N,O-Heterocyclics. **13** [1]. Isoxazolidinium Salts as Synthons to *N,N,O*-Trisubstituted Hydroxylamines

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Substituted isoxazolidinium salts react with lithium aluminium hydride to yield open-ring products which have hydroxylamine structures. The bimolecular reaction-mechanism has been investigated by substituent effect and the structure of the products ascertained by spectroscopic methods with the aid of the MIKE technique. The overall process of the ring-opening substitution is controlled by the polarisation of the C-N bond with steric and conformational factors acting mainly at the C-5 position of the nucleus. The mechanism of isoxazolidinium ion reaction defines the use of these synthons towards the synthesis of *N,N,O*-trisubstituted hydroxylamines and substituted 1,3-amino-alcohols.

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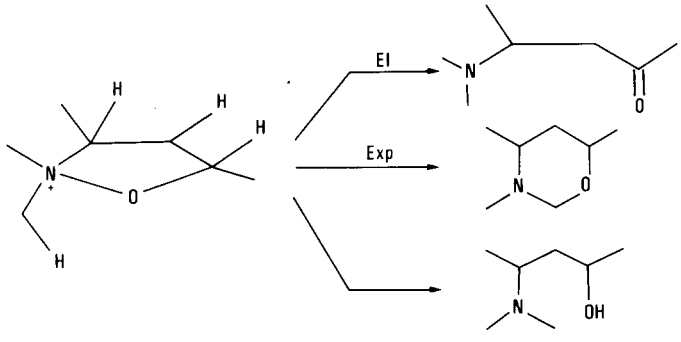
The products of [2 + 3]-cycloadditions show synthetic applicabiltiy when formed by the reaction of nitrones with alkenes and then modified to other functionalities which can serve as precursors of more complex reaction procedures [2]. The isoxazolidines are usually synthesized under mild experimental conditions and provide a novel approach to carbon-carbon formation, *via* a carbo-cyclic synthon. In the original derivative one substituted carbon atom belongs to the nitronic precursor and the other to the alkene. When isoxazolidines can be exploited in the field of the organic synthesis, the *N,O*-containing nucleus must be modified into open-chain products [3b].

The chemistry of isoxazolidinic derivatives whose general behaviour has been recently reviewed [3a] must be better investigated. A readily-available activation of the *N,O*-five membered ring can be obtained by simple procedures of quaternary ammonium ion formation [1]. It has been shown that the isoxazolidinium derivatives **1** thus obtained undergo ring opening either by basic attack [4-6] onto the hydrogen atoms adjacent to the nitrogen of the nucleus or by the reductive cleavage of the N-O bond to yield 1,3-amino-alcohols [7-10].

The conversion of the isoxazoline functional group into quaternary ammonium ions provides the possibility of modifying more bonds around the reactivity center which, according to the well-known chemistry of these species [11], is to be found in the positively charged nitrogen atom. Furthermore, the decomposition-reactions of the different ring-sized cyclic ammonium ions, have been recently investigated in terms of the structural and mechanistic effects on the competing paths of ring-opening substitution and elimination [12-14].

The ammonium group of the five membered ring containing N and O [1] should, in principle, increase the acidity of hydrogen atoms placed both on the α-carbon atoms around the nitrogen of the nucleus as shown below on C-3



and on the methyl groups [5]. Thermal decomposition of the ions **1** by basic reagents which attack the hydrogen atoms of C-5 [5,6] both β to the quaternary nitrogen, may well take place according to the Hofmann degradation scheme of the *N,O*-five membered nucleus. Most of the experimental evidences indicate that cyclic ammonium ions having isoxazolidinic structure **1** react with a variety of reagents essentially according to ring-opening elimination [5,6] (E1) and expansion [5] (Exp) *via* oxygen migration as shown in Scheme 1. When certain isoxazolidine derivatives are reduced with lithium aluminium hydride (LAH) [8,9], the amino-alcohols can be considered the result of a ring-opening nucleophilic substitution (S_N) onto the nitrogen atom of the nucleus **1**. Therefore, the substitution process itself must also be a reaction channel open on the cationic system **1** [1]. However, cyclic quaternary ammonium ions have shown a marked tendency for undergoing ring opening substitution reactions when, as in the case of the five membered systems [13], their reactivity is controlled by ring strain.

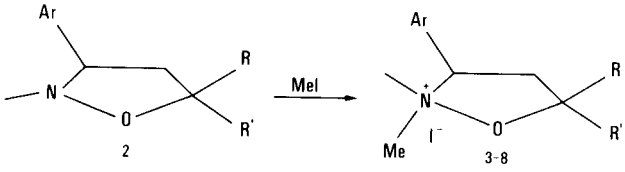
Formation of Some Isoxazolidinium Salts.

Certain substituted isoxazolidinium ions follow an alternative reaction path when the quaternary ammonium substrates **1** are made to react with a simple nucleophilic reagent like LAH. In this case substituted hydroxylamines

are synthesized [1].

Results and Discussion.

