[Chem. Pharm. Bull. 16(2) 320—325 (1968)] UDC 615.784/5-011

Synthesis of Pyrrolidine Derivatives with Anticholinergic Properties. IV.[1] Synthesis, Stereochemistry, and Pharmacological Activity of N,N-Diethyl- and N,N-(epimeric)-Ethylmethyl-2-methyl-3-diphenylmethylenepyrrolidinium Salts

Sadao Ohki, Motoyo Yoshino, and Fumiko Hamaguchi

Tokyo College of Pharmacy[2]

(Received May 18, 1967)

The ethobromide (IV) (Pyrodifenium bromide) and methiodide (VI) of N-ethyl-2-methyl-3-diphenylmethylenepyrrolidine (II) and the ethiodide (V) of N-methyl-2-methyl-3-diphenylmethylenepyrrolidine (I) were synthesized. Anti-acetylcholine action of IV, V, and VI was 0.5, 1.95, and 0.25 times, respectively, of that of atropine. A marked difference was found in the intensity of the action of the epimeric N,N-ethylmethyl compounds, V and VI.

It was found through the synthesis of N,N-dimethyl-2-alkyl-3-diphenylmethylenepyrrolidinium iodide that the 2-methyl compound (III) had the strongest anti-acetylcholine activity.[5] Later, various N,N-dialkyl-2-methyl compounds were synthesized and examination of their anti-acetylcholine activity showed that N,N-diethyl-2-methyl-3-diphenylmethylenepyrrolidinium halide[3] (IV) had a stronger activity.[4] IV was synthesized by the route shown in Chart 1, in accordance with that of III.

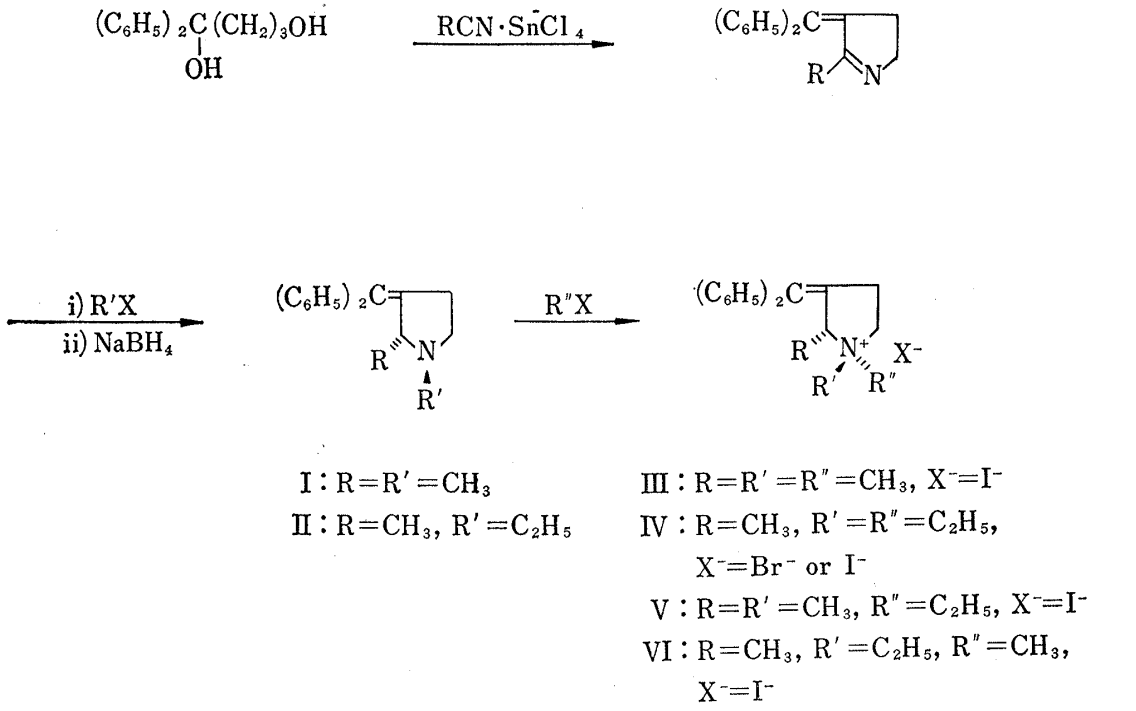
The anti-acetylcholine action of III and IV was 0.25 and 0.5 times, respectively, of that of atropine, and the difference in their potency is due only to the difference between the N,N-dimethyl and N,N-diethyl groups. This fact led to an interest in the pharmacological activities of epimeric N,N-ethylmethyl compounds (V and VI).

