322. *Stereoisomeric Pairs of Cyclic Quaternary Ammonium Salts. Part III.*[1] *Examination of Differential Reactivity of Certain* N-*Ethyl*-N-*Methyl Pairs in Nucleophilic Substitution Reactions*

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Study of the reactions of the diastereoisomeric *N*-ethyl-*N*-methylcamphidinium iodides, and of analogues derived from tropane and 2-methylpyrrolidine, with sodium thiophenoxide and with lithium aluminium hydride leads to a general conclusion about relative ease of attack by the nucleophilic agents on differently oriented ^{+}N-alkyl groups.

In this Paper we describe the results of attempts to uncover significant differences in reactivity between numbers of selected diastereoisomeric pairs of quaternary ammonium salts described in Part I.

The rates of formation of ethylene from the isomeric *N*-ethyl-*N*-methylcamphidinium iodides in hot alkaline diethylene glycol did not differ sufficiently to permit a clear distinction in reactivity in rough preliminary experiments, but we hope to carry out a more detailed study of this elimination reaction (following the rates by measurement of quantity of *N*-methyl-base formed) with several diastereoisomeric pairs of salts in due course. In the meantime, we have turned our attention to substitution reactions at $^{+}$N–Me and C–α in $^{+}$N–Et in the camphidine salts and analogous derivatives of 2-methylpiperidine and nortropane. Nucleophilic attack at C–α is a well-known competitor to Hofmann fission of quaternary ammonium salts—hydroxide or alkoxide ions, for example, readily attack benzyl, allyl, or methyl groups, and other saturated alkyl groups less readily (S_N2 reaction); analogous ring fission by substitution at α-methylene can arise with pyrrolidinium salts and related five-ring heterocycles.[2] With the less basic nucleophiles ethanolamine,[3] thiophenoxide anion,[4] and hydride ion or equivalent (in reaction of the quaternary salt with lithium aluminium hydride [5]) the tendency towards Hofmann fission (*i.e.*, by an elimination process) is diminished or eliminated. We studied the reactions of our quaternary salts with sodium thiophenoxide and with lithium aluminium hydride. Each reaction was expected to exhibit S_N2 characteristics, in particular, easier attack on $^{+}$N–Me than on $^{+}$N–Et, so that reaction of the isomers $>\overset{+}{\mathrm{N}}\mathrm{MeEt}\overset{-}{\mathrm{I}}$ with sodium thiophenoxide was expected to give mainly thioanisole plus *N*-ethyl-base, and to a lesser extent thiophenetole plus *N*-methyl-base. Reaction with lithium aluminium hydride should likewise give mainly methane plus *N*-ethyl-base, and less extensively ethane plus *N*-methyl-base. Our first interest was to examine whether within the limits of these general expectations (which were realised experimentally) there were any significant differences in product ratios (*e.g.*,

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[1] Part II, Becconsall, Jones, and McKenna, preceding Paper.

[2] See Cope and Trumbull, *Org. Reactions*, 1960, **11**, 317.

[3] Hünig and Baron, *Chem. Ber.*, 1957, **90**, 395, 403.

[4] Trumbull, Häberli, and Ammon, *Abs. Amer. Chem. Soc. Meeting Sep.* 1958, p. 76-P.

[5] Kenner and Murray, *J.*, 1950, 406; Cope, Ciganek, Fleckenstein, and Meisinger, *J. Amer. Chem. Soc.*, 1960, **82**, 4651.

thioanisole: thiophenetole in a total thioether product) as between diastereoisomeric reactants.

We carried out numerous reaction runs between the quaternary iodides and excess (about 5 moles) of sodium thiophenoxide in diethylene glycol at temperatures in the 170—190° range, the reactions proceeding to completion. The thioanisole : thiophenetole ratios in the total thioether products of the decompositions were determined initially by n.m.r. spectroscopy and subsequently by a more accurate procedure using gas–liquid chromatography (g.l.c.). We consistently found that the proportion of thiophenetole (minor product) in the total thioether fraction was markedly greater for an *N*-methyl-base ethiodide than for an *N*-ethyl-base methiodide * in degradations of quaternary camphidine (ratio of thiophenetole percentages *ca.* 2 : 1) and tropane (ratio *ca.* 2·5 : 1) salt; with salts derived from 2-methylpyrrolidine the contrast was smaller (ratio *ca.* 1·5 : 1). Results are summarised in the Table.