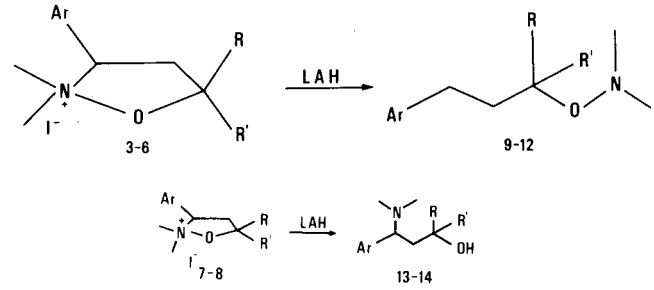
As described previously [1], substituted isoxazolidinium salts are easily prepared in an efficient way by dissolving **2** with a slight excess (*ca.* 10%) of methyl iodide in a few ml of carefully-dried diglyme: after proceeding for a few hours at room temperature an abundant yield of ammonium derivatives occurs. The isoxazolidinium salts **3-8** (Scheme 2) prepared according to this procedure and their corresponding yields are reported in Table 1. Since the signals of the nmr spectra of the salts **3-8** in the range 3.0-4.0 ppm are all four three-proton singlets, these can be assigned to the quaternary ammonium methyl groups. In fact, the starting isoxazolidines are mixtures of two epimers which result from a cycloaddition process. Consequently each epimer at C-5 should give two different methyl signals, as the situation around each methyl group, onto the nitrogen atom next to the chiral carbon at position 3 of the nucleus, is dissimilar.



Formation of Some Isoxazolidinium Salts

Compound No.	Ar	R	R'	Compound No.
3	Phenyl	Phenyl	H	**9**
4	*p*-Tolyl	*n*-Pentyl	H	**10**
5	*p*-Methoxyphenyl	*n*-Butyl	H	**11**
6	*p*-Methoxyphenyl	*n*-Pentyl	H	**12**
7	*p*-Tolyl	Phenyl	H	**13**
8	*p*-Methoxyphenyl	Phenyl	H	**14**

When the isoxazolidinium salts **3-8**, chosen by their substituent at C-3, react with LAH in suitable solvents the open-chain products **9-14** (see Scheme 3 and 4) are recovered after the conventional workup and are generally purified by preparative chromatography [15]; this process gives rise to a reasonably high yield in dimethoxyethane (DME) [1], lower yield is observed in THF (see below). The structure of the substituted hydroxylamines **9-12** and of the amino-alcohols **13, 14** are based on spectral information.



Since the isolated hydroxylamines appear to exert mutagenic effects [16], their relatively high volatility represents a serious drawback in the manipulation of the reaction product, purified and free of solvent. Therefore, the fraction containing the open-ring product after preparative chromatography has been treated with hydrogen chloride gas and the corresponding substituted hydroxylamine

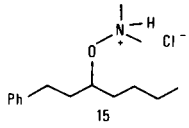
Table I

Formation of Some Isoxazolidinium Salts

Compound No.	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR cm^{-1}	^{1}H-NMR δ-Me
4	98	118-120	$C_{17}H_{28}INO$	52.44 52.53	7.20 7.04	3.60 3.71	3080-2800, 1600, 1455, 1360, 1220, 1190, 1020, 965, 860, 830, 730	3.2-3.9 3.5-3.8
5	98	oil	$C_{16}H_{26}INO_2$	49.10 49.23	6.65 6.48	3.58 3.49	3070-2800, 1600, 1510, 1455, 1310, 1255, 1180, 1020, 835	3.1-3.9 3.3-3.7
6	93	oil	$C_{17}H_{28}INO_2$	50.37 50.30	6.91 7.05	3.46 3.38	3080-2800, 1600, 1505, 1450, 1300, 1250, 1175, 1020, 945, 830	3.1-3.9 3.3-3.7
7	95	108-110	$C_{16}H_{22}INO$	54.68 54.49	5.57 5.54	3.54 3.46	3100-2730, 1600, 1450, 1220, 1015, 860, 825, 730	3.2-3.9 3.5-3.8
8	97	oil	$C_{16}H_{22}INO_2$	52.55 52.60	5.35 5.24	3.41 3.48	3100-2730, 1600, 1505, 1450, 1300, 1250, 1180, 1020, 830, 760	3.1-3.9 3.4-3.7

hydrochloride has been purified and characterized.

The hydroxylamine hydrochloride is more easy to handle. The nmr spectrum of the derivative **15** below reported show a marked downward shift of some of the original signals. A part from some minor modification of the other resonance absorptions, the major change in the nmr spectrum of the hydroxylamine **15** is observed in the chemical shifts of the Me-N, *i.e.* the singlet at 2.5 ppm for 6 protons becomes two singlets very close to each other at 3.1 and 3.0 ppm respectively. Also the methine at C-3 drifts towards lower field (a multiplet at 4.7-4.2 ppm) from the original position at the higher one, the same multiplicity at 3.7-3.5 ppm.



