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Synthesis of Pyrrolidine Derivatives with Anticholinergic Properties. III.[1] Syntheses and Stereochemistry of 1,2,5-Trimethylpyrrolidine and 3-(Diphenylmethylene)-1,2,5-trimethylpyrrolidine

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cis- and *trans*-1,2,5-Trimethylpyrrolidines(IIa and IIb) were synthesized. The two were distinguished by their NMR spectra and from the difference in their rate of quaternization with methyl iodide. This latter method was applied to the two kinds of diastereoisomers of 3-(diphenylmethylene)-1,2,5-trimethylpyrrolidine (I), and their *cis* (Ia) and *trans* (Ib) isomers were determined. The ethiodide of Ia was found to have antiacetylcholine action 0.5 times that of atropine.

In continuation of the work reported earlier,[3] the methiodide and ethiodide of 3-(diphenylmethylene)-1,2,5-trimethylpyrrolidine (I) were synthesized, and the ethiodide was found to show a comparatively strong antiacetylcholine activity. From this fact, the stereochemistry of I was examined, together with that of the related 1,2,5-trimethylpyrrolidine (II).

A) Stereochemistry of 1,2,5-Trimethylpyrrolidine (II)

Syntheses of *cis*- and *trans*-1,2,5-trimethylpyrrolidine (IIa and b) were effected by the route shown in Chart 1. Synthesis of *cis*- and *trans*-2,5-dimethylpyrrolidine (IIIa and b) had already been carried out by Overberger, *et al.*,[4] and by Evans and others,[5] and their configuration had been determined as the *cis* compound (IIIa) for the product obtained by the catalytic reduction of 2,5-dimethylpyrrole, and the other as the *trans* compound (IIIb). However, such a method of determination, based on the premise of *cis*-addition of hydrogen, is attended with exceptions and cannot be termed perfect.[6] In this connection, Hill and his co-worker[7] recently carried out a comparative examination of the NMR spectra of the N-benzyl derivatives of IIIa and IIIb with respect to their N-methylene proton and reconfirmed the correctness of the determined configurations for IIIa and IIIb as above.

It is certain from this fact that the N-methyl derivative obtained by the Eschweiler-Clark treatment of IIIb, synthesized by Evans' method, is the *trans* compound (IIb), and the main product obtained by the catalytic reduction of 1,2,5-trimethylpyrrole is the *cis* compound (IIa) since it differs from IIb.

The preferred conformation of the pyrrolidine ring is the C_2(half-chair) or C_s(envelop) form, and the former is said to be more preferable.[8] On the other hand, *cis*-1,3-dimethylcyclopentane takes the C_s form in which the carbon in 2-position is in a most puckered form, and the two methyl groups are oriented equatorially, and this is said to be the most stable form.[8] Considering these facts, it is most probable that the *cis* compound (IIa) takes the

1) Part II: *Yakugaku Zasshi*, **86**, 153 (1966).
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3) S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **14**, 187 (1966).
4) C.G. Overberger, L.C. Palmer, B.C. Marks, and N.R. Byrd, *J. Am. Chem .Soc.*, **77**, 4100 (1955).
5) G.G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).
6) J.F. Sauvage, R.H. Baker, and A.S. Hussey, *J. Am. Chem. Soc.*, **83**, 3874 (1961); S. Siegel and B. Dmochovsky, *ibid.*, **86**, 2192 (1964).
7) R.K. Hill and T. Hang Chang, *Tetrahedron*, **21**, 2015 (1965).
8) K.S. Pitzer and W.E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959).

