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# N,O-HETEROCYCLICS-12[1]

## FACILE RING OPENING OF SOME ISOXAZOLIDINIUM IONS

ANGELO LIGUORI, GIOVANNI SINDONA and NICOLA UCCELLA*
Dipartimento di Chimica, Università della Calabria, I-87030 Arcavacata di Rende (CS), Italy

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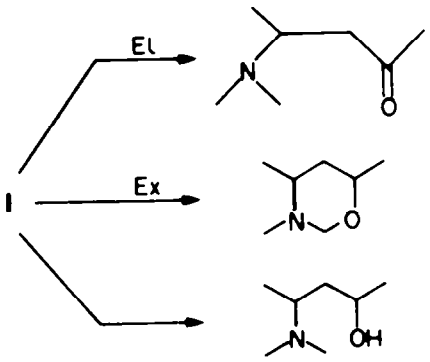
**Summary**—Substituted isoxazolidinium salts react with $LiAlH_4$ to yield ring opened hydroxylamines. The novel bimolecular reaction mechanism has been investigated by deuterium labelling and the structure of the products ascertained by spectroscopic methods with the aid of the MIKE technique. The overall process can be defined as a ring-opening substitution, which is controlled by steric and conformational factors that tend to prevent the alternative Hofmann-like degradation of the salts.

It has been recently shown that certain products of [2 + 3]-cycloadditions have great synthetic potentiality particularly when formed by the reaction of nitrones with alkenes and then converted to other functionalities which can be used as precursors of more complex reaction procedures.[2] The isoxazolidines thus obtained under mild conditions provide a novel approach to carbon-carbon bond formation, *via* a carbocyclic synthon, where one substituted carbon atom is provided by the nitronic precursor and the other by the alkene. If substituted isoxazolidines are to be utilized in the field of organic synthesis the product must be converted into open-chain products. Greater attention must, therefore, be paid to the chemistry of isoxazolidines, whose general behaviour has been recently reviewed.[3] Activation of the N,O-five membered ring can be achieved by simple procedures of quaternary ammonium ion formation. 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 reductive cleavage of the N–O bond to yield 1,3-amino alcohols.[7-10]

The transformation of the isoxazolidine functional group into quaternary ammonium ions provides the possibility of modifying more bonds around the reactivity centre 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]

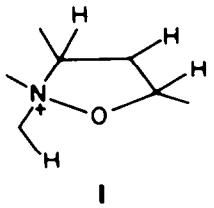
The positively-charged ammonium group of the five membered ring containing N and O (1) should, in principle, increase the acidity of hydrogen atoms placed both on the $\alpha$-carbon atoms around the nitrogen of the nucleus as shown below on C-3 and on the methyl groups.[5] Moreover, thermal decomposition of 1 by basic reagents which act on the hydrogen atoms of C-4 and C-5[5,6] $\beta$ to the quaternary nitrogen may well occur by the Hofmann degradation. The experimental evidence currently available indicates that the reactions of cyclic ammonium ions having isoxazolidinic structure 1 with a variety of reagents are essentially ring -opening eliminations[5,6] (El) and expansion[5] (Ex) via oxygen migration as shown in Scheme 1. If the formation of amino-alcohols




Scheme 1.

occurring when certain derivatives are reduced with lithium aluminium hydride (LAH)[8,9] can be considered the result of a ring-opening nucleophilic substitution ($S_N$) onto the oxygen atom of 1, then the substitution process itself must also be a reaction channel open on the cationic system 1. However, cyclic quaternary ammonium ions have shown a marked preference for undergoing ring opening substitution reactions when, as in the case of the five membered systems,[13] their reactivity is controlled by ring strain.

It has been discovered that 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 a substantial yield of substituted hydroxylamines is to be observed.