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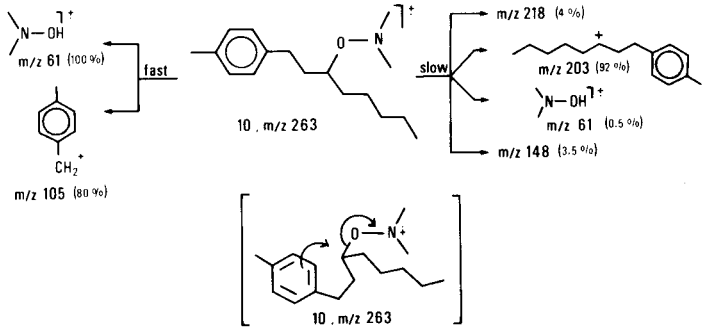
A much more simple experimental result is acquired when compound **10** hydrochloride is thermally desorbed under the electron-impact mass spectrometric conditions. The ms spectrum of **10** hydrochloride is here discussed as a model system. In fact what is essentially observed is the same ms spectrum of the original hydroxylamine **10**. The second most intense peak of the stable ion spectrum results the $C_8H_9^+$ (m/z 105, 80%) cation [17,18], which must be formed by a fast dissociative process with cleavage of the benzylic bond (see Scheme 5), directly in the ion source of the instrument with a reaction rate above 10^6. A competitive reaction path for the formation of m/z 105 from m/z 263 is below discussed. That this process does not occur from long lived m/z 263 ions is clearly demonstrated by the metastable ion analysis performed in a double focusing instrument with "inverse" geometry by the mass-analyzed ion kinetic energy (MIKE) technique [1]. The base peak of the ms spectrum results to be m/z 61 (100%), whose elemental composition is C_2H_6NO. This fragment derives from an elimination process of dimethylhydroxylamine radical cation, m/z 61, from the molecular ion m/z 263 (10%) directly, also at longer ion life time, between $10^{-6}-10^{-4}$ seconds. The counterpart of the molecular framework of **10** is seen at m/z 203 (8%). Thus, the ms spectrum is highly diagnostic for structural assignment of substituted hydroxylamines.



The MIKE analysis of some of the most important precursors and fragments, originated by unimolecular dissociation of the molecular ion **10**, is reported in Scheme 5. As can be observed by the comparison of the fast and slow unimolecular reactions of the ionized hydroxylamine **10**, the chemical behavior of the molecular ion is kinetically controlled by some stabilisation effect on the transition state for the attainment of cations m/z 203. In fact, while the formation of fragment ions m/z 61 is the most abundant process at high energy content of the precursor m/z 263, the same reaction, which must involve a tight transition state for the elimination of dimethylhydroxylamine radical cation, becomes the less favourite one when low energized ions are allowed to react in the second drift region of the instrument under the MIKE experimental conditions [17-21]. The stabilisation effect above involved may be seen in the anchimeric assistance of the tolyl group which is suitably placed γ to the carbonium ion center to participate in the formation of a novel five membered ring. The π-electrons of this aromatic substituent can become bonded or partially bonded to the carbon atom bearing the oxygen one, which is released as a radical stabilized by the adjacent low-pair of electrons on the nitrogen atom (see Scheme 5). Thus, the carbonium ion center of m/z 263 ion Scheme 5, stabilized in this way, exerts an increased rate of reaction due to the reduced enthalpy of activation, the entropy term being also that favoured by the cyclic structure of the transition state containing five atoms, even if the loss of degrees of rotational freedom works against this process at low energy the reacting system [20]. More information should be required in order to confirm the proposed mechanism for the unimolecular dissociation of the ionized hydroxylamines under investigation [1].

Some additional details on the chemistry of the precursor **10**, ionized under the electron-impact mode, can be derived from the further MIKE analysis of the product ions m/z 203. The MIKE spectrum is reported in the Figure.

Table II

Analytical Data for Substituted Hydroxylamines **10-12** and Amino-alcohols **13, 14**

Compound No.	Molecular Formula	Analysis % Calcd./Found C	H	N
10	$C_{17}H_{29}NO$	77.57	11.03	5.32
		77.53	11.08	5.28
11	$C_{16}H_{27}NO_2$	72.45	10.19	5.28
		72.41	10.22	5.24
12	$C_{17}H_{29}NO_2$	73.12	10.39	5.02
		71.98	10.44	5.11
13	$C_{18}H_{23}NO$	80.30	8.55	5.20
		80.25	8.63	5.07
14	$C_{18}H_{23}NO_2$	75.79	8.07	4.91
		75.68	8.15	4.83