The synthesis of V and VI were carried out by standing ether solutions of 1-methyl compound (I) and ethyl iodide, and 1-ethyl compound (II) and methyl iodide at 0—5° for 1 month and *ca.* 2 weeks, respectively. V, mp 157—159°, was obtained in 66% yield and VI, mp 186—188°, in 78% yield. It is clear that these crystalline substances are the main products of this reaction.

As for the conformation of I and II, it may be considered that, as in the previously reported 3-hydrogen-[5] (VII) and 3-diphenylmethylene-1,2,5-trimethylpyrrolidine[5] (VIII), both take the C_s form with the maximum puckering at N, with 2-CH_3 taking the equatorial, and N-CH_3 and N-C_2H_5 taking the equatorial conformations (A). This conclusion seems appropriate even from the comparison of the NMR spectra of I, II, VII,[5] and VIII (Table I).

It can be assumed that the reaction of alkyl halide with I and II which take the (A) conformation would proceed fairly stereoselectively under a mild condition. McKenna and others[6] have already reported on the quaternization of cyclic tertiary bases possessing a substituent in α-position, such as N-alkyl-2-methyl-pyrrolidine and -piperidine, and stated that the reagent attacked from the direction of N-lone pair, *i.e.*, from the axial direc-

1) Part III: S. Ohki and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **16**, 269 (1968).
2) Location: *Women's Division. 10-19 Sakuragi 1-chome, Ueno, Daito-ku, Tokyo.*
3) Generic name: Pyrodifenium bromide (or iodide).
4) The synthesis of this compound was carried out in co-operation with Dr. M. Ohara, *et al.* of the Central Laboratory, Fujisawa Pharmaceutical Ind., Ltd.
5) S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **14**, 187 (1966).
6) J. McKenna, J.M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, **1965**, 1711; *cf.* also J. McKenna, J.M. McKenna, and A. Tulley, *ibid.*, **1965**, 5439.



I : R=R′=CH_3
II : R=CH_3, R′=C_2H_5
III : R=R′=R″=CH_3, X^-=I^-
IV : R=CH_3, R′=R″=C_2H_5, X^-=Br^- or I^-
V : R=R′=CH_3, R″=C_2H_5, X^-=I^-
VI : R=CH_3, R′=C_2H_5, R″=CH_3, X^-=I^-

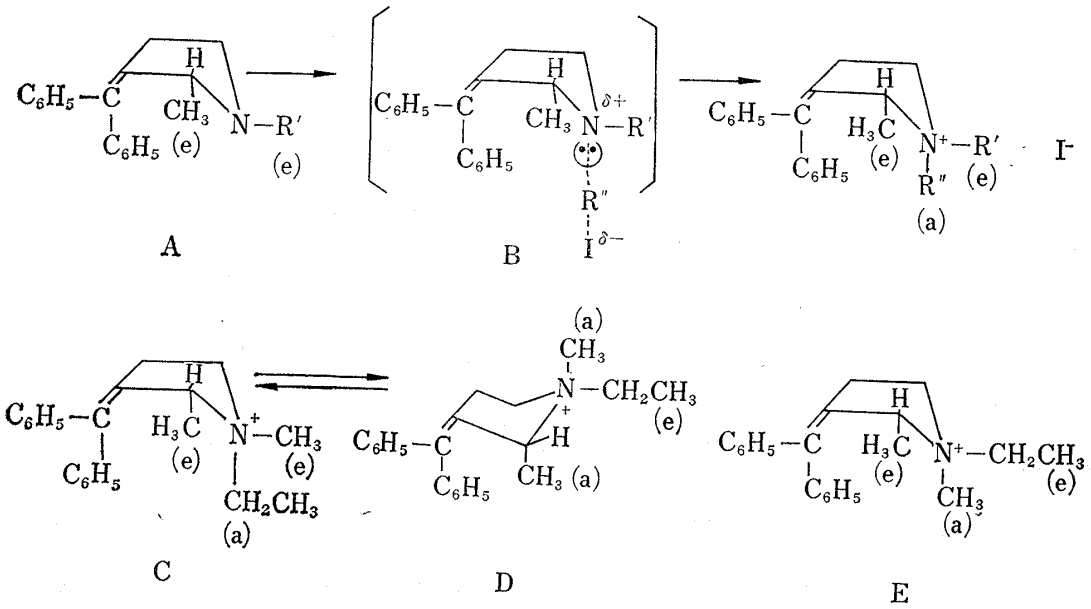


Chart 1

tion, and that the reaction progressed fairly stereoselectively *via* the transition state of Sp^3 or near Sp^3 hybridized tetrahedral nitrogen (*cf.* formula B). It had been shown in the preceding paper[1] that in the quaternization of *cis*– and *trans*–2,5–dimethyl compounds of VII, and *cis*– and *trans*–2,5–dimethyl compounds of VIII, with methyl iodide, the rate of quaternization was much slower in the *cis* compounds than in *trans* compounds, and this fact proves the effect of the α–substituent on the reaction rate and its contribution to the stereoselectivity. McKenna and others[6] also reported that in the reaction of N–methyl–2–methylpyrrolidine and ethyl iodide under a mild condition, formation of IX progressed preferentially,

