N-Heterocycles from Oxime and Oxime O-Benzyl Ethers *via* Electrophile Induced - Ring Formation. Route to Cyclic and Bicyclic Amine and Hydroxylamine

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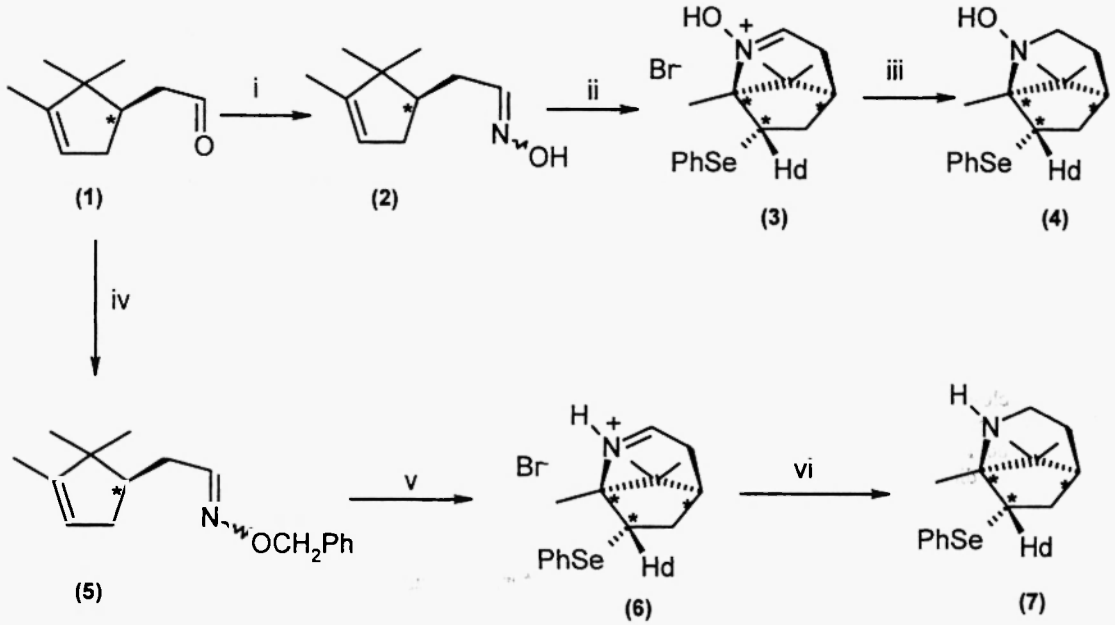
Abstract: Phenylselenyl and iodine induced chiral and achiral ring forming cyclisations creating bridged bicyclo-[3.2.1]- and cyclic ring N-hydroxylamines and bicyclo-[3.2.1]- ring amines occur stereo-, regio- and facially specifically that involve multiplication of chiral centres from one to two and three in one pot reactions in moderate to good yield. An example of bromine induced cyclisation and 1,3-dipolar cycloaddition creating isoxazolidine-ring were also reported.

Introduction: There have been many reports in the literature of electrophile induced cyclisation of alkenes containing nitrogen nucleophiles, such as amines[1], hydrazines[2] hydrazones[3], imines[4] , hydroxamic acid[5] and oximes[6] Among the products there are indolizidine, quinolizine, isoquinoline and indole alkaloids which have significant biological activities[1-8]. The 1,3-Dipolar cycloaddition (1,3-DC) reaction of nitrones with alkenes leading to isoxazolidines is one of the fundamental reactions in organic chemistry. Isoxazolidines are useful synthetic intermediate showing to the ready reductive cleavage of the N-O bond to generate the corresponding 1,3-aminoalcohol[7-10]. Grigg *et al* have recently reported a range of electrophile induced oxime -> nitrone -> cycloaddition cascades reactions furnishing nitrones and their cycloadduct in good yields[6, 11-13]. In recent papers we reported that phenylselenyl, iodine and bromine are excellent reagent for effecting stereo- and regio-specific spiro- fused and bridged- ring forming cyclisation of oximes onto proximate alkenes[14-17] We have also reported a related electrophile induced cyclisation of oxime O-allyl and O-benzyl ethers generating the corresponding oxime ether salts. These oxyiminium ions can, under appropriate conditions, be transformed into nitrones, imines or, by reduction, hydroxylamines[18]