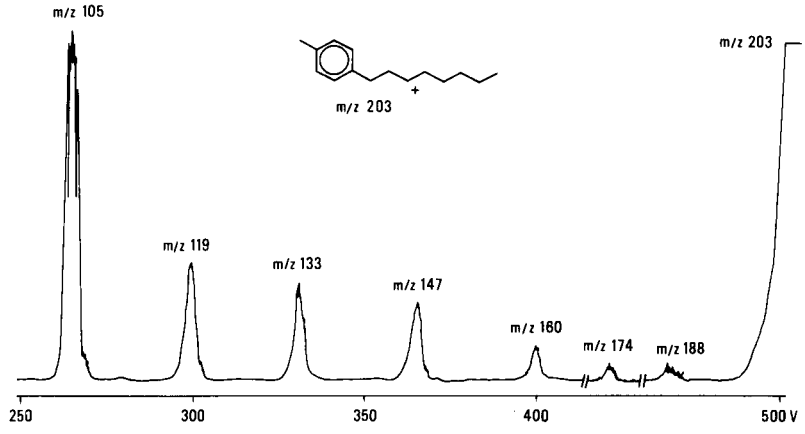


Figure. MIKE spectrum of m/z 203 precursor ion generated from ionized **10** hydrochloride.

As shown in Scheme 5, even if the precursor ions m/z 263 contain fully substituted nitrogen, the kinetically controlled dissociation of the molecular ions is characterized by loss of the $(CH_3)_2NO^{\cdot}$ radical which is still a cleavage β to the nitrogen atom with charge retention onto the moiety of those reacting ions having a greater degree of freedom. The ions m/z 203 thus formed react under the same experimental conditions losing methyl, ethyl and propyl radicals, in violation of the even electron rule [21]. This is in competition with the expulsion of butene, pentene, hexene and heptene.

The reaction of these new model isoxazolidinium systems occurring in THF solution may proceed by means of a mechanistic path similar to that already known [5]. This is essentially a Hofmann degradation activated by the action of a basic reagent onto the H-5 which in the case

Table III

Physical and Spectral Data for Substituted Hydroxylamines **10-12** and Amino-alcohols **13, 14**

Compound No.		IR, cm^{-1}	^{1}H-NMR Spectral Assignments, Chemical Shift	Mass Spectra m/z (relative intensity)
10	liquid	3130, 2700, 1510, 1465, 1420, 1330, 1260, 1220, 1090, 1030, 845, 810, 770, 690, 620	7.2-7.0 (4H, m, Ar-H), 3.7-3.3 (1H, m, 3-CH), 2.8-2.4 (2H, m , 1-CH_2), 2.5 (6H, s $N(CH_3)_2$), 2.3 (3H, s, Ar-CH_3), 2.1-1.5 (4H, m, 2,4$(CH_2)_2$), 1.4-1.1 (6H, m, 5,6,7 $(CH_2)_2$), 1-0.7 (3H, m, 8-CH_3)	263 ($M^{+\cdot}$, 9), 203 (8), 202 (5), 150 (5), 148 (5), 134 (5), 131 (8), 119 (6), 118 (6), 117 (5), 106 (12), 105 (79), 91 (5), 62 (13), 61 (100)
11	liquid	3020, 2980, 2925, 2900, 1600, 1510, 1470, 1420, 1260, 1220, 1030, 845, 810, 765, 690, 670, 620	7.5-6.6 (4H, m, Ar-H), 4.1-3.8 (1H, m, 3-CH), 3.8 (3H, s, OCH_3), 3.6-3.4 (2H, m, 1-CH_2), 2.7-1.5 (4H, m, 2,4 $(CH_2)_2$), 2.5 (6H, s, $N(CH_3)_2$), 1.5-1.1 (4H, m, 5, 6 $(CH_2)_2$), 1-0.7 (3H, m, 7-CH_3)	265 ($M^{+\cdot}$, 2), 205 (2), 204 (7), 203 (20), 161 (12), 147 (24), 122 (34), 121 (100), 108 (12), 107 (27), 92 (10), 91 (17), 77 (25), 61 (16)
12	liquid	3020, 2970, 2910, 1600, 1510, 1465, 1415, 1250, 1220, 1030, 845, 810, 765, 690, 670, 620	7.6-6.7 (4H, m, Ar-H), 4.1-3.8 (1H, m, 3-CH), 3.8 (3H, s, OCH_3), 3.6-3.4 (2H, m, 1-CH_2), 2.5 (6H, s, $N(CH_3)_2$) 2.8-1.5 (4H, m, 2,4 $(CH_2)_2$), 1.5-1.0 (6H, m, 5,6,7$(CH_2)_3$), 1-0.8 (3H, m, 8-CH_3)	279 ($M^{+\cdot}$, 5), 219 (9), 218 (19), 217 (35), 161 (6), 148 (6), 147 (35), 135 (8), 134 (9), 122 (13), 121 (100), 108 (6), 91 (11), 78 (5), 77 (10), 61 (23)
13	liquid	3370, 3100, 2800, 1600, 1445, 1200, 1150, 1050, 1020, 810, 750, 700	7.5-6.9 (9H, m, ArH), 6.1 (1H, sb, C-OH), 5.1-4.8 (2H, m, 1,3 $(CH)_2$), 4.1-3.4 (2H, m, 2-CH_2), 2.4 (3H, s, Ar-CH_3), 2.24 (3H, s, NCH_3), 2.20 (3H, s, NCH_3)	269 ($M^{+\cdot}$, 2), 224 (9), 149 (18), 148 (100), 132 (4), 119 (4), 118 (9), 117 (5), 107 (6), 105 (12), 91 (6), 79 (8), 77 (9)
14	liquid	3380, 3100, 2800, 1600, 1450, 1200, 1180, 1150, 1055, 1025, 815, 750, 695	7.5-6.7 (9H, m, Ar-H), 5.1-4.4 (2H, m, 1.3 $(CH)_2$), 4.8 (1H, sb, C-OH), 4.1-3.4 (2H, m, 2-CH_2), 3.7 (3H, s, Ar-CH_3), 2.24 (3H, s, NCH_3), 2.16 (3H, s, NCH_3)	285 ($M^{+\cdot}$, 1), 179 (12), 165 (10), 164 (42), 151 (13), 148 (13), 138 (29), 137 (35), 136 (13), 135 (31), 134 (23), 122 (18), 121 (100), 109 (31), 108 (29), 107 (43), 105 (26), 104 (20), 103 (11), 91 (31), 79 (44), 78 (29), 77 (61)

