results the first ionisation potential, measured by photoelectron spectroscopy of the first two amines [8] are significantly lower than those for 1-azabicyclo[2.2.2]octane [9] and hexamethylenetetramine.[10] This increased reactivity to one-electron oxidation has been attributed to through-bond stabilisation of the aminium radicals.[11] The through-bond coupling between the nitrogen atoms and the three C–C bridges in the 1,4-diazabicyclo[2.2.2]octane system has been the subject of detailed discussion.[5,12] The inertness of hexamethylenetetramine to oxidation arises from the unfavourable inductive effects of the three α-nitrogens on the forming aminium radical and the rigidity of the tricyclic ring system. Unlike the aminium radical from 1,3,5,8-tetra-azatricyclo[4.4.1.1^{3,8}]dodecane the hexamethylenetetraminium radical is not stabilised by through-bond or through-space effects.[8]

1,5-Diazabicyclo[3.2.1]octane, however, with the nitrogens suitably arranged for coupling through one C–C bridge is less than five times as reactive as 1-azabicyclo[2.2.2]octane. Clearly the destabilising influence (—I) of the second nitrogen upon the forming aminium radical is not compensated for by a through-bond coupling. These results agree with the theoretical calculations that predict that the interaction between the nitrogens should be smaller for 1,5-diazabicyclo[3.2.1]-octane than for the isomeric 1,4-diazabicyclo[2.2.2]-octane [13] and with the following first ionisation potentials as measured by photoelectron spectroscopy, 1-azabicyclo[2.2.2]octane (8.02 eV),[9] 1,4-diazabicyclo[2.2.2]-octane (7.7 eV),[13] and 1,5-diazabicyclo[3.2.1]octane (8.24 eV).[13] 3-Amino-1-azabicyclo[2.2.2]octane has approximately the same reactivity as 1-azabicyclo[2.2.2]octane suggesting a balance between the inductive and through-bond effects.

The introduction of electronegative atoms into the *N*-methylpiperidine ring, as expected, decreases its ease of oxidation; only *N*-methylpiperazine which is almost three times more reactive than its homomorph and 18 times more reactive than *NN'*-dimethylpiperazine is an exception. The preferred conformation of *NN'*-dimethyl- and *N*-methyl-piperazine has the nitrogen lone pairs in axial positions (I; R = Me or H).[14] However, the difference in energy between (I) and an alternative conformation (II; R = Me or H) is smaller for



N-methyl- than for *NN'*-dimethylpiperazine so that a significant proportion of the former compound exists as conformer (II). Through-bond stabilisation of the piperazinium radical is only possible in conformer (III), arising from electron abstraction from (II), for only in this conformation can the nitrogen lone pair orbital, the C–C bridges, and the aminium radical *p*-orbital approach the required parallel arrangement. This type of stabilisation of the forming aminium radical could account for the oxidation of *N*-methylpiperazine being easier than that of *NN'*-dimethylpiperazine. It is noteworthy that *trans*-1,5-dimethyldecahydronaphthyridine is oxidised at almost the same rate as *NN'*-dimethylpiperazine.

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The rate constant for the oxidation of *NN'*-dimethylhexahydropyrimidine (4.05×10^{-5} dm^3 mol^{-1} s^{-1}) is smaller than that for *NN'N''*-trimethylhexahydro-*s*-triazine (2.48×10^{-4} dm^3 mol^{-1} s^{-1}) whereas from inductive effect arguments the reverse would have been expected. The explanation for this is unclear but it could arise from through-space stabilisation of the forming aminium radical by the neighbouring nitrogen lone pairs being more effective with the hexahydrotriazine than the hexahydropyrimidine. In the latter compound the preferred conformation has the lone-pair orbitals in a *trans* equatorial-axial arrangement.[14c]

The transient red colour that develops during the oxidation of *NN'*-dimethyl-1,5-diazacyclo-octane is indicative of aminium radical formation[15] although attempts to observe the species by e.s.r. spectroscopy were unsuccessful. With aminium radical (IV) a transannular stabilisation should be possible.