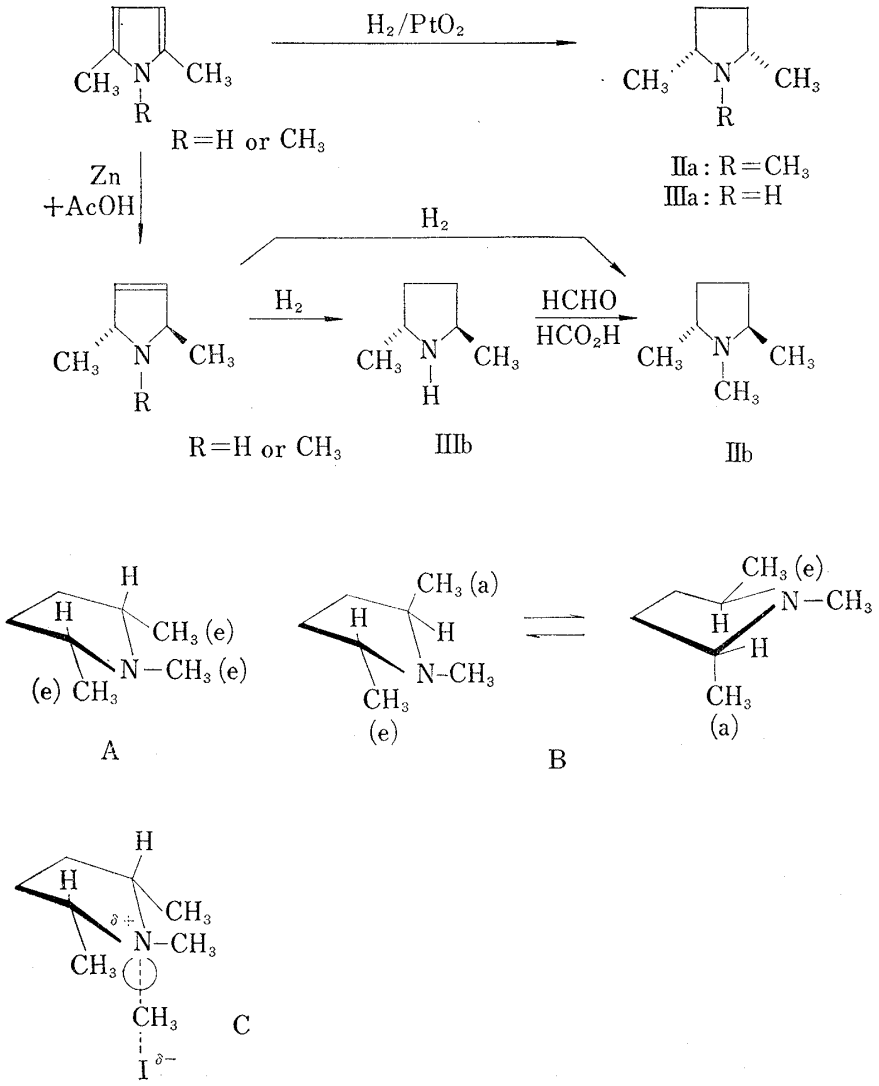


Chart 1

C_s form with maximum puckering at N, with the two methyl groups oriented in an equatorial position to take the steric configuration shown by (A) in Chart 1. In this case, the methyl group attached to the ring–nitrogen is thought to take the equatorial conformation since the lone–pair electrons of the nitrogen occupy the smaller space as compared to hydrogen and the methyl group.[9] The C_2 form may be considered for the *trans* compound (IIb) but in such a form, the methyl group at 2– or 5–position will be too close to the N–methyl group and there might arise some interaction between them. Consequently, it is most probably that it would take the C_s form, same as IIa, and there might be an interconversion of the ring (formula B). The NMR spectra of IIa and IIb are given in Table I.

The presence of C–methyl signal of IIa in a lower field than that of IIb is considered to be due to the statistical difference in the effect of bond anisotropy between IIa and IIb because the two C–methyls in IIa are equatorial–equatorial while those in IIb are equatorial–axial, and to the fact that the direction of the lone–pair electrons of the ring–nitrogen and the C–methyl makes a smaller angle in IIa than in IIb.

The methyl group at 5–position in Ia and Ib, to be described later, and the C–methyl in IIa and IIb have approximately the same values, and are considered to be in a similar environ-

9) *cf.* N.L. Allinger, J.G.D. Carpenter, and F.M. Karkowski, *Tetrahedron Letters*, **1964**, 3345.

Table I. NMR Spectra of IIa, b

Comp.	2-CH_3, 5-CH_3	N-CH_3	2-H, 5-H
IIa	8.90 τ (6H, doublet, J=5.6 cps)	7.80 τ (3H, singlet)	7.6 τ<
IIb	9.01 τ (6H, doublet, J=6.0 cps)	7.71 τ (3H, singlet)	*ca.* 7.11 τ (2H, multiplet)

ment. The assignment of 2-H and 5-H in IIa is very difficult (absorption in magnetic field higher than 7.6τ) but they are in a higher field than that of *ca.* 7.11τ(2H, multiplet) for 2-H and 5-H in IIb, endorsing the above facts.