In the lithium aluminium hydride reductions, also run to completion, g.l.c. analysis of the *N*-methyl and *N*-ethyl components of the total basic fractions showed that members of diastereoisomeric pairs of quaternary iodides examined (derived from camphidine and tropane) differed much more from one another than in the thiophenoxide degradation, attack on ^+N-ethyl being relatively much more extensive for the *N*-methyl-base ethiodides than for the *N*-ethyl-base methiodides (see Table). We do not report results for the quaternary salts related to 2-methylpyrrolidine, as the volatility of the mixed basic product was too high for the simple isolation techniques employed.

(*a*) Thiophenetole percentages in thioether products from total degradation of *N*-ethyl-*N*-methyl quaternary iodides with sodium thiophenoxide in diethylene glycol at 170—190°; (*b*) percentages of *N*-methyl-bases in basic products from total reduction of the iodides with lithium aluminium hydride in boiling tetrahydrofuran.

Base system	Quaternary salt	(*a*) % Thiophenetole (PhSNa degradns)	(*b*) % *N*-Methyl-base ($LiAlH_4$ degradns)
Camphidine	*N*-Me-base EtI [a]	20—25 [d]	15—25
	N-Et-base MeI [a]	8—15 [d]	*ca.* 2
Tropane	*N*-Me-base EtI [c]	15—25 [d]	20—25
	N-Et-base MeI [c]	5—10 [d]	*ca.* 4
2-Methylpyrrolidine	*N*-Me-base EtI [b]	10—15	—
	N-Et-base MeI [a]	7—10	—

a, Pure quaternary salts. *b*, Sample used contained *ca.* 30% of isomeric salt; the experimental thiophenetole percentage has been modified to give result for pure isomer. *c*, Samples used contained *ca.* 10% of isomeric salts; no modification in experimental figures (quoted) would be meaningful. *d*, In no comparative degradations and analysis run under the same conditions for a diastereoisomeric pair did a higher thiophenetole percentage within the ranges quoted from a methiodide degradation correspond with a lower figure for the ethiodide.

If an *N*-methyl group is removed more readily by nucleophilic attack when in one particular orientation in a quaternary salt of the type studied, it would be expected that the same would be true for an *N*-ethyl (or other primary *N*-alkyl) group similarly oriented in the same framework. The explanation of the results summarised in the Table appears to be that in the systems studied ***nucleophilic attack*** by hydride or thiophenoxide ***removes an alkyl group more readily when this is in the orientation it preferentially adopts during its introduction in a quaternisation*** of tertiary base. To prove this hypothesis, the actual decomposition rates of diastereoisomeric salts must be measured. Attempts to measure the rate of hydrocarbon (methane plus ethane) evolution during lithium aluminium hydride reductions were frustrated by the size of the " blank " gas evolution with the hydride from the volume of solvent (dioxan or tetrahydrofuran) required for quaternary salt reductions under homogeneous conditions. However, we obtained accurate decomposition rates for the *N*-ethyl-*N*-methylcamphidinium iodides with *ca.* ten molar proportions of sodium

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* The chief product in a quaternisation is indicated by this nomenclature.

thiophenoxide in diethylene glycol at 100°. Total thioether produced was initially estimated spectrophotometrically, and subsequently more accurately by g.l.c. This work at 100° is described in the Experimental section; earlier, rather less accurate work at 180° leading to qualitatively similar conclusions about reactivity order was summarised in a preliminary communication.[6] At 100° in diethylene glycol the relative rates of removal of equatorial *N*-ethyl, axial *N*-ethyl, equatorial *N*-methyl, and axial *N*-methyl from the diastereoisomeric *N*-ethyl-*N*-methylcamphidinium iodides * by thiophenoxide are approximately 1 : 4 : 9 : 13, respectively; the first and fourth of these figures are derived from results for the *N*-ethyl-base methiodide, the second and third from results for the *N*-methyl-base ethiodide. The overall rate of degradation of each diastereoisomeric iodide is, coincidentally, the same for each salt.

