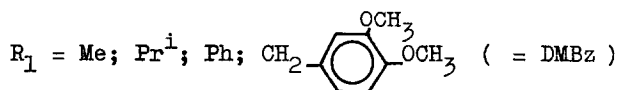
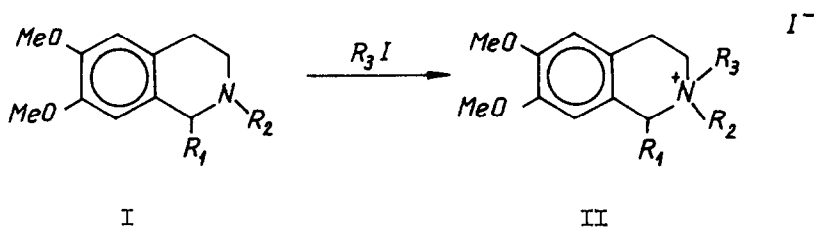


QUATERNIZATION OF 1,2-DISUBSTITUTED 6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISO-  
QUINOLINES

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Quaternization of N-alkyl heterocycles has been extensively studied in several laboratories in order to obtain informations on the conformational properties of hetero rings on one hand (1), and to elucidate the mechanism, steric course and kinetics of quaternization process on the other (2). With both of these purposes we started recently a series of experiments with some 1,2-disubstituted tetrahydroisoquinolines (I). The main results of the first part of our studies are summarized and briefly discussed in this Letter.



Ia :  $R_2 = \text{Me}$

IIa :  $R_3 = \text{Et}; \text{Pr}^n; \text{Bu}^n; \text{Bz}$

Ib :  $R_2 = \text{Et}; \text{Pr}^n; \text{Bu}^n; \text{Bz}$

IIb :  $R_3 = \text{Me}$

Quaternization of N-methyl-bases (Ia) with alkyl iodide, and N-alkyl-bases (Ib) with methiodide ("direct" and "reverse" quaternizations, respec-

tively) were carried out by treatment of the base with a large excess of the alkylating agent and refluxing the methanolic solution. The crude reaction mixtures containing diastereomers IIa and IIb were subjected to quantitative NMR analyses and subsequent fractional crystallization. Deductions concerning the stereochemistry of quaternary salts are based on NMR spectra recorded with the isolated and in most cases homogeneous diastereomers\*.

Results of quantitative analyses are presented in Table 1. The compositions of reaction mixtures are given in percentages of diastereomers (relative accuracy  $\pm 5\%$ ); the stereoisomers predominating in direct reactions are labelled by A.

T A B L E 1.

Fractional Yields of Stereoisomeric Salts in Crude Reaction Mixtures

Substituents			% of Isomers		Substituents			% of Isomers	
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	"A"	"B"	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	"A"	"B"
Me	Me	Et	70	30	Pr <sup>i</sup>	Me	Bz	95	5
Me	Et	Me	35	65	Pr <sup>i</sup>	Bz	Me	40	60
Me	Me	Pr <sup>n</sup>	75	25	Ph	Me	Et	76	24
Me	Pr <sup>n</sup>	Me	35	65	Ph	Et	Me	14	86
Me	Me	Bu <sup>n</sup>	75	25	Ph	Me	Bz	100	0
Me	Bu <sup>n</sup>	Me	45	55	Ph	Bz	Me	35	65
Me	Me	Bz	100	0	DMBz	Me	Et	65	35
Me	Bz	Me	55	45	DMBz	Et	Me	30	70
Pr <sup>i</sup>	Me	Et	60	40	DMBz	Me	Bz	95	5
Pr <sup>i</sup>	Et	Me	17	83	DMBz	Bz	Me	40	60

\* All spectra were recorded in CDCl<sub>3</sub> solutions with an A.E.I. RS2 spectrometer operating at 60 Mc/s.

Thus the quaternization of bases I occurs, with a few exceptions, with moderate degrees of stereoselectivity. Within the series  $R_1 = \text{Me}$ , the direct reaction is of higher selectivity; the predominance of isomers A increases with the bulkiness of alkylating group  $R_2$ , and when  $R_2 = \text{Bz}$ , the reaction is practically stereospecific. If the substituent at C-1 is bulkier than Me, higher selectivity is characteristic either of the direct, or the reverse reaction, depending on the relative space demands of groups at nitrogen,  $R_2$  and  $R_3$ . Thus, if  $R_1 = \text{Pr}^i$ , or Ph, and  $R_2$  and  $R_3$  are both small (Me, Et), the methylation is of higher selectivity. On the other hand, if  $R_2$  and  $R_3$  are of different size (Me and Bz), higher product ratios are found with the benzylation reactions.