under investigation leads to aminoketones. The formation of products **9-12** from the methiodide precursors could be due to a different activation of the H-4 atom of the isoxazolidinium ring, where again a Hofmann mechanism is probably in operation, since the H-4 atom is β to the quaternary ammonium center [1]. The subsequent reduction of the double bond, initially placed in a polarized moiety [22], would then take place in solution in the presence of LAH, thus yielding the substituted hydroxylamine. If this mechanism does in effect operate during the ammonium cation transformation, some parallels might be drawn with the unimolecular reactions of similar gaseous systems [19]. If this were the case, an intramolecular attack of the nitrogen onto the H-4 atom would result in the formation of the products [19].

Labelling experiments using lithium aluminium deuteride (LAD) as a reagent, have provided detailed information on the reaction mechanism controlling the ring-opening of the substituted isoxazolidinium ions studied. In fact, if LAH acts as base in the first step of the reaction sequence, deuterium atoms should not become incorporated in the primary product of the process during the step, where LAD is employed. On the contrary, deuterium atoms should be found at the appropriate position of those final products having hydroxylamine functional groups, since the tracer would, according to previous results [22], be introduced at β-position with respect to the oxygen during the reductive step of the process.

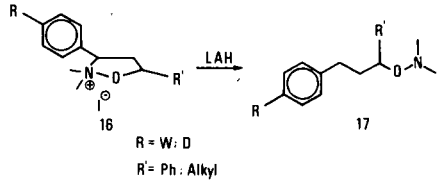
The labelling experiment has shown that the deuterium atom is introduced into the reaction product and that its position is γ with respect to the oxygen atom [1].

The further experiment definitively confirmed that a Hofmann-like mechanism cannot occur under the reaction conditions described for the ring-opening of isoxazolidinium salts **3-6**. This all confirms that the novel ring-opening reaction must occur under the experimental conditions so far described also for **3-6**. The more rational route from the precursor isoxazolidine salts **3-5** to compounds **9-12** would appear therefore to be that depicted in Scheme 6. Those experiments yielding the open-chain products **9-12** reveal that, independently from substitution on C-3 the reacting system **1** undergoes facile ring-opening substitution

rather than elimination or expansion as shown in Scheme 1. This also occurs in the case of other five membered ring ammonium salts [12,13]. Even when the reacting center of the nucleus is a polysubstituted carbon atom, where the benzylic position favours double bond formation for its steric crowding and conjugation, the process is highly competitive with all other possible reaction paths. It has in fact been shown [1], that nucleophilic substitution at C-3 of the isoxazolidinium ring occurs with a reasonably high yield when DME is used, except in the case of the precursor with two substituent groups at C-5, where a marked decrease in the corresponding hydroxylamine derivative has been observed. The only difference occurring is the structural change at position 5 of the starting reagent. The different reactivity observed for this isoxazolidinium derivative has been ascribed to factors affected by the steric and conformational requirements [13] of the transition state for the substitution process, since the ring-strain remains unaltered [1].

The new isoxazolidinium systems studied here, *i.e.* **3-8** in Scheme 2, give a further insight into the chemistry of the synthons investigated. In fact, while the different reaction yielded for the precursor mentioned above was interpreted as due to some crowding of the reacting center at C-3 of the *N,O*-five membered ring **1**, the new experimental results, here reported, clearly show the electronic effect which is in operation when the ring-opening substitution of isoxazolidinium salts takes place *via* LAH treatment.