The rate of quaternization of IIa and IIb with methyl iodide was examined by the measurement of electric conductivity.

Table II. Rates of Methiodide Formation

Compound	$k_1 \times 10^3$/min	Relative Rate
IIa	70	7.8
IIb	273	30
Ia	24	2.7
Ib	235	26
V[a)]	9	1

a) 3-(Diphenylmethylene)-1,2,5,5-tetramethylpyrrolidine

In general, the quaternization is considered to begin with an attack of the agent from the direction of the lone-pair electrons and the transition state is thought to take the Sp^3 or near-Sp^3 hybridized tetrahedral nitrogen form (formula C in Chart 1), and is considered to have a fairly marked direction specificity.[10] Since the quaternization of cyclic bases like N-alkyl-2-methyl-pyrrolidines and -piperidines is strongly affected by the stereospecific

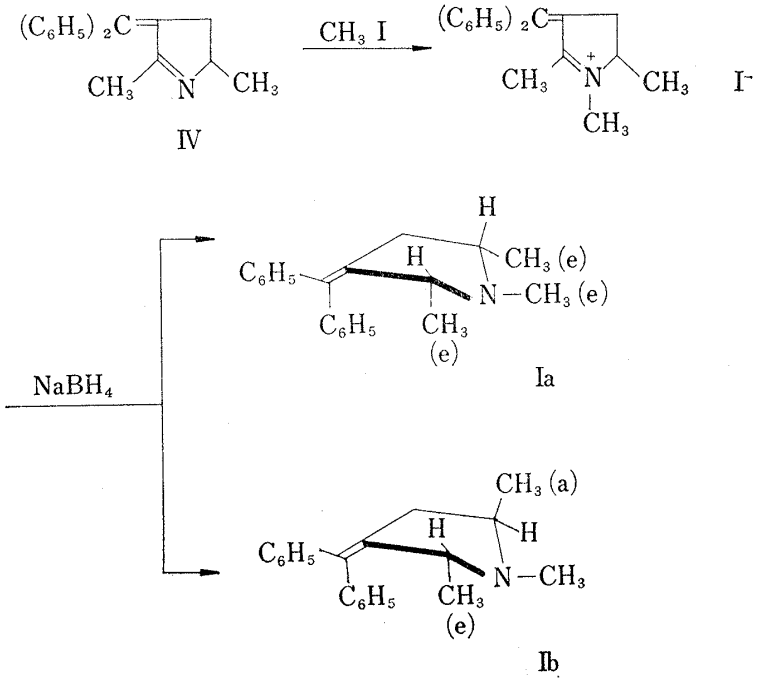


Chart 2

10) J. McKenna, J.M. McKenna, and J. White, *J. Chem. Soc.*, **1965**, 1733; J. McKenna, J.M. McKenna, and A. Tulley, *ibid.*, **1965**, 5439.

nature of the 2–methyl group,[11] quaternization of IIa and IIb is expected to be strongly affected by the 2– and 5–methyl groups. Results of the mesaurement showed that the reaction rate was slower in IIa than in IIb, proving that *cis*–2,5–dimethyl group effects greater steric hindrance than the *trans*–2,5–dimethyl group. This fact supports the steric configurations shown by the formulae A and B and, at the same time, this method of electric conductivity measurement seems to be a valuable tool in the determination of this kind of steric structure.

B) Synthesis and Stereochemistry of 3-(Diphenylmethylene)-1,2,5–trimethylpyrrolidine (I).

The methiodide of 3–(diphenylmethylene)–2,5–dimethyl–1–pyrroline[3] (IV), synthesized earlier, was reduced with sodium borohydride and a mixture of *cis* and *trans* isomers of 3–(diphenylmethylene)–1,2,5–trimethylpyrrolidine (I) were obtained as an oily substance. This oily product was submitted to alumina chromatography and the comparatively sparingly adsorbed fraction (hydrochloride, mp 225—227°(decomp.)) was found to be the main product, and the by–product was obtained as a hydrochloride of mp 231° (decomp.). Since the compound with masked lone–pair electrons of the ring–nitrogen tends to be less adsorbed, the main product is assumed to be the *cis* isomer[12](Ia).