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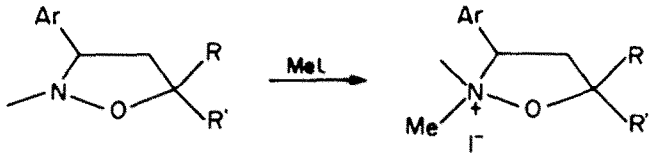
### RESULTS AND DISCUSSION

As described in the experimental section substituted isoxazolidinium salts are easily prepared in an efficient way by dissolving slight excess (10% *ca.*) of methyl iodide in a few mls of carefully dried diglyme: after proceeding for a few hours at room temperature an abundant yield of ammonium derivatives occurs. The isoxazolidinium salts 3–10 (Scheme 2) obtained according to this procedure and their corresponding yields are




2 3-10

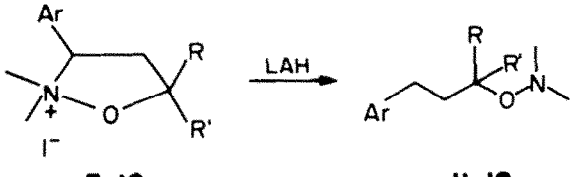
Scheme 2.

Table 1. Formation of some isoxazolidinium salts

| Compound | Ar | R | R' | yield(%) | m.p.° | δ-Me |
|---|---|---|---|---|---|---|
| 3 | Ph | Ph | H | 90 | — | 3.2; 4.0<br>3.5; 3.8 |
| 4 | Ph | n-$C_4H_9$ | H | 92 | — | 3.2; 4.0<br>3.4; 3.8 |
| 5 | Ph | n-$C_5H_{11}$ | H | 95 | — | 3.1; 3.9<br>3.3; 3.7 |
| 6 | Tol | n-$C_4H_9$ | H | 91 | — | 3.1; 3.9<br>3.3; 3.7 |
| 7 | p-$ClC_6H_4$ | Ph | H | 94 | 81–83 | 3.2; 4.0<br>3.4; 3.8 |
| 8 | p-$ClC_6H_4$ | n-$C_4H_9$ | H | 96 | — | 3.2; 3.9<br>3.3; 3.7 |
| 9 | p-$ClC_6H_4$ | n-$C_5H_{11}$ | H | 95 | — | 3.2; 3.9<br>3.4; 3.8 |
| 10 | Ph | Ph | Me | 93 | 163–165 | 3.0; 3.9<br>3.4; 3.7 |

reported in Table 1. Since the signals of the NMR spectra of the salts **3–10** 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.

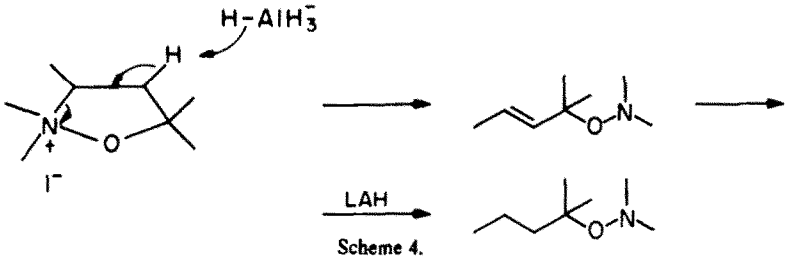
When the isoxazolidinium salts **3–10** thus obtained are allowed to react with LAH in suitable solvents the open-chain products **11–18** (see Scheme 3) are recovered in high yields after the conventional workup and are generally purified by chromatography.[15] The structure of the substituted hydroxylamines **11–18** was determined by spectroscopic methods.




3-10 11-18

Scheme 3.