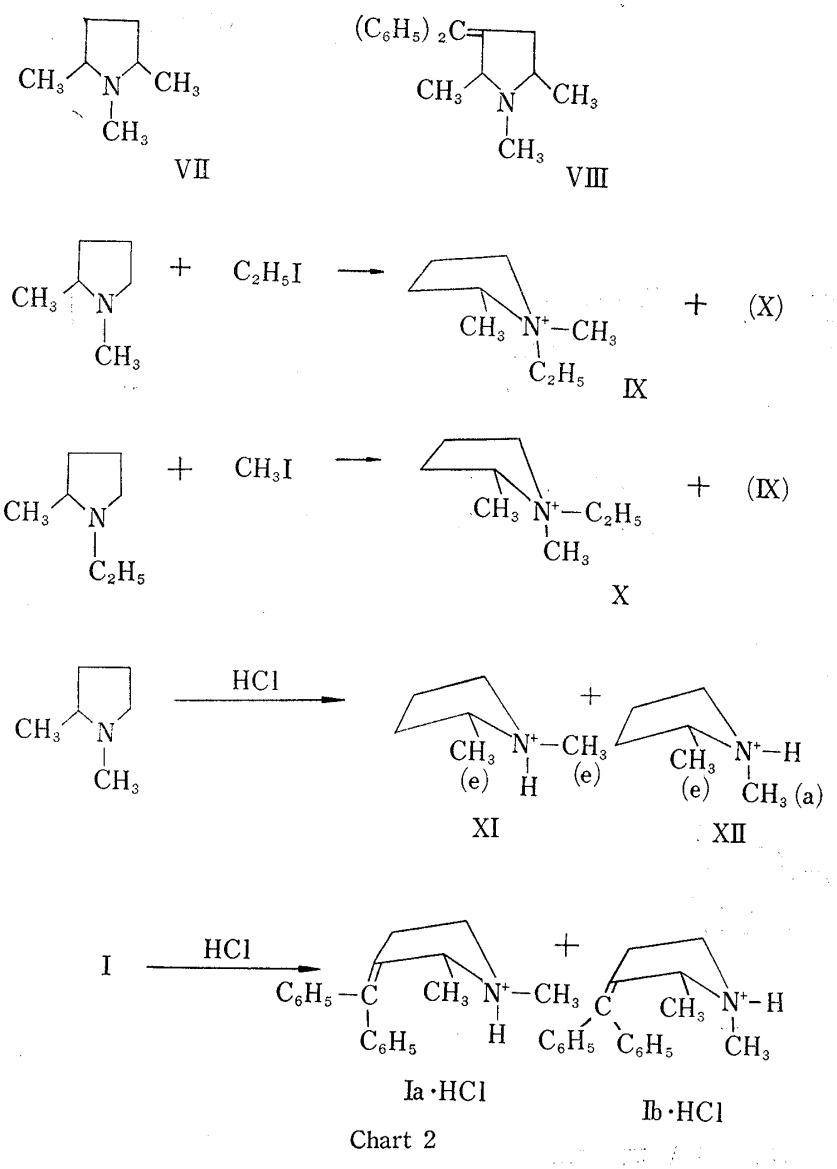


Chart 2

while that of N–ethyl compound and methyl iodide gave X as the main product, indicating stronger selectivity of the latter.

Based on the foregoing considerations, it is assumed that V takes the C– or D–form, and VI, the E form.

The rate of quaternizaton of I by methyl iodide is about twice faster than that of II,[7] while the reaction rate of I and ethyl iodide to form V is slower than that of II and methyl iodide to form VI. This may be due to the fact that the activity of ethyl iodide is weaker than that of methyl iodide and that the former is more bulky than the latter.

