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QUATERNIZATION OF 1-SUBSTITUTED 2-METHYL-6,7-DIALKOXY-1,2,3,4-TETRAHYDROISO - QUINOLINES AND DEMETHYLATION OF THE QUATERNARY SALTS USING D, T AND ^{14}C MARKING.

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Investigations on quaternization of cyclic tertiary nitrogen compounds have been the subject of many recent papers [1]. We studied earlier the effect of different substituents in position 1 and 2 on the stereoselectivity of the quaternization reaction of 1,2-disubstituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines [2-3]. It seemed reasonable to extend these investigations by applying D, T and ^{14}C isotope technique, eliminating the effects arising from the different sizes of the substituents attached to the nitrogen atom, and permitting the study of the dequaternization. We performed the quaternization of $N-CH_3$ bases (I) with CD_3-I ("direct") and of $N-CD_3$ bases (II) with CH_3-I ("reverse" quaternization) (Fig. 1). The purity of the quaternary products (IIIa, b) was checked by IR spectroscopy and the isomer ratio was determined by NMR spectroscopy. The results obtained are listed in Table I.

Conformational lability of the 1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives was concluded earlier from the marked difference (0.15 ppm and 0.7 ppm) in the relative NMR shifts of the epimeric hydroiodides of the 1,2-dimethyl- and 1-phenyl-2-methyl derivatives [4]. The validity of our earlier statements is now confirmed by the present investigations with labelled compounds. With R_1=H or CH_3, the NMR separation of the $N-CH_3$ absorption cannot be observed in the N-epimeric salt pairs; the discrete orientation disappears because of the flexibility of the ring, and the $N-CH_3$ shift appears at a single sharp δ value.

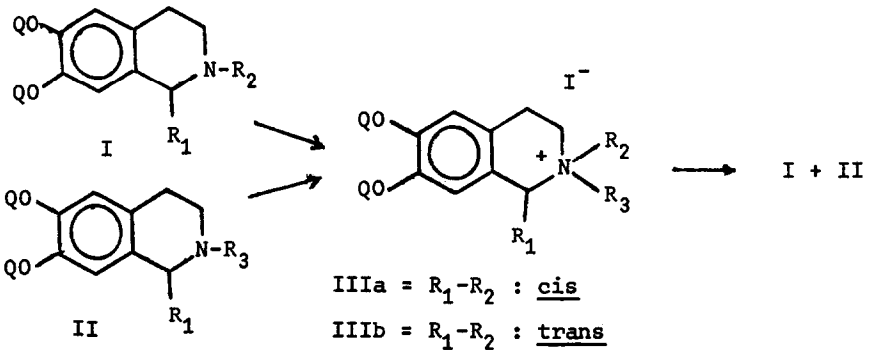

Fig. 1

In the case of other substituents in position 1, the relative values of the shifts of the R_2-R_3 = CH_3-CD_3 isomeric salt pairs and the difference between the δ values run parallel to those found for the corresponding isomeric 1-substituted methyl-ethyl salt pairs. The selectivity of the direct and reverse quaternization performed with deuterium labelling also shows a marked difference, though in this case the space requirements of the substituents attached to the nitrogen atom and of those entering in the quaternization are nearly the same.

According to our earlier results [4], preferred steric orientation of the 1-phenyl substituent in the above tetrahydroisoquinoline salts is pseudo-equatorial, whereas that of the isopropyl and 3,4-dialkoxybenzyl substituents is pseudoaxial. According to recent ORD investigations of Schnatzke et al. [5] the preferred orientation of the latter substituents in related tetrahydro - isoquinoline tertiary alkaloid bases is also pseudoaxial. In view of the preferred trans quaternization with respect to the actual orientation of the substituent at C-1 [2,6], the isomer ratio found can be understood, and it follows that the smaller δ value corresponds to the axial N-CH_3 group.

Under identical conditions, the direct and reverse quaternizations of the derivatives with R_1 = H, CH_3, phenyl, 3,4-dialkoxybenzyl were performed with T and ^{14}C marking. The mixtures of the epimeric quaternary salts and the products obtained on demethylation with ethanolamine are listed in Table II.

TABLE I

CHEMICAL SHIFTS (δ) OF THE N-CH_3 PROTONS AND ISOMER RATIOS OF THE QUATERNARY SALTS IIIa, b.