The reaction of model isoxazolidinium systems occurring in 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 H-5 which in the case under investigation leads to aminoketones. On the other hand, the formation of products **11–18** 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 $\beta$ to the quaternary ammonium centre (see Scheme 4). The subsequent reduction of the double bond, initially placed in a polarized moiety,[16] would then take place in solution in the presence of LAH, thus yielding the substituted hydroxylamine, as shown in Scheme 4. If this mechanism does in effect operate during the ammonium cation transformations so far studied, some parallels might be drawn with the unimolecular degradation of similar systems reacting in the gas-phase.[17] If this were the case, an



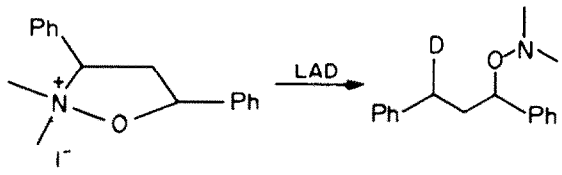

Scheme 4.

intramolecular attack of the nitrogen onto the H-4 atom would result in the formation of the products.[17]

Labelling experiments using lithium aluminium deuteride (LAD) as a reagent, can provide 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 as described in Scheme 4, 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,[16] be introduced at $\beta$-position in respect to the oxygen during the reductive step of the process.

The experimental results from LAD treatment of precursor **3** are interpreted on the basis of mass spectral and NMR data. Mass spectral examination of the major reaction product shown in Scheme 3, obtained from compound **3**, i.e. **11**, reveals a molecular ion *m/z* 255 of low abundance (7% of the base peak being *m/z* 91) which, decomposing at longer life time in the second drift region of the double focussing instrument used,[18] gives rise to fragment ions *m/z* 195 (86% in the stable ion spectrum and 92% in the MIKE spectrum being *m/z* 61. 8%). As shown in Scheme 5, even if the precursor ions *m/z* 255 contain fully substituted nitrogen, the kinetically controlled dissociation of the molecular ions is characterized by loss of the $(CH_3)_2NO$ radical, which is still a cleavage $\beta$ to the nitrogen atom with charge retention onto the moiety of those reacting ions having a greater degree of freedom. The ions *m/z* 195 thus formed react under the same experimental conditions losing both the methyl and ethyl radicals, in violation of the even electron rule.[19] This is in competition with the expulsion of benzene and styrene. Since neither of these eliminations involves an intramolecular rearrangements prior to the dissociative process, they can provide valuable information concerning the location of the labelling species when the deuterated reagent is used. In fact, the most abundant unimolecular dissociation of precursor ions *m/z* 195 is the elimination of benzene which can be assumed to proceed through the expulsion of a phenyl group with an adjacent hydrogen atom. Furthermore, the formation of $C_7H_7^+$ cations from *m/z* 195 precursors can be considered simply as a heterolytic process occurring through the expulsion of styrene molecules whilst the $C_7H_7$ moiety remains intact.

On the basis of the above reported discussion, the experimental data, obtained by analysing product **19** (see Scheme 6) recovered by LAD treatment of salt **3** under

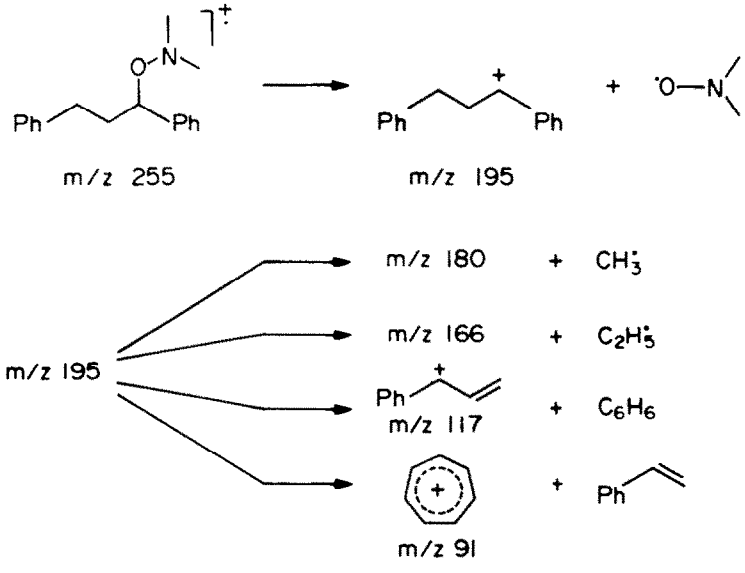



**3** **19**

Scheme 6.

the electron impact ionization mode, show the presence of molecular ions at *m/z* 256 (5% of the base peak being *m/z* 92) which decompose under MIKE conditions to give ions *m/z* 196. These, then, react at longer life time and produce fragment ions of diagnostic value *m/z* 118 and *m/z* 92, whose relative abundance is 52 and 15% respectively.