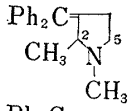
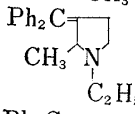
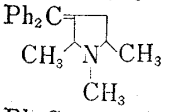
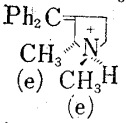
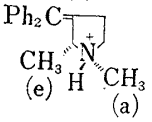
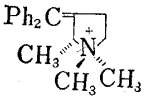
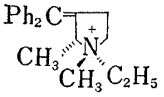
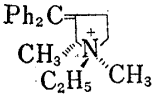
There was no interconversion between V and VI during recrystallization and other procedures.[8]

Next, NMR spectra of V and VI were examined. McKenna and others[9] noted that, in the NMR spectrum of N–methyl–2–methylpyrrolidine hydrochloride, the signal of N–methyl appeared strong at 6.97τ (doublet) and weak at 7.29τ (doublet), and assigned the former to the N–CH_3(eq.) of stabilized XI and the latter to the N–CH_3(ax.) of XII. They applied

7) Measured by the electric conductivity in acetonitrile.
8) J. McKenna, J.M. McKenna, and J. White, *J. Chem. Soc.*, **1965**, 1733.
9) J.K. Becconsall, R.A.Y. Jones, and J. McKenna, *J. Chem. Soc.*, **1965**, 1726.

this relationship to the N–methyl signals (6.72τ and 7.02τ) of IX and X, and concluded that the N–methyl in IX took the equatorial form and that in X the axial configuration. In order to see if this method could be applied for the determination of the configurations of V and VI, their NMR spectra were examined (Table I).

Table I. Chemical Shifts (τ)

Compound	No.	N–CH_3	$C_{(2)}$–CH_3	$C_{(5)}$–CH_3
	I	7.74 ($s^{a)}$)	9.28 ($d^{b)}$) (J=6.0 cps)	
	II	—	9.25 (d) (J=6.0 cps)	
	VIII (*cis*) VIII (*trans*)	7.82 (s) 7.65 (s)	9.27 (d) (J=6.0 cps) 9.25 (d) (J=6.0 cps)	8.92 (d) (J=5.9 cps) 9.06 (d) (J=6.0 cps)
	Ia·HCl	7.16 (d) (J=5.0 cps)	8.71 (d) (J=6.5 cps)	
	Ib·HCl	?	8.90 (d) (J=6.5 cps)	
	III	6.76 (s) 6.54 (s)	8.78 (d) (J=6.5 cps)	
	V	6.83 (s)	8.73 (d) (J=7.5 cps)	
	VI	6.68 (s)	8.60 (d) (J=7.2 cps)	

a) s=singlet *b*) d=doublet I, II, VIII: in CCl_4 solution Ia, b·HCl, III, V, VI: in $CDCl_3$ solution

The strong signal of N–CH_3 in the hydrochloride of I is at 7.16 τ but the weaker signal is indistinct and it seemed difficult to apply McKenna's method in this case. It also seemed difficult to find any definite correlation from the N–CH_3 signals of various compounds. The C–CH_3 signal of the hydrochloride of I is deshielded by $>\overset{+}{N}H$,[10] but is separated into a strong doublet (8.71 τ) and a doublet (8.90 τ) of about one-quarter its intensity, and this clearly indicates the presence of two kinds of stereoisomer (Ia and Ib hydrochlorides). It is considered that the former (Ia) is the stable form and its $\overset{+}{N}$–CH_3 takes the equatorial configuration, and the latter (Ib) is the quasi-stable form, its $\overset{+}{N}$–CH_3 taking the axial configuration. There would be an interaction between the C–CH_3 and N–CH_3(ax) in Ib hydrochloride which would produce a strain in the ring and the C–CH_3 would tend to axial orientation, and resulting in the shift of its C–CH_3 to a higher magnetic field than that in Ia hydrochloride by the effect of bond anisotropy and by the larger shielding effect of the diphenylmethylene group. If this relationship were to be adapted to that between V and VI, the N–C_2H_5(ax) of V would have large effect on C–CH_3 than N–CH_3(ax) of VI, and might be accompanied in some cases by a drastic change in the conformation (D form), and the C–CH_3 of V would shift to a higher

10) *cf.* A.F. Casy, *Tetrahedron*, **22**, 2711 (1966).

magnetic field than that of VI. In the above-mentioned report by McKenna and others,[9] the assignment of configuration was made on the understanding that there was little possibility of a drastic change in the conformation. This point will be examined further.

Anti-acetylcholine activity of III,[11] IV,[11] V, and VI was summarized in Table II.

Table II. Anticholine Activity[a]

Compd. No.	ED 50: g/ml	Relative Potency, Atropine=1
III	6.5×10^{-8}	0.25
IV (Pyrodifenium bromide)	1.8×10^{-8}	0.50
V	1.9×10^{-8}	1.95
VI	2.0×10^{-7}	0.25

a) Pharmacological tests were made by the Magnus method. These tests were carried out by Dr. S. Kumada and Dr. M. Hitomi of the Central Laboratory, Fujisawa Pharmaceutical Industries, Ltd.