Similarly as in the case of IIa and IIb, the quaternization rate of the two fractions of I with methyl iodide was measured (Table II). The reaction rate was slower in the main product than the by–product and, if the relative rate of IIa and IIb were to be applied, the former would be the *cis* isomer (Ia) and the latter, the *trans* isomer (Ib). As for the ring conformation of Ia and Ib, they are considered to take the C_s form in which the maximum puckering is present at N, because the presence of the diphenylmethylene group at 3–position makes it difficult to have this 3–position with maximum puckering. Consequently, quater-

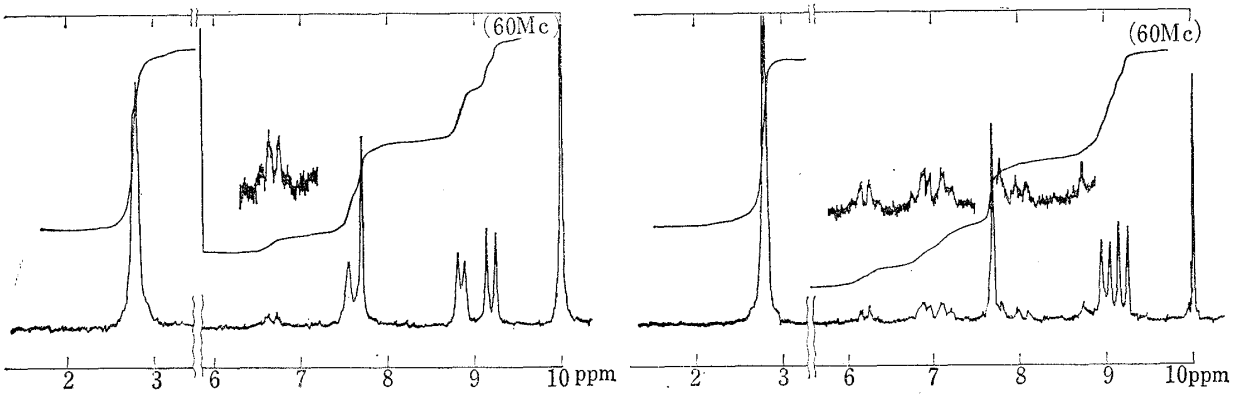
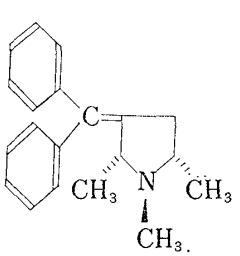
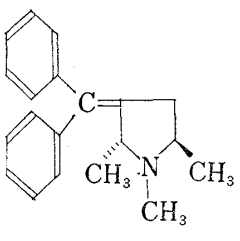


Fig. 1.



(*cis* isomer)

Fig. 2.



(*trans* isomer)

11) J. McKenna, J.M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, **1965**, 1711.
12) In thin–layer chromatography (Wako–gel B–5, benzene–acetone=4:1), the main product gave a spot at *Rf* 0.31 and the by–product, one at *Rf* 0.12, showing the same tendency.

nization seems to have started in the direction of the lone-pair electrons as in the case of II. For the sake of comparison, 3-(diphenylmethylene)-1,2,5,5-tetramethylpyrrolidine (V) was synthesized and the same measurement was made. The formation of the *cis* isomer (Ia) as the main product is thought to be due to the attack of sodium borohydride from the direction with least steric hindrance in the methiodide of IV. The NMR spectra of Ia and Ib are shown in Fig. 1 and 2.

From the signals of 2-CH_3 at 9.28τ (3H, doublet) and of N-CH_3 at 7.73τ (3H, singlet) of previously synthesized 1,2-dimethyl-3-(diphenylmethylene)pyrrolidine,[3] the singnals at 9.18τ(3H, doublet) in Ia and Ib, and those at 7.71τ in Ia and 7.68τ(both 3H, singlet) in Ib may be assigned respectively to 2-CH_3 and N-CH_3. From the close similarity of these values, the steric relation of the 2-methyl group to the diphenylmethylene group and the lone-pair electrons of the ring nitrogen is considered to be approximately the same in Ia and Ib. In this case, the methyl group at 2-position is thought to be oriented equatorially, and receives a stronger shielding effect of the diphenylmethylene group than the deshielding effect of the lone-pair electrons of the ring nitrogen. The methyl group at 5-position would take the equatorial and axial configuration in *cis* and *trans* isomers, respectively, and the signal for 5-CH_3 in the *cis* isomer should shift to a lower field due to the effect of the lone-pair electrons. Since the signal for 5-CH_3 in Ia is at 8.85τ(3H, doublet, J=5.8 cps) and that in Ib is at 8.98τ (3H, doublet, J=6.0 cps), Ia may be assigned to the *cis* isomer.