The above reported conclusion, which is based on mass spectral data, can be further checked by analyzing the NMR spectra of compounds **11** and **19** respectively. A multiplet at $\delta$ 2.5 ppm, corresponding to two protons, can be assigned to the methylene at the $\gamma$-C position with respect to the oxygen atom of molecule **11**. The corresponding $\beta$-methylene and $\alpha$-methine groups show a multiplet at $\delta$ 1.9 ppm and a triplet at $\sigma$ 4.4 ppm. The remaining, readily-characterizable absorptions in spectrum **11**, appear at $\delta$ 7.2 and 2.4 ppm and can be attributed to the aromatic and N-methyl protons. The equivalent position for the NMR absorption assignable to the $\gamma$-methylene group of compound **19** reveals on inspection a triplet at $\delta$ 2.5 ppm and, consequently, a quartet at $\delta$ 1.9 ppm and a triplet at $\delta$ 4.4 ppm for the $\beta$-methylene

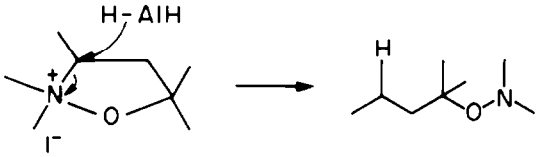



Scheme 5.

and $\alpha$-methine groups. The decreased multiplicity of the absorptions at $\delta$ 2.5 and 1.9 ppm in spectrum **19** with the signal at $\delta$ 4.4 ppm unaltered, clearly confirms the structural assignment based on the above-mentioned mass spectral data.

However, since the Hofmann-like mechanism for the ring-opening olefin-forming elimination of **3** has been based on previously reported experimental results[16] which refer to a differently-substituted double bond where only the electronic environment is similar, the above mentioned reductive step might well occur differently with the deuterium atoms attached to the $\gamma$- rather than the suggested position $\beta$ in respect to the oxygen. Should this be the case the mechanism of Scheme 4 would still be operative with only the final step changed, i.e. the reduction of the conjugated double bond of the substituted hydroxylamine: further experiments could clarify the exact procedure responsible for the formation of product **11** from **3** by LAH treatment. In fact, if the last step in the reaction shown in Scheme 4 is due to a reduction of the double bond present in the intermediate molecule hydrolysis of the reduction complex intermediate should give rise to the introduction of deuterium atoms when a particular reagent sequence such as LAH followed by $D_2O$ is chosen.

The isolated reaction product of **3** treated with LAH and then hydrolized with $D_2O$ was compound **11**: deuterium incorporation can therefore be excluded. The experiment definitively confirms that the mechanism in Scheme 4 cannot occur under the reaction conditions described for the ring-opening if isoxazolidinium salts **3–10**. This all indicates that a novel ring-opening reaction must occur under the experimental conditions so far described. A more rational route from the precursor isoxazolidine salts **3–10** to compounds **11–18** would appear therefore to be that depicted in Scheme 7.




Scheme 7.

Those experiments yielding the open-chain products **11–18** reveal that in some instances 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] The process is highly competitive with all other possible reaction paths even when the reacting centre of the nucleus is a polysubstituted carbon atom with the benzylic position favouring double bond formation because of steric crowding and conjugation. We have shown (experimental section) that nucleophilic substitution at C-3 of the isoxazolidinium ring occurs with a reasonably high yield, except in the case of precursor **10**, where a marked decrease in the corresponding hydroxylamine derivative is to be observed: the only difference is the structural change at position 5 of the starting reagent. The different reactivity observed for **10** may therefore be 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. Such a proposal requires further investigation in order to discriminate between the different factors controlling the chemical behaviour of system **1**.