By the use of ten molar proportions of thiophenoxide, calculation of pseudo-first-order rate constants for the degradations was possible, this excess being therefore adequate to hold not only nucleophile concentration but also ionic strength during runs sensibly " constant " within the limits of our analytical procedure.

There seems no reason to fear that the (in any case unlikely) competitive Hofmann elimination of ethylene induced by thiophenoxide attack on β-hydrogen is a factor complicating the interpretation of the results. Not only have we continued our kinetic runs to a point where 80—85% of thioether (based on quaternary salt) is found analytically, but in development work at 140° we have accounted for the quaternary salt quantitatively as thioether, and near quantitatively as mixed tertiary bases, which are in the ratio (*N*-methyl : *N*-ethyl) expected for correspondence with the thioether ratio (thiophenetole : thioanisole).

As no degradation of either quaternary salt resulted from heating it in water or diethylene glycol at 100°, one can state with some assurance that the pseudo-first-order degradations observed under the particular conditions of our experiments correspond to S_N2 attack by thiophenoxide at *N*-methyl or *N*-ethyl groups.

The theoretical aspects of these results will be discussed in Part IV.

EXPERIMENTAL

Gas-liquid chromatography was carried out in a Pye argon chromatogram fitted with an " Apiezon "-" Celite " column at 150 or 175° as appropriate.

Reaction of Quaternary Iodides with Sodium Thiophenoxide.—(a) *Complete decomposition.* Quaternary iodides (x g.; 0·1—1·0 g.) were heated for 3 days † with sodium thiophenoxide ($2x$ g.) in diethylene glycol (10 c.c.) at a temperature which was the same for each isomer of a diastereoisomeric pair in any comparative experiment, and within the range 170—190°. After addition of water to the reaction mixture, ether extracts of basic and neutral fractions were obtained in the usual way. The organic bases obtained in these experiments were not analysed in detail, but conversion into picrates and fractionation gave results in qualitative concord with the results of thioether analysis—a higher proportion of thiophenetole corresponded to stronger indications of admixture of some *N*-methyl-base in the predominantly *N*-ethyl-base extracts. The thioether fractions were analysed by both the n.m.r. method (by appropriate comparison of *N*-methyl and *N*-ethyl signal areas) and by g.l.c.

(*b*) *Kinetic investigation.* Sealed tubes, each containing 25 mg. ($7{\cdot}7 \times 10^{-5}$ moles) of quaternary *N*-ethyl-*N*-methylcamphidinium iodide in 5 c.c. of a 0·157M-solution of sodium thiophenoxide in diethylene glycol, were heated for varying times at 100° and cooled; the contents were diluted with water (20 c.c.) to which a few c.c. of 2N-aqueous potassium hydroxide had been added, and the aqueous mixture was extracted three times with ether. The combined ethereal extracts (*ca.* 100 c.c.) were extracted twice with 2N-hydrochloric acid (20 c.c. in all), then with water (20 c.c.) to remove the tertiary bases and finally with 2N-aqueous potassium

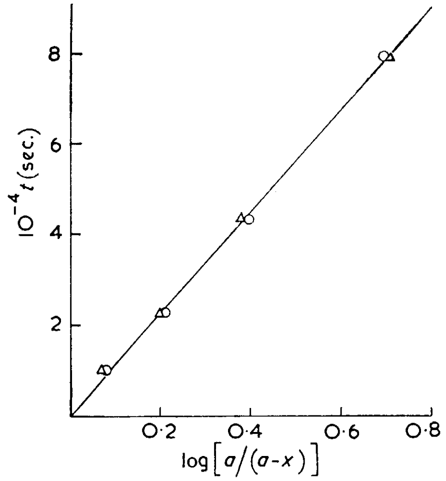
* For comments on possible conformation of camphidine quaternary salts see Part I.

† It is clear from the subsequent kinetic work that this heating period was unnecessarily long, at any rate for the camphidinium salts.