Results and Discussion: We now report some more example of our work with bridged, fused - ring forming cyclisations creating cyclic and bicyclic ring systems occur in good yield. Chiral bridged-ring systems have been prepared that involve multiplication of chiral centres from one to three in one pot reactions. Formation of chiral bicyclic bridged ring N-hydroxylamine (**4**) and amine (**7**) were prepared from aldoxime (**2**)[19] and oxime O benzyl ether (**5**)[19] respectively via phenylselenyl induced cyclisations reactions. Creating bicyclo-[3.2.1]-ring systems occur stereo-, regio- and facially specifically that involve multiplication of chiral centres from one to three in one pot reactions in moderate to good yield.

Thus aldoximes (**2**) (1:1 E/Z-isomer) was treated with phenylselenyl bromide in acetonitrile at ambient temperature for 1h to afford the corresponding bridged nitrone salt (**3**) which, upon treatment with. $NaBH_4$,

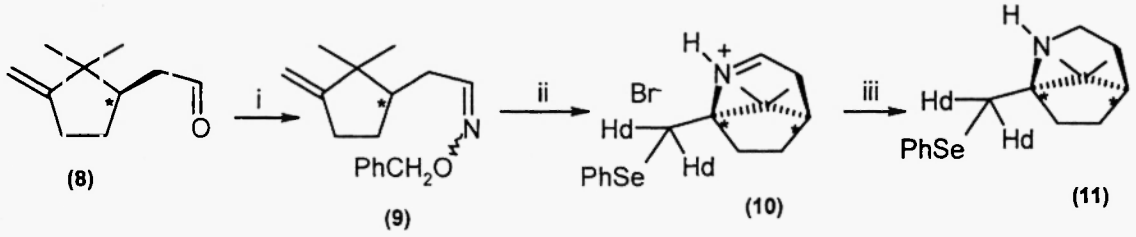
were converted to bridged bicyclic N-hydroxylamine **(4)** in 69% yield (Scheme 1). The stereochemistry of **(4)** was assigned from n.O.e. data and ^{2}D-COSY and by the related previous studies[16]



i. NH_2OH HCl, CH_3COONa, CH_3CN/H_2O ii. PhSeBr, CH_3CN, N_2 iii. $NaBH_4$, CH_3OH/DCM

iv. $PhCH_2ONH_2$.HCl, CH_3COONa, CH_3CN/H_2O v. PhSeBr, CH_3CN, N_2 vi. $NaBH_4$, CH_3OH/DCM

Scheme 1



i. $PhCH_2ONH_2$.HCl, CH_3COONa, CH_3CN/H_2O ii. PhSeBr, CH_3CN, N_2 iii. $NaBH_4$, CH_3OH / DCM

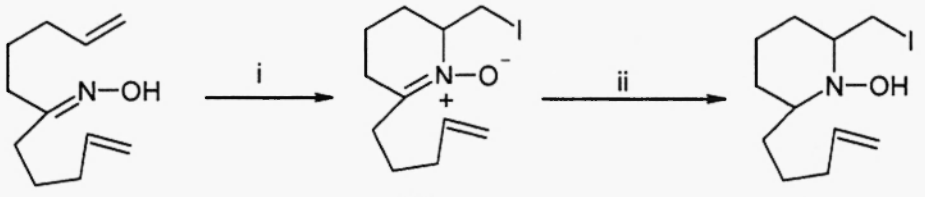
Scheme 2

Oxime O-benzyl ether **(5)**[19] was synthesised as a 2:1 mixture of E- and Z-isomers from **(1)** and O – benzylhydroxylamine in 88% yield which was then treated with phenylselenyl bromide (1.0 eq) at rt for 16h. At this stage, analysis by t.l.c showed some remaining oxime O-benzyl ether **(5).** Additional phenylselenyl bromide (0.1eq) was therefore added and the solution stirred at rt for additional 6 h. The ^{1}H n.m.r spectrum showed the presence of benzaldehyde suggesting fragmentation to iminium ion **(6)** together with a singlet at δ 4.8 ppm for for yhe benzyl protons of salt **(6).** Reduction ($NaBH_4$, rt, 1h) and flash column chromatograpy of **(6)** gave a complex mixture and a trace amounts (<5%, ^{1}Hn.m.r) of desired product **(7)** which was also

confirmed by an M^+ ion in the mass spectrum. This lack of reaction probably arose from the steric inhibition of the gem-dimethyl group.