## 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 steric and conformational factors that reduce the competetivity of the reaction. The activation of isoxazolidinic functionalities as synthons by methiodide formation can then be exploited in synthesizing substituted hydroxylamines where the $\alpha$- and $\beta$-carbon atoms belong to an alkene and the $\gamma$ to an aldelyde, while the N–O moiety derives from a simple hydroxylaminic precursor.

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 377 instrument and NMR on a Varian EM360 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.[18]

Substituted isoxazolidines were prepared according to previously reported methods.[20]

*General procedure for isoxazolidine methiodide formation*

To a solution of substituted isoxazolidine (3 mmol) in 3 ml of dry diglyme 3 mmol of methyl iodide with 20% excess were added. The solution was stirred at room temperature for 7 h. A yellow oil was separated by adding petrol ether, which sometime crystallized to give a yellow solid, whose yield and m.p. data are reported in Table 1.

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

*Reaction of isoxazolidinium salts with* $LiAlH_4$

A solution of isoxazolidinium salt (2 mmol) in dry dimethoxyethane (3 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1 mmol) in dry dimethoxyethane (5 ml). The mixture was refluxed for 7 h, cooled, and decomposed by the cautious addition of NaOH 10% solution. The alkaline solution was extracted with ether. The combined extract was dried ($Na_2SO_4$) and the solvent removed under vacuum. The oil recovered was then purified by colum chromatography[15] under slight pressure to yield the expected substituted hydroxylamine (**11**, 70%; **12**, 89%; **13**, 80%; **14**, 75%; **15**, 60%; **16**, 85%; **17**, 83%; and **18**, 39%).

The isoxazolidinium salt **3** was also treated with lithium aluminium deuteride under the same experimental conditions described above to give N,N-dimethyl-O-1,3-diphenyl-3-$^2H_1$-n-propylhydroxylamine **19** (68%). When **3** was made to react as reported above but with the workup modified by the addition of NaOD 10% solution in $D_2O$ to hydrolyse excess hydride, the previously separated product **11** was recovered.

All those compounds which had not previously been prepared gave satisfactory $^1H$ NMR, IR and mass spectra, reported in Table 2.