[6] McKenna and White, *Tetrahedron Letters*, 1963, 1493.

hydroxide (10 c.c.). The ether solution was filtered to remove water droplets, the filter paper was rinsed with more ether, and the combined filtrate was divided into two equal parts. One was evaporated nearly to dryness on a steam-bath, the residue was treated with a little (*ca.* 1 c.c.) alcohol, and this solution was used to determine the ratio of thioanisole to thiophenetole in the extract by g.l.c. of portions (usually $<0\cdot1$ µl.). It was consistently found that 31·5—32·5% (29·5—30·5 moles-%) of the thioether mixture from the *N*-methyl-base ethiodide was thiophenetole; the corresponding proportion for the isomeric salt was 7·5—8·5% (7—8 moles-%). To the other half was added an accurately weighed quantity of thiophenetole and the above process was repeated to give a different thioether ratio. The results enabled calculation of the weights of thioanisole and thiophenetole in the degradation mixture since independent experiments showed (*a*) that thioether could be extracted quantitatively into ether by the described procedure, and (*b*) that the ratio of thioanisole to thiophenetole in an ether extract was not disturbed by the precise evaporation conditions used.

Total thioether concentrations in ether extracts were also checked from time to time spectrophotometrically by measuring optical densities at 240 and 253 mµ. The extracts usually also contained some diphenyl disulphide formed by oxidation of excess of thiophenoxide during work-up, but, by solving the appropriate simultaneous equations, mixed thioether concentrations were readily obtained. For pure thioanisole and thiophenetole log ε_{240} = 3·47, log ε_{253} = 3·99; for diphenyl disulphide log ε_{240} = 4·21, log ε_{253} = 3·84.



Degradation of *N*-ethyl-*N*-methylcamphidinium iodides by 0·157M-sodium thiophenoxide in diethylene glycol at 100°

△, *N*-Methyl-base ethiodide.
○, *N*-Ethyl-base methiodide.

The overall pseudo-first-order rate constant for a degradation was obtained from the slope of the plot (Figure) of $10^{-4}t$ against $\log_{10}[a/(a-x)]$, where x of an initial a moles of quaternary salt are decomposed in t seconds; from this the rate constants for attack at $^+$N–Me and $^+$N–Et were obtained for each salt by division of the overall rate constant to accord with the molar proportions of thioanisole and thiophenetole formed in each degradation. Results are as follows:

	10^5k (sec.$^{-1}$)		
Salt	Overall	Attack on $^+$NMe	Attack on $^+$NEt
N-Methyl-base ethiodide	2·05	1·44	0·61
N-Ethyl-base methiodide	2·05	1·90	0·15

The hydrochloric acid extracts (above) yielded the mixed bases by treatment with aqueous alkali and extractions with ether. In development work at 140° an analytical technique (g.l.c.) similar to that described above was explored for the amines also, and the following results in a particular degradation of the *N*-methyl-base ethiodide are typical: Found, moles of *N*-ethyl-base, $4\cdot0 \times 10^{-5}$, moles of thioanisole, $4\cdot4 \times 10^{-5}$; moles of *N*-methyl-base $2\cdot2 \times 10^{-5}$, moles of thiophenetole, $2\cdot0 \times 10^{-5}$.

Reduction of Quaternary Iodides with Lithium Aluminium Hydride.—Quaternary iodide (0·1 g.) was reduced with lithium aluminium hydride (0·15 g.) in refluxing dry tetrahydrofuran over 2—3 days. Excess of reagent was decomposed with water, the solids were separated, and the solution was concentrated for g.l.c. analysis.

Reaction of Diastereoisomeric N-*Ethyl*-N-*Methylcamphidinium Iodides with Potassium Hydroxide in Diethylene Glycol.*—A solution of the quaternary salt (100 mg.) in diethylene glycol (8 c.c.) was mixed with a solution (5 c.c.; 5%) of potassium hydroxide in the same solvent in a divided flask (two compartments) after each solution had come to thermostat temperature: experiments were carried out in the range 150—155°. With this apparatus it was not possible to measure the rate of ethylene evolution with adequate precision for rate differentiation. In the temperature range quoted, about 30—40 min. were required for effectively complete elimination of ethylene. *N*-Methylcamphidine was identified in the reaction mixture * by its i.r. spectrum and by conversion into the picrate, m. p. and mixed m. p. 236°.

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* Even in the decomposition of *NN*-dimethylcamphidinium hydroxide there is little ring fission.[7]

[7] McKenna and White, unpublished work.