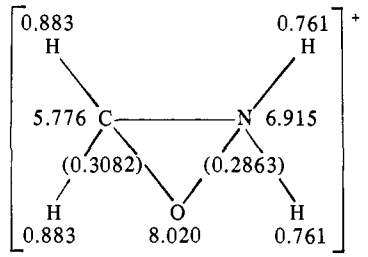
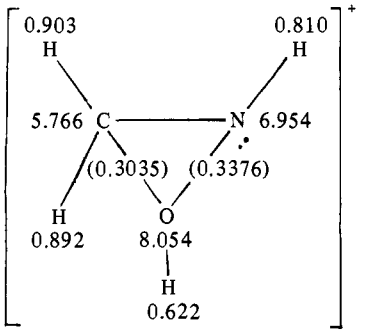
(a) oxaziridinium ion (N-protonated)



−39.9237 au

(b) oxaziridinium ion (O-protonated)



−39.8331 au

Figure 4. Mulliken atomic populations and energies and the C–O, N–O bond orders (in parentheses) of N- and O-protonated oxaziridinium ion. The oxaziridine geometry used in the calculations was taken from J. M. Lehn, B. Munsch, Ph. Millie, and A. Veillard, *Theor. Chim. Acta*, 13, 313 (1969).

ion, isopropylimmonium ion, and *N,N*-dimethyloxaziridinium ion are shown in Figure 3.

The postulate of an intermediate oxaziridinium ion is not completely unfounded considering the work of Parli, *et al.*,[23] who alternatively suggested a direct cytochrome P-450 mediated oxidation of an imine to an oxime. Although none of the recovered products of the *in vitro* oxidation was an oxaziridine, one might speculate that such a species may be an intermediate as outlined in Scheme II.

As shown, the mechanism might involve oxidation to the oxaziridine followed by "protonation" at either the oxygen or nitrogen, possibly by an enzyme as suggested by Watabe and Suzuki[24] for the hydrolysis of aziridines.

Another possibility for the breakdown of the oxaziridine not shown in Scheme II, but suggested by Watabe and Suzuki's[24] work on aziridines, is attack by other nucleophiles such as a hydroxyl group of water to give directly a carbinol hydroxylamine which could then dehydrate to give oxime or ketone. The CNDO/2 calculations (Figure 4) of the two protonated species **1** and **2** indicate favored N-protonation and differences in the C–O *vs.* N–O bond orders (numbers in parentheses) which might lead to preferential opening of the protonated oxaziridine as shown in Scheme II to ultimately produce the observed ketone and oxime.[23,25,26]

The substituent effects on immonium ions are very interesting. Substituting methyl groups on the positive carbon (isopropylimmonium ion) makes the carbon *more* positive [relative to the unsubstituted immonium ion, where $\zeta(C) = 5.75$ and $\zeta(N) = 7.01$ were found in CNDO/2 calculations][27] and the nitrogen more negative. Substitution of methyl groups on nitrogen makes the nitrogen more positive and the carbon more electron rich. These results show that the simple electron-donating inductive model to describe the substituent effect of methyl groups does not work for immonium ions and probably should be applied with caution to any system involving heteroatoms.

In conclusion, our electronic structure calculations on some postulated intermediates in amine metabolism have allowed us to say the following. (1) If the *N*-oxide is an intermediate in oxidative dealkylation, it is probably subjected to electron loss prior to forming the carbinolamine, since the positive character of the adjacent carbon atoms is small in the *N*-oxide. (2) An N-protonated oxaziridinium ion would be energetically favored over an O-protonated form. (3) Methyl groups appear to be electron withdrawing on the positive carbonium immonium ions ($R_2N\text{-}^{+}CR_2'$) when directly bonded to it (R_2') but electron donating to the carbon when bonded to the nitrogen (R_2).

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Effects of Small Changes in Chemical Structure on Stereospecificity

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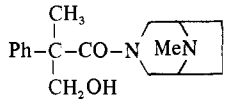
In further investigation of the effects of changes in chemical structure on stereospecificity it has recently been possible to examine the effects of methylation on the affin-

Table I. Affinity for Postganglionic Acetylcholine Receptors of the Isolated Guinea-Pig Ileum

Compound		Log K^a	SSI[b]
8-Methyl-3α-methyltropoyl-3,8-diazabicyclo[3.2.1]octane			
Base	(−)	8.165 + 0.029 (7)	1140:1
	(+)	5.107 + 0.039 (6)	
Methiodide	(−)	7.527 + 0.042 (6)	46:1
	(+)	5.867 + 0.019 (6)	
Hyoscyamine			
Base	*S*	9.380	330:1
	R	6.861	
Methiodide	*S*	9.666	87:1
	R	7.725	