The reaction leading to the formation of substituted hydroxylamines, shown in Scheme 3, appears to be less efficient than that performed on differently substituted substrates [1], where the aromatic group at C-3 bears electron-withdrawing substituents. This effect seems to be due to both the substituents on C-3 and the reacting medium chosen, *i.e.* THF instead of DME. When the aromatic substituent linked to the reacting center, shown in Scheme 7,



carries an electron-withdrawing group (W), *i.e.* Cl at the *p*-position and R′ = *n*-butyl, the reaction yield of the ring-opening substitution leading to the hydroxylamines is among the highest observed after 5 hours reaction time; greater than 85% [1] in DME, being 56% when THF is used as solvent, the other experimental conditions being unchanged. However, the new model system, here reported, clearly demonstrates a marked trend toward a decrease in reactivity, when the same group on the aromatic substituent becomes electron-donating, *i.e.* *p*-Me and *p*-MeO.

In order to observe and appreciable effect which can operate in modifying the reaction rate of the ring-opening substitution of the isoxazolidinium salts studied, the reaction conditions have been chosen with regard to the possible attenuation of the excess energy of the transition state for the process leading to the formation of substituted hydroxylamines **9-12**. Since it is well known that substitu-

tion processes are more competitive at low reacting temperature, the experiments have been carried out in THF solution, thus decreasing the reaction temperature which, as expected, reduces the overall reaction rates. In fact, in addition to the experimenal results mentioned above, the different medium effect can also be qualitatively considered observing the reaction yield after the same reaction time (7 hours). When THF is used as solvent, the precursor **16** (R = H and R′ = Ph, **3**) gives 26% of the corresponding hydroxylamine **17**, 60% being the yield in DME after 7 hours. Thus correlation has been made assuming that electrostatic interactions are the dominant influence on the reaction rates of the ring-opening substitution of the isoxazolidinium salts **3-8**, due to the solvent effect. The media used for the process under investigation are both polar and aprotic solvents, *i.e.* THF and DME, and the dielectric constant-reaction rate correlation should hold, even being aware of the well knwon limitation of this approach. Therefore, the new experimentals have been performed in THF at 67° *ca.* ($\epsilon^{50°}$ = 6.0) in comparison with those carried out in DME at 85° *ca.* ($\epsilon^{50°}$ = 5.8), thus assuming that the temperature effect is the only one to be in operation. The mechanistic implication of the use of the THF as solvents is also discussed below.

The ring-opening of the isoxazolidinium salts **3-6** occurs through the nucleophilic substitution of LAH on the C-3 of the *N,O*- containing nucleus of Scheme 3, under the same experimental condition, with a completely different rate according to the electronic effects of the substituent group on the *p*-position of the aromatic moiety at C-3. In fact, when R = H and R′ = Ph; *n*-butyl, the reactions under study are completed after 7 hours with 26% and 60% yield respectively, while with R = Cl and R′ = Ph; *n*-butyl, the isoxazolidinium precursors react faster than the previously mentioned ones. All the starting materials are completely converted in 5 hours, instead of 7 with an overall yield which was observed to be 58% and 85% in DME [1], being 28% and 56% in THF for R′ = Ph and *n*-butyl respectively. On the other hand, a marked decrease of the reaction rate of precursor **16** can be clearly observed when the tolyl group replaces the phenyl one at C-3 of the *N,O*-five membered heterocyclic ring system of Scheme 7. The experimental yield for the latter precursor with R′ = *n*-butyl results 89% in DME and 61% in THF after 7 hours of reaction time, while the isoxazolidinium derivative **16**, where R = Me and R′ = *n*-butyl, generates the corresponding hydroxylamine **17** which results to be 70% (in DME) and 47% (in THF) of the reaction mixture. Similar experimental data have been obtained when **16** is substituted at C-3 and C-5 with R = H and R′ = *n*-pentyl, the yield being 80% in DME and 58% in THF.

A different replacement of a *p*-hydrogen atom of the phenyl group linked at C-3 of the isoxazolidinium nucleus **16**, see Scheme 7, by a methoxy substituent produces a further fall in the reactivity; apparently other reaction channels being populated in this case in competition with the ring-opening nucleophilic substitution under investigation. The reactivity of the isoxazolidinium salts **16**, where R = MeO and R′ = *n*-butyl; *n*-pentyl, follows the same trend observed for the tolyl derivatives (see above). Electronic effects on the reacting center at C-3 of the *N,O*--five-membered nucleus **16** affect the rate of the substitution reaction obtained by the LAH attack, owing to the well known characteristics of the *p*-MeO-C_6H_4 substituent group. The electronic effect of the MeO moiety is transmitted towards the C-3 position by the operation of the conjugative mechanism, thus, causing these derivatives to undergo ring-opening reaction at a much slower rate than the corresponding substrates with R = H and Cl. In fact, compounds **5** and **6** undergo substitution reaction with an overall yield of 35% and 31% in THF respectively, giving rise to products **11** and **12**. Similar observation can be drawn comparing the latter experimental results with those obtained with precursors discussed above, when R = Me in **16** of Scheme 7.