R_1	R_2	R_3	Isomer	Q = CH_3 ppm	%	Q = C_2H_5 ppm	%
H	CH_3	CD_3		3.30	100		
	CD_3	CH_3		3.30	100		
CH_3	CH_3	CD_3		3.50	100	3.52	100
	CD_3	CH_3		3.50	100	3.52	100
Ph	CH_3	CD_3	a	3.19	80	3.19	76
			b	3.63	20	3.64	24
	CD_3	CH_3	a	3.19	36	3.19	31
			b	3.63	64	3.64	69
iPr	CH_3	CD_3	a	3.38	65		
			b	3.21	35		
	CD_3		a	3.38	32		
			b	3.21	68		
DABz	CH_3	CD_3	a	3.49	70	3.47	70
			b	3.26	30	3.12	30
	CD_3	CH_3	a	3.49	27	3.47	30
			b	3.26	73	3.12	70

The primary kinetic isotope effect of the ^{14}C in the methylation and demethylation reactions, calculated from the Bigeleisen equation [7], is less than 4.3%. This is about equal to the error in the integration of the NMR peaks and the uncertainty of counting. The secondary isotope effect of deuterium and tritium is even less. Tritium exchange during the demethylation was not observed.

In the compounds with R_1 = H or CH_3, the equivalence of the N-CH_3 groups arising from the flexibility of the skeleton is shown by a drop of the specific and molar activities by 50% in the nucleophilic demethylation process. If R_1 = phenyl, isopropyl or 3,4-dialkoxybenzyl, both with simple and double marking, a preferential splitting out of the methyl group in trans position to the C-1 substituent, i.e. that entering preferentially in the quaternization process, was equally observed in the case of 6,7-dimethoxy and 6,7-diethoxy compounds. The changes of the specific activity by values different from 50% on dequaternization are in accordance with the selectivity of the quaternization experienced and at the same time constitute evidence for the stereoselectivity of the nucleophilic demethylation, though the latter is somewhat less than that of the quaternization. A similar tendency of the stereoselectivity of the nucleophilic demethylation has been found in quaternary tropane salts [8].

TABLE II

MOLAR ACTIVITIES (mμCi/μmole) OF THE QUATERNARY SALTS AND THEIR DEMETHYLATION PRODUCTS (I+II)

R_1	R_2	R_3	Q = CH_3						Q = C_2H_5					
			quaternary salts		demethylation product				quaternary salts		demethylation product			
			^{14}C	^{3}H	^{14}C	%	^{3}H	%	^{14}C	^{3}H	^{14}C	%	^{3}H	%
H	$^{14}CH_3$	CH_2T	1.10	8.01	0.45	41	4.10	51						
	CH_2T	$^{14}CH_3$	0.67	8.25	0.33	49	3.95	48						
	CH_3	CH_2T		7.90			3.90	49						
	CH_2T	CH_3		7.60			3.76	50						
CH_3	$^{14}CH_3$	CH_2T	1.18	7.35	0.61	52	3.56	49	1.15	8.11	0.56	49	4.04	56
	CH_2T	$^{14}CH_3$	1.10	8.05	0.52	48	4.00	50	1.20	8.34	0.62	52	4.11	50
	CH_3	CH_2T		8.36			4.09	49						
	CH_2T	CH_3		8.03			4.02	50		7.75			3.95	51
Ph	$^{14}CH_3$	CH_2T	1.15	8.60	0.76	66	2.90	33	1.12	7.74	0.70	63	3.00	38
	CH_2T	$^{14}CH_3$	1.24	7.79	0.47	38	4.66	60	1.16	7.62	0.46	40	4.53	60
	CH_3	CH_2T		8.19			3.04	37		7.80			2.90	37
	CH_2T	CH_3		8.11			4.85	60		7.90			4.37	56
iPr	$^{14}CH_3$	CH_3	1.48		1.00	67								
	CH_3	$^{14}CH_3$	1.45		0.60	40								
DAB	$^{14}CH_3$	CH_2T	0.15	8.94	0.09	60	4.02	45	1.07	7.96	0.71	66	3.50	44
	CH_2T	$^{14}CH_3$	1.13	0.53	0.48	42	0.37	70	1.21	8.12	0.43	36	5.30	65
	CH_3	CH_2T		8.58			3.90	45						
	CH_2T	CH_3		0.39			0.23	59						

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