[a] Estimates of the mean value of log *K* are shown with the standard error and number of results. Values for hyoscyamine and hyoscyamine methiodide, included for comparison, were obtained by exactly the same method by Barlow, Franks, and Pearson.[2] [b] The ratio of the affinity constants of the enantiomers is referred to as the stereospecific index (SSI).

ity of the (+) and (−) forms of 8-methyl-3α-methyltropoyl-3,8-diazabicyclo[3.2.1]octane (I). The enantiomers were described by Scarselli, Cignarella, and Maffii[1] and samples were obtained from Professor G. Nathansohn (Gruppo Lepetit SPA). The (+) enantiomer was in the form of the base (monohydrate) and the (−) enantiomer was the hydro-



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chloride and there was sufficient material for the preparation of small quantities of the methiodides. These had identical ir spectra (KCl disks) and mp 214–216° dec. The molar rotations ($c = 5 \times 10^{-2} M$, water) at 300 nm were estimated to be −635 and +669°

The affinity constants for the postganglionic acetylcholine receptors of the guinea-pig ileum at 37° were measured as described previously[2] in conditions in which the antagonists were allowed time to come into equilibrium with the tissue, with carbachol as the agonist and in the presence of hexamethonium. The results are shown in Table I, which includes values for (*R*)- and (*S*)-hyoscyamine to which the compounds bear some resemblance.

The enantiomeric forms of the base differ over 1000-fold in affinity, indicating their high stereochemical purity.[3] The stereospecific index is reduced 25-fold by methylation, however, which decreases the affinity of the more active enantiomer of the base whereas it increases the affinity of the less active enantiomer. As the compounds are amides of α-methyltropic acid, it is unlikely that quaternization has been accompanied by racemization or hydrolysis. The difference between the molar rotations suggests that the more active enantiomer may be slightly less stereochemically pure but this would make little difference to the stereospecific index and is almost certainly due to errors in the measurement of the rotations.

The values for the enantiomeric forms of hyoscyamine which have been included in Table I show that in spite of their superficial resemblance to the diazabicyclooctane compounds they have about ten times the affinity for the receptors. This may be because the amide link is less flexible than an ester group but, whatever the cause of the difference in affinity, it is remarkable that the bases with lower affinity are nevertheless highly stereospecific and that this stereospecificity is drastically reduced by methylation. Although the bases may not be completely ionized at pH 7.6, so the estimates of log affinity constant may be less than the true value for the ion, the stereospecific index should not be affected as both enantiomers will have the same pK_a It appears, then, that increasing the size of the onium group of the more active (−) enantiomer appreciably disturbs the binding to the receptor and possibly this disturbance is greater in the rather inflexible amides than in the esters, such as hyoscyamine methiodide where it may be offset to some extent by changes in conformation.

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Potential Organ- or Tumor-Imaging Agents. 14.† Myocardial Scanning Agents

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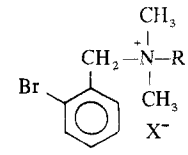
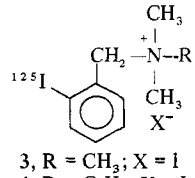
A γ-emitting radiopharmaceutical capable of selectively concentrating in cardiac muscle would be of potential clinical value for the diagnosis of a variety of myocardial disorders. Although several agents have undergone clinical evaluation, no myocardial scanning agent is currently available for routine clinical use.

Carr and associates[1-3] have made the most concerted effort to find a myocardial scanning agent. A survey of radionuclides among elements of group IA in the periodic table showed cesium-131 to be the most promising. Suitable myocardial scans in humans have been obtained within 3 hr after the administration of 1.25 mCi of carrier-free cesium-131.[2] Unfortunately, this radionuclide is also retained in skeletal muscle for a long period and prevents rescanning the patient for at least 5 weeks.[3]

The rather high uptake of Toluidine Blue by cardiac tissue following intravenous administration to rats[4] and dogs[5] prompted evaluation of radioiodinated Toluidine Blue as a myocardial imaging agent. Although preliminary results were encouraging, the use of this labeled compound required a priming dose of stable Toluidine Blue, a serious practical disadvantage.[3]



1, R = CH_3; X = I
2, R = C_2H_5; X = $CH_3C_6H_4SO_3$



3, R = CH_3; X = I
4, R = C_2H_5; X = I
5, R = H; X = Cl

As illustrated by previous papers in this series, our approach to specific organ- or tumor-localizing agents has been based to a considerable degree on well-established biochem-

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