Table 2. Physical and spectral data for substituted hydroxylamines **11–18**

| Compound | | IR, $cm^{-1}$ | $^1H$ NMR spectral assignments, chemical shift, $\delta$ | Mass spectra *m/z* (rel. intensity) |
|---|---|---|---|---|
| **11** | oil | 3080, 2720, 1590, 1480, 1435, 1345, 1200, 1090, 970, 910, 695. | 7.6–6.8 (10H, m, ArH) 4.4(1H, t, 1-CH), 2.7–2.3 (2H, m, 3-$CH_2$), 2.4(6H, s, $N(CH_3)_2$), 2.2–1.6(2H, m, 2-$CH_2$). | 269($M^+$,3), 195(11), 194(7), 118(24), 116(6), 92(11), 91(100), 65(5), 61(45), 60(8) |
| **12** | oil | 3100, 2790, 1600, 1475, 1460, 1390, 1340, 1040, 1010, 760, 705. | 7.2–6.8(5H, m, ArH), 3.7–3.5(1H, m, 3-CH), 2.8–2.5(2H, m, 1-$CH_2$), 2.5 (6H, s, $N(CH_3)_2$), 2.0–1.5(4H, m, 2.4-$(CH_2)_2$), 1.4–1.2(4H, M, 5.6-$(CH_2)_2$), 1.0–0.8(3H, m, 7-$CH_3$) | 235($M^+$, 4), 117(5), 105(11), 104(6), 92(11), 91(96), 77(5), 65(7), 62(14), 61(100), 60(26), 55(8). |
| **13** | oil | 3080, 2720, 1490, 1445, 1390, 1330, 1210, 1060, 1010, 760, 710. | 7.2–7.0(5H, m, ArH), 3.7–3.2 (1H, m, 3-CH; 2.8–2.4 (2H, m, 1-$CH_2$), 2.5(6H, s, $N(CH_3)_2$), 2.1–1.4 (4H, m, 2, 4-$(CH_2)_2$), 1.5–1.1 (6H, m, 5, 6, 7, -$(CH_2)_3$), 1.1–0.8(3H, m, 8-$CH_3$). | 249($M^+$, 11), 209(6), 131(5), 119(5), 117(10), 105(35), 104(17), 92(19), 91(96), 79(7), 78(6), 77(10), 69(5), 65(15), 62(23), 61(100), 60(32), 55(14). |
| **14** | oil | 3130, 2660, 1520, 1490, 1420, 1406, 1340, 1280, 1220, 1170, 1090, 1070, 1050, 1020, 830. | 7.1–6.9(4H, m, ArH), 3.6–3.3 (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-$CH_3$), 1.9–1.4(4H, m, 2, 4-$(CH_2)_2$), 1.5–1.2(4H, m, 5, 6-$(CH_2)_2$), 1.1–0.8(3H, m, 7-$CH_3$). | 249($M^+$, 4), 189(6), 131(8), 119(6), 118(5), 106(14), 105(91), 91(6), 79(8), 77(6), 62(15), 61(100), 60(12), 57(7). |
| **15** | oil | 3080, 2800, 1500, 1450, 1220, 1100, 1050, 1030, 920, 840, 780, 720. | 7.4–6.9(9H, m,ArH), 4.4(1H, t, 1-CH), 2.4(6H, s, $N(CH_3)_2$), 2.7–2.2(2H, m, 3-$CH_2$), 2.1–1.6(2H, m, 2-$CH_2$). | 289($M^+$, 5), 192(5), 151(12), 127(34), 126(6), 125(100), 117(6), 115(10), 105(15), 104(23), 103(19), 92(5), 91(60), 90(7), 89(15), 79(6), 78(16), 77, (30), 65(8), 63(8), 61(60), 60 (27), 51(15). |
| **16** | oil | 3020, 2780, 1480, 1460, 1420, 1200, 1090, 1015, 1000, 820, 805. | 7.2–6.8(4H, m, ArH), 3.6–3.2 (1H, m, 3-CH), 2.7–2.2(2H, M, 1-$CH_2$), 2.5(6H, s, $N(CH_3)_2$), 1.8–1.3(4H, m, 2, 4-$(CH_2)_2$), 1.3 – 0.6(9H, 4, 5, 6-$(CH_2)_3$ + 7-$CH_3$). | 269($M^+$, 4), 127(9), 125(28), 62(5), 61(100), 60(9). |
| **17** | oil | 3080, 2720, 1490, 1470, 1430, 1390, 1330, 1210, 1100, 1030, 835, 825. | 7.3–7.0(4H, m, ArH), 3.6–3.2 (1H, m, 3-CH), 2.8–2.4(2H, m, 1 – $CH_2$), 2.5(6H, s, $N(CH_3)2$), 1.9–1.4(4H, m, 2, 4-$(CH_2)_2$), 1.4–1.1(6H, m, 5, 6, 7-$(CH_2)_3$), 1.0–0.8(3H, m, 8-$CH_3$). | 283($M^+$, 5), 127(7), 125(17), 61(100), 60(8), 54(5). |
| **18** | oil | 3110, 2740, 1600, 1500, 1450, 1370, 1310, 1280, 1150, 1090, 1065, 1030, 880, 755, 695. | 7.6–6.5(10H, m, ArH) 2.8–2.0 (4H, m, 3, 4-$(CH_2)_2$), 2.4(6H, 1, $N(CH_3)_2$), 1.6(3H, s, 1-$CH_3$). | 209(21), 208(6), 207(26), 136(11), 134(34), 131(12), 130(7), 129(23), 105(37), 92 (7), 91(100), 65(27), 61(7), 60(9). |

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