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The Stereochemistry of the Quaternization of 5-Methyl-5-nitro-1,3-dialkylhexahydropyrimidines

Tadakazu Tsuji

Department of Chemistry, Japan Women's University[1]

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The proportions of isomers existing in the quaternization products were estimated from the nuclear magnetic resonance (NMR) and thin-layer chromatography data. Based on those data, the stereoselectivity of the quaternization of some 5-methyl-5-nitro-1,3-dialkylhexahydropyrimidines with alkyl iodide was discussed.

NMR characteristics and particularly the chemical shifts of axial and equatorial N-methyl and N-ethyl groups were used to assign the configurations.

Numerous reports have appeared concerning the stereochemistry and stereospecificity of the quaternization for a wide range of piperidines.[2] Except piperidine series, only quinolidines,[3] 2-methylpyrrolidines,[4] certain tertiary aziridines,[5] and N-alkyl-5-methyl-5-nitrotetrahydro-1,3-oxazines[6] are the cases which have been studied on the stereochemistry of the quaternization. There seems to be no work concerning the quaternization of hexahydropyrimidines up to date.

Urbanski, *et al.* studied on the conformation of 5-methyl-5-nitro-1,3-dialkylhexahydropyrimidines and concluded that the 5-nitro axial and 1,3-diequatorial conformation was favoured for the 1,3-dibenzyl and 1,3-dicyclohexyl substituents.[7] Further, we reported in the previous paper[8] that 1,3-diethyl-5-methyl-5-nitrohexahydropyrimidine (II) was in an equilibrium of two conformers, in which each conformer possessed the 1,3-diequatorial and 5-nitro axial or equatorial conformation, though the 5-nitro axial conformation was preferential.

Now, we prepared the quaternary salts of 5-methyl-5-nitro-1,3-dialkylhexahydropyrimidines, since the salts were water-soluble and considered to be of interest to examine the antimicrobial activities in relation to the antimicrobial active 5-amino-5-methyl-1,3-dialkylhexahydropyrimidines[9] and N-alkyl-5-methyl-5-nitrotetrahydro-1,3-oxazines.[10] The present paper describes the examination on the stereoselectivity of the quaternization of some 5-methyl-5-nitro-1,3-dialkylhexahydropyrimidine [R=Et (II), iso-Pr (III), cyclohexyl (IV), *tert*-Bu (V)] with methyl iodide and the quaternization of 1,3-dimethyl-5-methyl-5-nitrohexahydropyrimidine (I) with alkyl halide (R=Et, iso-Pr, *tert*-Bu).

Quaternization was carried out upon treatment of the hexahydropyrimidine base with alkyl halide in an etheral solution at room temperature. In such a case as the quaternization

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1) Location: *Mejiro-dai, Bunkyo-ku, Tokyo.*

2) H.O. House, B.A. Tefertiller, and C.G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966); D.R. Brown, R. Lygo, J. McKenna, and J.N. McKenna, *J. Chem. Soc.* (*B*), **1967**, 1184; M.A. Iorio and S. Chiavarelli, *Tetrahedron*, **25**, 5235 (1969).

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6) D. Gürne, T. Urbanski, M. Witanowski, B. Karniewska, and L. Stefaniak, *Tetrahedron*, **20**, 1173 (1964).

7) H. Piotrowska and T. Urbanski, *J. Chem. Soc.*, **1962**, 1942; D. Gürne, T. Urbanski, M. Witanowski, and L. Stefaniak, *Tetrahedron*, **20** *Suppl.*, 195 (1964).

8) T. Tsuji and Y. Okamoto, *Chem. Pharm. Bull.*(Tokyo), in press.

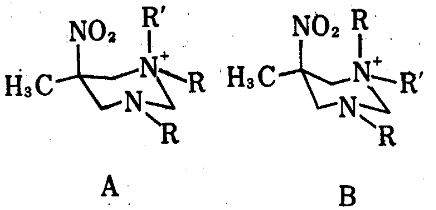
9) F.A. Barkely and B.S. Schwartz, *Antimicrobial Agent Ann.*, **1960**, 507 [*C.A.*, **56**, 14402f (1962)].

10) D. Rozniecka, *Med. Doswiadczalnai Mikrobiol.*, 3, 149 (1951) [*C.A.*, **46**, 4675e (1952)].

of II or III with methyl iodide, or the quaternization of I with ethyl iodide, the quaternary salt was obtained as a mixture of two diastereomers. In other cases except the above, the quaternization was failed, and the starting material was recovered.