The antiacetylcholine actions of the methiodide and ethiodide of the *cis* isomer (Ia) are 0.04 and 0.5 times that of atropine, and their anti-histamine activity is very weak, when tested by the Magnus method using the excised ileum of a guinea pig.[13]

Experimental

***trans*-1,2,5-Trimethylpyrrolidine (IIb)**——a) To 770 mg (0.0078 mole) of *trans*-2,5-dimethylpyrrolidine[5] (IIIb), synthesized according to the method of Evans, 1.79 g (0.0078×5 mole) of HCOOH and 678 mg (0.0078 mole) of 37% HCHO were added and the mixture was heated in an oil bath of 120—130° for 7 hr. After allowing the reaction mixture to stand over night, *ca.* 1.5 g of conc. HCl was added and the mixture was refluxed for 40 min. The solvent was evaporated, the residue was basified with 40% NaOH while cooling, and the oil that separated was extracted with ether. The extract was dried over Na_2SO_4 and ether was evaporated. Yield, 528 mg (60%). Picrate, needles (from Me_2CO), mp 229—230°. *Anal.* Calcd. for $C_{13}H_{18}O_7N_4$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.84; H, 5.49; N, 16.20.

b) To a solution of 0.574 g (0.005 mole) of 1,2,5-trimethyl-3-pyrroline dissolved in 10 ml of glacial AcOH, 50 mg of PtO_2 was added and the mixture was submitted to catalytic reduction by the usual method. Yield, 252 mg (43%). The picrate of this product showed no depression of mp on admixture with the picrate obtained by the above method (a).

***cis*-1,2,5-Trimethylpyrrolidine (IIa)**——A solution of 1.45 g (0.0133 mole) of 1,2,5-trimethylpyrrole dissolved in a mixture of 5 ml of glacial AcOH and 5 ml of EtOH, added with 150 mg of PtO_2, was submitted to catalytic reduction. During this reduction, the solution which had colored violet and then changed to red on dissolving the pyrrole, faded to pale yellow. Theoretical volume of H_2 was absorbed easily. After filtration of the catalyst, the solvent was evaporated and the residue was basified with 20% NaOH. The oil that separated out was extracted with ether, the extract was dried over Na_2SO_4, and the solvent was evaporated. The oily residue was distilled and gave a fraction of bp 120—130° (oil bath temp.). Yield, 1.35 g (90%). It formed a picrate (recrystallized from acetone) of mp 213—214°, which was identical with the product of the Eschweiler-Clark treatment of the *cis* compound, obtained by the catalytic reduction of 2,5-dimethylpyrrole. *Anal.* Calcd. for $C_{13}H_{18}O_7N_4$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.55; H, 5.34; N, 16.73.

2,5-Dimethyl-3-(diphenylmethylene)-1-pyrroline (IV) Methiodide——CH_3I was added to dehyd. ether solution of 6 g (0.023 mole) of 2,5-dimethyl-3-(diphenylmethylene)-1-pyrroline and the mixture was allowed to stand over night. The quaternary base that separated out was collected by filtration and washed thoroughly with dehyd. ether. Yield, 8 g (86%).

13) The pharmacological tests were carried out by Dr. M. Hitomi and his group in the Central Laboratory of the Fujisawa Pharmaceutical Industries, Ltd.

3-(Diphenylmethylene)-1,2,5-trimethylpyrrolidine (I)——To a solution of 2.42 g (0.006 mole) of the above quaternary base dissolved in MeOH, MeOH solution of 0.7 g of $NaBH_4$ was added with stirring and cooling, and the mixture was further stirred for 1.5 hr at room temperature. The mixture was then acidified with 10% HCl and MeOH was evaporated under a reduced pressure. The residue was basified with 20% NaOH and the liberated base was extracted with ether. After drying over Na_2SO_4, ether was evaporated and the residue was distilled under a reduced pressure, collecting a distillate of colorless liquid, bp 157° (7 mm Hg). The thin-layer chromatogram of this liquid gave two spots at *Rf* 0.31 and 0.12 (benzene:acetone =4:1).