The large difference between the rate constants for the oxidation of 1-azabicyclo[2.2.2]octane and those of its 3-hydroxy- and 3-oxo-derivatives in 0.5M-KOH disappears when the derivatives are oxidised in 1×10^{-3}M-KOH with 0.499M-KCl. The anomalous ease of oxidation of these 3-substituted 1-azabicyclo[2.2.2]octanes is attributable to significant concentrations of the more reactive alkoxide and keto-enolate anions in the more concentrated alkali. The greater reactivity of the anions over their conjugate acids is probably due in part to the difference in inductive properties of the ionised and un-ionised substituents, and in part to a through-bond coupling stabilising the forming aminium radicals. Through-bond coupling between the nitrogen and carbonyl in 1-aza-3-oxobicyclo[2.2.2]octane has been observed using photoelectron spectroscopy although the first ionisation potential of the ketoamine is higher than that of the parent 1-azabicyclo[2.2.2]octane.[16]

The rate constants for the oxidation of the acyclic and monocyclic 1,2-amino-alcohols are all greater than those of the homomorphous tertiary amines and that of *NN*-dimethylaminoethanol is 25 times greater than that of its methyl ether and five times greater than the rate constant of *NN*-dimethylaminopropanol. This increased reactivity of the 1,2-amino-alcohols probably arises from ionisation and oxidation of the amino-alkoxides. The differences in the relative reactivities of the three hydroxypiperidines when compared with their homomorphous piperidines are possibly due to through-bond or through-space stabilisation of the forming aminium radical by the negative oxygen atom.

The interactions that have been observed in this research are being investigated further using cyclic voltammetry and photoelectron spectroscopy.

EXPERIMENTAL

The spectroscopic and analytical methods and the kinetic procedure have been reported.[2c]

Materials.—Potassium hydroxide, chloride, and hexacyanoferrate(III), diethyl ether, and methanol were research grade or AnalaR reagents. The amine substrates were either commercially available materials which were purified before use or they were prepared as described below. The preparation of the substituted *NN*-dimethylphenethylamines has been reported.[6] The following tertiary amines were prepared by methylation[17] of the commercially available primary or secondary amine; 3-hydroxy-*N*-methylpiperidine, b.p. 82—83° at 16 mmHg (lit.,[18] 80—82° at 15 mmHg), *NNN'N'*-tetramethyldiamino-1,4-butane, b.p. 168° (lit.,[19] 169°), -1,5-pentane, b.p. 90° at 26 mmHg (lit.,[20] 190—191°), -1,6-hexane, b.p. 120—122° at 30 mmHg (lit.,[21] 103° at 20 mmHg), -1,7-heptane, b.p. 114° at 20 mmHg (lit.,[20] 228°), -1,8-octane, b.p. 95° at 3 mmHg (lit.,[22] 83—84° at 2 mmHg), and -1,9-nonane, b.p. 92—93° at 1 mmHg (lit.,[22] 93—94° at 1.5 mmHg), *NN*-dimethylaminopentane, b.p. 121—122° (lit.,[20] 122—123°), and *NN*-dimethylphenethylamine, b.p. 82—83° at 12 mmHg (lit.,[23] 89—91° at 16 mmHg). *NNN'*-Trimethyl-1,2-diaminoethane and -1,3-diaminopropane were prepared from the corresponding *NN*-dimethyldiamine *via* the formamide followed by reduction ($LiAlH_4$)[24] and were purified by preparative g.l.c. 4-Dimethylaminobutan-1-ol and 5-dimethylaminopentan-1-ol were prepared by reduction ($LiAlH_4$)[25] of *NN*-dimethylsuccinamic acid and *NN*-dimethylglutamic acid and had b.p. 87—88° at 15 mmHg (lit.,[25] 78° at 12 mmHg) and 114—115° at 22 mmHg (lit.,[18] 115—116° at 25 mmHg) respectively. *NN*-Dimethyl-2-aminoethyl methyl ether was prepared from (1-*NN*-dimethylamino)-2-chloroethane following Grail *et al.*[26] and had b.p. 86—88° (lit.,[26] 68°), τ 6.80 (2 H, t), 6.93 (3 H, s), 7.80 (2 H, t), and 8.02 (6 H, s). 1-(NN-*Dimethylamino*)-5-(3,4-*dimethoxyphenyl*)*pentane* was prepared by reduction (Zn–Hg and HCl)[27] of 5-(3,4-dimethoxyphenyl)-4-oxopentanoic acid[28] to give 5-(3,4-dimethoxyphenyl)pentanoic acid followed by conversion to the acid chloride ($SOCl_2$), reaction with dimethylamine, and reduction ($LiAlH_4$)[29] and had b.p. 135—137° at 0.5 mmHg, τ 3.25 (3 H, m), 6.19 (6 H, s), 7.45 (2 H, t), 7.82 (8 H, s), and 8.2—9.0 (6 H, m). It was characterised as its *picrate*, m.p. 108—109° (Found: C, 52.7; H, 5.75; N, 11.7. $C_{21}H_{28}N_4O_9$ requires C, 52.5; H, 5.85; N, 11.65%). *N*-(2-Aminoethyl)piperidine was prepared by reduction ($LiAlH_4$) of *N*-cyanomethylpiperidine and had b.p. 67.5° at 12 mmHg (lit.,[30] 70° at 11 mmHg). *NN'*-Dimethylhexahydropyrimidine was prepared from *NN'*-dimethyl-1,3-diaminopropane