Configurations of the quaternary salts obtained hereof were decided from their nuclear magnetic resonance (NMR) spectra, which were taken at 60 MHz in D_2O with DSS as an internal standard. Chemical shifts of the methyl groups and isomer ratios are summarized in Table I, where chemical shifts are quoted as Hz upfield from the signal of HDO proton in D_2O for the purpose to compare with the NMR spectrum of the methiodide of N-ethyl-5-methyl-5-nitrotetrahydro-1,3-oxazine.[6] In these spectra, the signal of HDO proton always appeared at 4.73 ppm.

Table I. NMR Spectral Data of Quaternary Salts and Approximate Isomer Ratios



Stereoisomer			Chemical shift (Hz from HDO signal)					Isomer ratio A:B	
No.	R	R′	N-CH_3	N^+-CH_3	N-CH_2-CH_3	N^+-CH_2-CH_3	5-CH_3	from NMR	from TLC
IA	CH_3	C_2H_5	+133	+99	—	+207	+186	2:1	2:1
IB	CH_3	C_2H_5	+133	+105	—	+196	+186		
IIA	C_2H_5	CH_3	—	+105	+219	+196	+186	1.1:1	1:1
IIB	C_2H_5	CH_3	—	+100	+219	+207	+186		
IIIA	$(CH_3)_2CH$	CH_3	—	+108	—	—	+187	>12:1	—

As shown in Table I, the signal for the 5-methyl group in the quaternary salt of I or II was observed as a singlet, which means the chemical shifts of 5-methyl protons in the isomers A and B to be equal. Accordingly, the 5-methyl groups in both diastereomers might exist in the same environment, *i.e.*, in an equatorial position avoiding the severe 1,3-dialkyl diaxial interaction.

The signal for the N^+-methyl group appeared at 106 or 101 Hz upfield than the signal of HDO proton. Similarly, the signal of methyl protons for the N^+-ethyl group appeared at 207 or 196 Hz upfield than the signal of HDO proton. The NMR spectrum at 60 HMz of the methiodide of N-ethyl-5-methyl-5-nitrotetrahydro-1,3-oxazine was taken by Urbanski, *et al.*[6] Taking into consideration with the anisotropic effect of the 5-nitro group oriented at an axial position, they concluded that the signals for the axial and equatorial N^+-methyl groups appeared at 106 and 101 Hz, and that the signals of methyl protons for the axial and equatorial N^+-ethyl groups appeared at 207 and 196 Hz, respectively, upfields than the signal of HDO proton. Hence the observed two different chemical shifts of the methyl group were considered to represent the axial and equatorial environments for this group. Proposed configurations for the present two isomers are described in Table I.

It was known that the preferred conformation of 1,3-dialkyl derivatives of 5-methyl-5-nitrohexahydropyrimidine, III,[11] IV,[7] and V,[11] was the 5-nitro group axial and 1,3-diequatorial.

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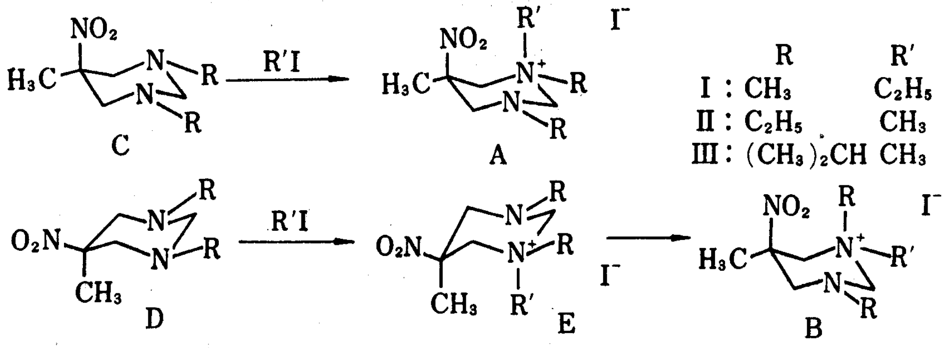
[11] T. Tsuji and Y. Okamoto, Papers read at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.

Further, II was found in the previous study[8] to be in an equilibrium of two conformers, C and D, bearing the 1,3-diequatorial conformation. Therefore, the present quaterinization might be explained as illustrated in Chart 1.