Some generalisation of the electronic effect of the ring-opening nucleophilic substitution, occurring when the nucleophile LAH attacks the *N,O*-five-membered nucleus of the precursor **1**, as shown in Scheme 3, can thus be attempted. The mechanism of transmission of the electronic effect by delocalisation allow the electron-withdrawing substituent, *i.e.* Cl, to increase the reactivity of the isoxazolidinium salts **16** towards LAH, generating substituted hydroxylamines **17** in good yield, both in DME and THF, at a shorter reaction time. On contrary, the electron donating substituents, *i.e.* Me and MeO, give rise to a consistent rate decrease.

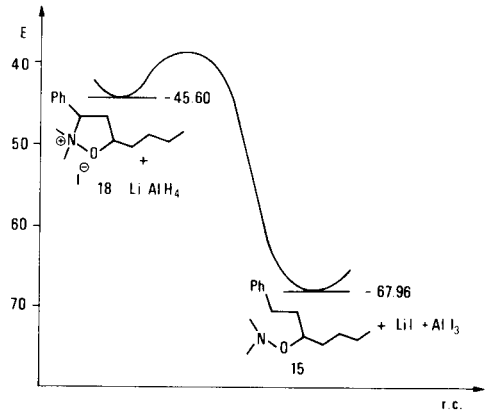
The structural modification of precursors **1** at position 5, above quoted and clearly observed in DME [1], induces a striking influence in the reactivity, as is confirmed by the experiments previously discussed and performed in the different medium, *i.e.* THF. Further data, shown in Scheme 4, are commented below.

However, the conclusion that has been drawn above, according to the electronic effects experimentally observed, is in striking contrast with the generally accepted electrostatic interaction through space exerted in S_N2 processes. In this case, the positive charge development on the carbon reactive center can be stabilized by electron-donating substituents and destabilized by electron-withdrawing ones.

The ring-opening process of the isoxazolidinium system **1** under investigation can be seen as a dealkylation of a quaternary ammonium salt [23], where three substituents are carbon atoms and one is oxygen. The latter reaction has received considerable attention and several reagents were used in order to obtain the displacement of the *t*-amine leaving group [24]. Some halides undergo also substi-

tution reaction with LAH [25]; for this process the S_N2 mechanism has been proposed [26]. However, a detailed study of the latter mechanism has not yet been performed and the simple nucleophilic displacement on carbon atom seems not applicable [27]. The reaction of quaternary ammonium salts to the corresponding amines by LAH treatment has been postulated to occur *via* S_N2 mechanism [24]. The experimental results here reported indicate that the simple S_N2 process is evidently not the only mechanism which governs the formation of substituted hydroxylamines from precursors **3-6** by LAH treatment.

In order to explain the substituent effect on the reactivity of the isoxazolidinium synthons **3-6** and previously investigated [1], the nature of reagents can be important to the establishment of the most probable transition state. Therefore, the experiments here described have been carried out in THF, as discussed above and are reported in the experimental section. The change of the solvent in the procedure chosen does not alter the previously reported data [1], which show the consistency of the experiment in both solvents used, *i.e.* DME and THF. The solvent now employed with appropriate concentration of LAH, *i.e.* $3 \times 10^{-2}M$, permits to assume that LAH is better described as solvent-separated ion pair [28]. Moreover, since lithium aluminum hydride has been shown to be more reactive than sodium aluminum hydride towards the same ketone, the polarisation of the carbonyl bond has been taken as the explanation of the difference during the well studied reaction of complex metal hydrides with ketones [29]. Experimental observation on the latter processes are consistent with a mechanism for the common LAH reaction with ketones where an exothermic process should take place with low activation energies [29]. Thus, on the basis of the Hammond principle, the transition state should resemble the starting reagents and reflect the structural features that are present in the precursors of the reaction. When the reactant isoxazolidinium salt is a relatively good electrophile at C-3 of the nucleus **16**, so that hydride-transfer from LAH to the reacting center is energetically more favourable, the transition state for the ring-opening substitution should be reagent-like. This requires that the process under investigation should be exoenergetic. In order to gain more information on the course of the ring-opening reaction, a model energy diagram has been constructed to ascertain whether the hydroxylamine and the other reaction products are thermodynamically more stable than the isoxazolidinium reactants. The approximate standard heat of formation (ΔH_f°) for the comparison of the reactants, *i.e.* the chosen isoxazolidinium salt **18** and LAH, and reaction products, *i.e.* the hydroxylamine **15** and the lithium and aluminium salts reported in Scheme 8, has been calculated using the known values for lithium iodide, aluminum iodide, hydroxylamine hydroiodide and hydroxylamine [30] and for lithium aluminum hydride [31].



The resulting ΔH_f° for **18**, *i.e.* -38.60 Kcal mole^{-1} at 298°K, and for **15**, *i.e.* -32.96 Kcal mole^{-1} at 298°K, has been obtained by the application of the Group method [32]. Conventional ring strain energy (CRSE) for the isoxazolidinium salt **18** has been considered as the average of the known values for THF and pyrrolidine [32b]. This assumption on the CRSE leads to an underestimation of the resulting ΔH_f°, since some of the vibrational and rotational degrees of freedom of the *N,O*-five-membered nucleus are blocked as a consequence of the nitrogen alkylation. This is clearly confirmed by the nmr data reported in Table 1.