On the basis of proton resonance spectra of isolated diastereomers we concluded that the relative orientation of  $R_1$  and the bulkier substituent at nitrogen is the same in each isomer A. A similar conclusion is true for stereoisomers B with another relative orientation of relevant groups. Equilibration experiments with N-methyl-N-benzyl quaternary salt pairs yielded predominantly isomers A, while, on the other hand, higher barrier to free rotation of N-benzyl group (larger magnetic non-equivalence of benzyl-methylene and benzyl-aromatic protons (3)) was observed in isomers B. These findings suggest that diastereomers A represent the more stable form in which  $R_1$  and the larger substituent at nitrogen are trans-oriented.

In view of this assignment we may interpret the stereoselectivity data by assuming a preferred trans N-alkylation with respect to the actual orientation of substituent at C-1. The changes in product ratios than should be attributed to interactions between substituents in positions 1 and 2 influencing the preference for trans reaction according to their relative space demands. The unexpected higher product ratios in the reverse quaternization of 1-phenyl-N-ethyl and 1-isopropyl-N-ethyl bases may also be understood in this approximation if we suppose that in these cases the trans orientation of methyl, rather than ethyl group is favoured.

Deductions concerning the steric course in terms of preferred axial

or equatorial approach cannot be made unequivocally at present owing to the lack of reliable data on the conformational properties of N-alkyl-bases and quaternary salts investigated. Because of the presumably high flexibility of hetero ring in tetrahydroisoquinoline skeleton both trans and cis diastereomers are expected to exist in two rapidly interconverting conformers of nearly equal amount (if conformations other than half-chair are not considered). Comparison of the chemical shift differences between N-methyl protons in various diastereomeric pairs (see Table 2) suggests that this expectation is probably met with 1-methyl quaternary salts characterized by

T A B L E 2

Chemical Shifts of N-Methyl Protons. Solvent  $CDCl_3$ 

Substituents			$\delta$ (ppm) in Isomers		Substituents			$\delta$ (ppm) in Isomers	
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	"A"	"B"	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	"A"	"B"
Me	Me	Me	3,53		Pr <sup>i</sup>	Me	Bz	3,48	3,10
Me	Me	Et	3,38	3,28	Ph	Me	Me	3,68 3,24	
Me	Me	Pr <sup>n</sup>	3,42	3,33	Ph	Me	Et	3,08	3,50
Me	Me	Bu <sup>n</sup>	3,42	3,33	Ph	Me	Bz	2,95	3,45
Me	Me	Bz	3,29	3,12	DMBz	Me	Me	3,82 3,51	
Pr <sup>i</sup>	Me	Me	3,73 3,43		DMBz	Me	Et	3,71	3,27
Pr <sup>i</sup>	Me	Et	3,55	3,24	DMBz	Me	Bz	3,43	3,09

relatively small ( $\sim 0,1$  ppm) differences, while for other derivatives it seems likely that averaging effects are of minor importance\*. With the exceptions of 1-methyl derivatives, the relative shifts of N-Me protons in diastereomeric pairs are very close to values observed in corresponding N,N-di-

\* The resulting anisotropy effect of aromatic ring at C-1 expected in case of complete, or nearly complete averaging cannot account for the observed large differences in N-Me resonances.

methyl salts. This in turn suggests that in cases of conformational preference the same conformation may be ascribed to trans as well as cis diastereomers having an identical substituent at C-1, i.e. the orientation of a given R<sub>1</sub> is the same in each stereoisomer<sup>‡</sup>.

Since, however, the actual orientation of substituents at C-1 cannot be elucidated with certainty even for quaternary salts with presumably preferred conformations, the question whether axial or equatorial approach of incoming group is preferred, or the quaternization is governed solely by the relative orientations of interacting groups, needs additional investigations. In continuing the present series of experiments we plan to perform detailed conformational analyses, X-ray and kinetic measurements.

A full account of the results presented in this Letter will be published elsewhere (4).

#### R E F E R E N C E S

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<sup>‡</sup> The sign reversal of the relative N-Me shifts observed with 1-phenyl derivatives may probably be attributed to a change in preferred orientation of 1-phenyl group as compared with that of other C-1 substituents.