As shown in Chart 1, the quaternization of the conformer D might involve the formation of intermediate salt (E), followed by the ring inversion into the stable salt B as a result to avoid the severe 1,3-dialkyl diaxial interaction in E.



	R	R'
I :	CH_3	C_2H_5
II :	C_2H_5	CH_3
III :	$(CH_3)_2CH$	CH_3

Chart 1

The existence ratio of diastereomers (A:B) was determined from the relative magnitudes of the signals of axial and equatorial methyl protons for the N^+-methyl group or the N^+-ethyl one, which appeared as separate singlets or triplets in the NMR spectrum of a product. Thin-layer chromatography (TLC) on silica gel of each crude mixture, using acetone–methanol as a developing solvent, showed the presence of two spots. Isomer ratios obtained from integrals of TLC spots were in agreement with those derived from the relative magnitudes of two methyl signals, as shown in Table I.

The quaternization of II with methyl iodide took place with a moderate degree of stereo selectivity, giving in major amount of the stereoisomer with the axial N^+-methyl group, and the quaternization of III with methyl iodide afforded the result to yield almost only one stereoisomer with the axial N^+-methyl group. The reaction of IV or V with methyl iodide did not occur, probably because of the steric hindrance. On the other hand, the quaternization of I with ethyl iodide occurred with a slight degree of stereoselectivity. When the entering group was as large as isopropyl or *tert*-butyl, the quaternization did not take place.

McKenna[12] has provided a general consideration on the stereospecificity of the quaternization of piperidines (VI) and described as follows: (1) The quaternization of the N-alkyl derivative of VI with methyl iodide will usually show a preference for the axial quaternization. (2) The reaction of the N-methyl derivative of VI with alkyl halide will show a reduced preference for the axial quaternization, near-zero stereoselectivity, or some preference for the equatorial quaternization, and there is often likely to be a much stronger tendency towards the equatorial isopropylation than the alkylation with a *n*-alkyl group.

On the contrary, Urbanski, *et al.*[6] reported that the equatorial alkylation solely took place to result the retention of the conformation of employed base in the quaternization of 5-methyl-5-nitrotetrahydro-1,3-oxazines possessing the axial N-*n*-alkyl group.

The product ratio in the present quaternization did not reflect the conformational equilibrium of the original base, since we found[8] that the mole fractions of two conformers, C and D of II, were 0.79 and 0.21, respectively. Thus, it could be said that the stereospecificity of the present quaternization might resemble to that of piperidines more than to that of 5-methyl-5-nitrotetrahydro-1,3-oxazines.

Antimicrobial properties of the present quaternary salts are now under investigation.

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[12] J. McKenna, "Topics in Stereochemistry," Vol. 5, ed. by E.L. Eliel and N.L. Allinger, Wiley–Interscience Publishers, New York, 1970, p. 300.

Experimental

NMR spectra (60 MHz) were taken at 22° with a JEOL-C-60H spectrometer in a 0.2M solution in D_2O.

General Procedure for the Quaternization of 5-Methyl-5-nitro-1,3-dialkylhexahydropyrimidines— To a solution of the hexahydropyrimidine base in ether was added alkyl halide (1.2 mole) dropwise under cooling and the whole was kept at room temperature until the precipitation was complete. The solid was collected and washed with ether. This crude sample was employed for the purpose to determine the existence ratio of two diastereomers. For the elementary analysis, the crude material was purified by recrystallization from EtOH to form colorless prisms. The quaternary salts thus obtained are listed in Table II.

TABLE II

Product	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	128—130	$C_9H_{20}O_2N_3I$	33.05	6.10	12.77	32.83	6.25	12.88
II	132—134	$C_{10}H_{22}O_2N_3I$	34.94	6.46	12.24	34.83	6.62	12.49
III	136—137	$C_{12}H_{26}O_2N_3I$	38.82	7.06	11.32	38.62	7.31	11.58

Thin-Layer Chromatography——Chromatoplates (20 cm × 5 cm) were made with a 0.25 mm layer of silica gel and dried at 105° for 1 hr. A mixture of acetone–MeOH (7: 3) was used as an eluent. Development was carried out until the solvent front had run *ca.* 10 cm from the starting line. Spots were observed under ultraviolet ray (3650 Å), and *Rf* differences were about 0.11. Two spots observed on the chromatoplates were outlined with a needle, and then copied on a paper, which was weighed for determination of the ratio of two areas.

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