This fraction was purified by Al_2O_3 chromatography and the fraction that gave a spot at *Rf* 0.31 in thin-layer chromatography was eluted with hexane, yielding 1.11 g of colorless plates (*cis* compound), mp 70—71°.

The fraction that gave a spot at *Rf* 0.12 in the thin-layer chromatography was eluted with benzene–acetone (70:1) and afforded 276 mg of the *trans* compound. The ratio of *cis*:*trans* products was 4:1, and the total yield of the *cis* and *trans* isomers was 83%.

Hydrochloride of the *cis* compound: mp 255—257° (decomp.).

Hydrochloride of the *trans* compound: mp 231° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}NCl$: C, 76.53; H, 7.71; N, 4.46. Found (for *cis* compd.) (Ia): C, 76.66; H, 7.59; N, 4.72. Found (for *trans* compd.) (Ib): C, 76.54; H, 7.78; N, 4.79.

***cis*-2,5-Dimethyl-3-(diphenylmethylene)-1-methylpyrrolidine Methiodide**——Dehyd. benzene solution of MeI (0.0027 × 4 mole) was added to the dehyd. benzene solution of 739 mg (0.0027 mole) of Ia and the mixture was refluxed for 3 hr. The crystals that separated out were collected by filtration, washed with ether, and recrystallized from acetone to colorless plates, mp 221—222°. Yield, 72%. *Anal.* Calcd. for $C_{21}H_{26}NI$: C, 60.15; H, 6.24; N, 3.34. Found: C, 60.09; H, 6.07; N, 3.20.

***cis*-2,5-Dimethyl-3-(diphenylmethylene)-1-methylpyrrolidine Ethiodide**——Exactly the same reaction as above was carried out with EtI and colorless needlse, mp 194—196°, were obtained. *Anal.* Calcd. for $C_{22}H_{28}NI$: C, 60.97; H, 6.51; N, 3.23. Found: C, 61.32; H, 6.94; N, 2.92.

3-(Diphenylmethylene)-1,2,5,5-tetramethylpyrrolidine——Dehyd. benzene solution of 204 mg (0.00036 × 3 mole) of MeI was added to the dehyd. benzene solution of 100 mg (0.00036 mole) of 3-(diphenylmethylene)-2,5,5-trimethylpyrroline,[3] the mixture was refluxed for 2 hr, and allowed to stand overnight. After benzene was distilled off, the residue was washed with ether, dissolved in MeOH, and reduced as in the case of I, from which 81 mg of colorless syrupy distillate (200° oil bath at 6 mmHg) was obtained. Its picrate was recrystallized from EtOH, mp 190—191°. *Anal.* Calcd. for $C_{27}H_{28}O_7N_4$: C, 62.30; H, 5.42. Found: C, 62.68; H, 5.51.

Measurement of the Formation Rate of the Quaternary Base——The measurement followed the report of Shamma, *et al.*[14] The sample (*ca.* 10 mg, 0.00004 mole) was dissolved in 25 ml of acetonitrile (Spectrograde), placed in a thermostatic bath of 25° ± 0.5°, 1 ml of MeI was added, and the electric conductivity (υ_t) that increased with time was read until the conductivity became constant (υ_∞). (Since MeI used is in excess, the second order reaction is considered to follow the pseudo-first order).

In this case, concentration of the salt formed will be equal to the elelctric conductivity of the solution, and the initial concentration of the tertiary base will be equal to the final concentration of the salt. Therefore, the reaction rate will be expressed by the formula:

$$-\ln(\upsilon_\infty - \upsilon_t) = kt - \ln \upsilon_\infty$$

When $-\log(\upsilon_\infty - \upsilon_t)$ is plotted against time, the value obtained by multiplying its slope with 2.3 will be equal to the reaction rate, k_1.

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14) M. Shamma and J.M. Richery, *J. Am. Chem. Soc.*, **85**, 2507 (1963).