The two main concepts, above mentioned, related to the reactivity of LAH towards ketones can now be applied to the action of the same reagent on the isoxazolidinium salts studied. Assuming that the counter ion is mainly solvated, the hydride anion attacks more easily the substrate which shows a large degree of polarisation at the reacting center on C-3 of the *N,O*-five-membered nucleus. This implies a lower enthalpy of activation for the reaction of LAH with isoxazolidinium precursors having R = W, see Scheme 7, and an early, reactant-like transition state, as shown in Scheme 8, in which the entering hydride group approaches the soft acid center at C-3, while, when R = D, the ring-opening substitution becomes less competitive, due to the lower polarisation of the C_3-N bond.

The structural effect on the reaction rate of the ring-opening substitution of the isoxazolidinium salts **1** is also clearly observed when the same modifications are introduced at C-5. The different reactivity, revealed on going from R = aryl to R = alkyl, with R′ = H (Scheme 3), has been already experimentally evidenced in both DME [1] and THF solvents. The most dramatic change is, however, here ascertained, when both structural effects are exerted, *i.e.* on C-3 and on C-5. Therefore, the isoxazolidinium precursors **7** and **8**, where Ar is *p*-tolyl and *p*-$MeOC_6H_4$, R = Ph and R′ = H, react under the experimental conditions here defined giving rise to the substituted amino-alcohols **13** and **14** only. The more hindered substituent on C-5 induces, therefore, a high restriction towards the attainment

of the transition state for the ring-opening substitution of the isoxazolidinium salts studied.

Conclusion.

The bimolecular reaction of LAH with isoxazolidinium salts proceeds through the action of the nucleophilic reagent onto the C-3 position of the ring: the C-N bond cleavage occurring brings about the formation of open-chain products of substituted hydroxylamine structure. The overall process can be described as a ring-opening substitution which is also controlled by the polarisation of the C-N bond with steric and conformational factors reducing also the competitivity of the reaction. The activation of isoxazolidinic functionalities as synthons by methiodide formation can then be exploited in the preparation of hydroxylamines and amino-alcohols. The novel mode of synthesizing substituted acyclic hydroxylamines [33] develops with the α- and β-carbon atoms belonging to an alkene and the γ to an aldehyde, while the *N,O*-moiety is derived from a simple hydroxylaminic precursor.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Analyses were performed on a Perkin-Elmer 240 elemental analyzer. The ir spectra were measured on a Perkin-Elmer 377 and nmr on a Varian EM 360 using tetramethylsilane as internal standard. Mass spectra were performed on a Varian MAT CH-5 DF spectrometer, operating at 70 eV, 3 kV and an ion source temperature of 200°. Samples were introduced *via* the direct inlet system with the insertion probe kept at a low temperature. MIKE spectra were measured as previously described [20].

Substituted isoxazolidines were prepared according to previously reported methods [34].

General Procedure for Isoxazolidine Methiodide Formation.

To a solution of substituted isoxazolidine (3 mmoles) in 3 ml of dry diglyme 3 mmoles of methyl iodide with 20 % excess were added. The solution was stirred at room temperature for 7 hours. A yellow oil was separated by adding petroleum ether, which sometime crystallized to give a yellow solid, whose yield and mp data are reported in Table 1. Isoxazolidinium salts **3-10** are very hygroscopic and, therefore, must be carefully treated to preserve them as crystals.

Similarly, the products can be obtained by treating isoxazolidine (3 moles) with 2 ml of methyl iodide overnight at room temperature after ether addition. The yield increased by about 5%.

Reaction of Isoxazolidinium Salts With Lithium Aluminium Hydride.

A solution of isoxazolidinium salt (2 mmoles) in dry tetrahydrofuran (18 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1 mmole) in dry THF (5 ml). The mixture was then refluxed for 7 hours, cooled, and decomposed by the cautious addition of a 10% solution of sodium hydroxide. The alkaline solution was extracted with ether. The combined extract was dried (sodium sulphate) and the solvent removed under vacuum. The recovered oil was then purified by column chromatography [15] under slight pressure to yield the expected substituted hydroxylamine (**19**, 26%; **10**, 43%; **11**, 35% and **12**, 31%). The physical properties of the *N,N,O*-trisubstituted hydroxylamines, as those prepared according to the experimental procedure described above and isolated as liquid, are in agreement with literature data [33], since substitution on oxygen should result in a lowering of the boiling point of the products.

The same experimental procedure was followed to isolate the amino-alcohols **13**, 85% and **14**, 80%. The hydroxyl amine hydrochlorides have been prepared by bubbling hydrogen chloride gas into the solution of the products after preparative chromatography.

All those compounds which had not previously been prepared gave satisfactory analytical data and ^{1}H nmr, ir and ms spectra, which are reported in Tables II and III.

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