There are many examples of difference in the intensity of pharmacological activity according to substituents on the nitrogen atom[12] but it is extremely interesting that a marked difference in pharmacological effect exists between V and VI, the diastereoisomeric N-methyl and N-ethyl quaternary ammonium salts. Besides the anti-acetylcholine action, IV (pyrodifenium halide) possesses analgesic and anti-convulsant actions.

Experimental

1-Ethyl-2-methyl-3-diphenylmethylenepyrrolidine (II)——Excess EtI was added to the MeOH solution of 2-methyl-3-diphenylmethylene-1-pyrroline[5] and the mixture was heated in a water bath for 5 hr. After standing over night, MeOH and excess EtI were removed by low-pressure distillation, the residue washed with dehyd. ether. The residue was dissolved in MeOH, *ca.* 4 equiv. of $NaBH_4$ was added with stirring, and the mixture was stirred at room temperature for 4 hr. The mixture was acidified with 10% HCl, MeOH was distilled off in a reduced pressure, the residue was basified with 20% NaOH, and extracted with ether. The ether layer was dried over Na_2SO_4, the solvent was distilled off, and the residue was distilled in a reduced pressure to collect a fraction of bp 170—180° (0.33 mmHg) (oil bath temp.) as colorless liquid. Yield, 50%.

N,N-Diethyl-2-methyl-3-diphenylmethylenepyrrolidinium Iodide (IV)——Excess EtI was added to the MeOH solution of II and the mixture was heated in a water bath for 5 hr. After standing over night, MeOH and excess EtI were removed by low-pressure distillation and the precipitated crystals were collected by filtration. The crystals were dried, washed with ether, and recrystallized from acetone to crystals of mp 209°. Yield, quantitative. *Anal.* Calcd. for $C_{22}H_{28}NI$: C, 60.50; H, 6.46; N, 3.23. Found: C, 60.92; H, 6.76; N, 2.93.

N,N-Diethyl-2-methyl-3-diphenylmethylenepyrrolidinium Bromide (IV)——Prepared by the same procedure as above, using EtBr. IV was obtained as colorless crystals, mp 218° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}NBr$: C, 68.39; H, 7.30; N, 3.63; Br, 20.68. Found: C, 68.11; H, 7.19; N, 3.63; Br, 20.78.

1,2-Dimethyl-3-diphenylmethylenepyrrolidine Ethiodide (V)——Excess of dehyd. ether solution of EtI was added to dehyd. ether solution of 1,2-dimethyl-3-diphenylmethylenepyrrolidine[5] and the mixture was allowed to stand in a refrigerator. After about one month, excess EtI and ether were removed by distillation and the residue was washed with dehyd. ether to collect crystals of mp 157—159°, which were recrystallized from acetone. Yield, 66%. *Anal.* Calcd. for $C_{21}H_{26}NI$: C, 60.14; H, 6.25; N, 3.34. Found: C, 59.76; H, 6.38; N, 3.39.

1-Ethyl-2-methyl-3-diphenylmethylenepyrrolidine Methiodide (VI)——Excess MeI was added to the dehyd. ether solution of II and the mixture was allowed to stand in a refrigerator for about 2 weeks. The crystals that separated out were collected, washed with dehyd. ether, and recrystallized from acetone to plate crystals of mp 186—188°. Yield, 78%. *Anal.* Calcd. for $C_{21}H_{26}NI$: C, 60.14; H, 6.25; N, 3.34. Found: C, 60.52; H, 6.16; N, 3.02.

11) M. Hitomi, H. Nojima, and S. Uchida, *Yakurigaku Zasshi*, **62**, 427 (1966).
12) *cf.* P. Acred, *Brit. J. Pharmacol.*, **12**, 447 (1957).

Reaction rate from I to III: $k_1 \times 10^3/\text{min} = 398$
Reaction rate from II to VI: $k_1 \times 10^3/\text{min} = 192$

Acknowledgement The authors are indebted to Dr. Sigenobu Kumada and Dr. Masahiro Hitomi of the Central Laboratory, Fujisawa Pharmaceutical Industries, Ltd., for pharmacological tests, and to Dr. Tohru Hino of the National Institute of Radiological Sciences for NMR spectral measurements. Thanks are due to Misses Yoshiko Baba and Akiko Shimada, and Mr. Shigeru Suzuki for elemental analytical data.