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following Evans [31] and had b.p. 136—138° (lit.,[31] 132—136°). *NN'N''*-Trimethylhexahydro-*s*-triazine was prepared by the method of Graymore [32] and had b.p. 160—162° (lit.,[32] 160—164°). trans-1,5-*Dimethyldecahydronaphthyridine* was prepared by reduction of 1,5-naphthyridine [33] followed by methylation.[17] It was characterised as its *dihydrochloride*, m.p. 247° (decomp.) (Found: C, 49.75; H, 8.95; N, 11.55. $C_{10}H_{22}Cl_2N_2$ requires C, 49.8; H, 9.2; N, 11.6%). *N*-Methylthiomorpholine was prepared from bis-2-chloroethyl sulphide following Clarke [34] and was purified by sublimation of its hydrochloride. The hydrochloride had m.p. 234—236° (lit.,[34] 236°). 2-Hydroxymethyl-*N*-methylpiperidine was prepared by reduction ($LiAlH_4$) of 2-hydroxymethyl-*N*-formylpiperidine and had b.p. 93—94° at 16 mmHg (lit.,[35] 96—98° at 19 mmHg). NN'-*Dimethyl*-1,5-*diazacyclo-octane* was prepared by methylation [36] of the parent diazacycloalkane [37] and purified as its *dihydrochloride*, m.p. 244—246° (ether–methanol), τ 6.44 (8 H, m), 7.02 (6 H, s), and 7.30—7.9 (4 H, m) (Found: C, 44.4; H, 9.1; N, 12.95. $C_8H_{20}Cl_2N_2$ requires C, 44.6; H, 9.35; N, 13.0%). *NN'*-Dimethyl-1,4-diazacycloheptane was prepared by methylation [36] of 1,4-diazacycloheptane and had b.p. 156—158° (lit.,[38] 161°). 1,4-*Diazabicyclo*[2.2.2]*octane mono*(*methoperchlorate*) was prepared from the monomethiodide using silver perchlorate in methanol solution. It decomposes before melting (Found: C, 37.25; H, 6.4; N, 12.55. $C_5H_{17}ClN_2O_4$ requires C, 37.1; H, 6.65; N, 12.35%). 1,5-Diazabicyclo[3.2.1]-octane was prepared from 1,4-diazacycloheptane following Poppelsdorf [39] and was purified by sublimation. 1,3,6,8-Tetra-azatricyclo[4.4.1.1^{3,8}]dodecane, prepared following Simkins and Wright,[40] had m.p. 185—189° (lit.,[40] 204—206°) (Found: C, 56.95; H, 9.55; N, 33.35. Calc. for $C_8H_{16}N_4$: C, 57.1; H, 9.6; N, 33.3%).

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