Syntheses of optically active bridged-ring amine involving dublication of stereocentres from one to two one pot reactions have also been achieved by analogous sequences from chiral non racemic oximes O benzyl ether (**9**). Thus *(1R)*-(2,2-dimethyl-3-methylenecyclopentyl)-1-acetaldehyde (**8**) was prepared from 6,6-dimethylbicyclo[3.1.1]-hept-2-ene-2-ethanol (Nopol) according to the literature procedure[20] this was converted to its oxime eher (**9**) by using O –benzylhydroxylamine in 86% yield (scheme 2). The optically active oxime ether was a colourless liquid which comprised a 2:1 mixture of E- and Z- isomers. The versatility of the phenylselenyl induced cyclisation process is demonstrated by the cyclisation of (**9**) to iminium ion (**10**) despite the potential for steric inhibition by the gem-dimethyl group. Upon treatment with $NaBH_4$, were converted to chiral bridged bicyclic amine (**11**) $[\alpha]_D$ +24.2 (c=0.3, $CHCl_3$) in 34% yield (Scheme 2). The stereochemistry of (**11**) was assigned from ^{1}Hn.m.r and related previous studies[16].

This methodology has also been applied to generate cyclic N-hydroxylamine from acyclic oxime. Thus the oxime (**14**) was prepared by double alkylation of dithiane as a colourless liquid which comprised a 3:2 mixture of *E*-and *Z*-isomers[18,19]. This mixture of isomers underwent electrophile mediated cyclisation, (CH_2Cl_2, I_2, 25°C, 16h) to give (**13**). Reduction [2eq. $NaBH_4$, 25°C, CH_2Cl_2/MeOH(1:1) 1h] of (**13**) gave (**14**) which was obtained as colourless prisms in 57% overall yield from (**12**).

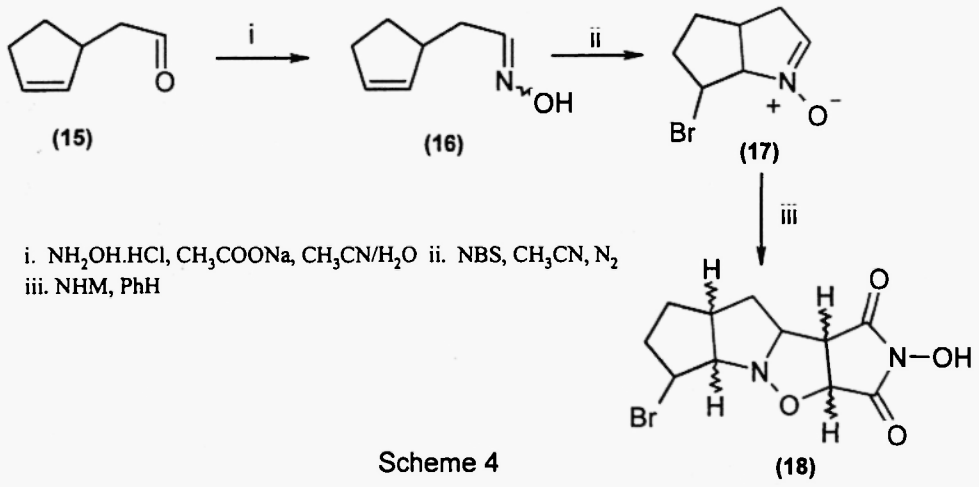


(12) (13) (14)

i. I_2, CH_2Cl_2, N_2 ii. $NaBH_4$, CH_3OH

Scheme 3

An example of fused rings nitrogen heterocycles were also prepared via N-bromosuccinimide (NBS) induced nitrone generation –cycloaddition reactions of oximes onto proximate alkenes. Thus oxime (**16**) were prepared according to litterarure procedure[16] which were then submitted to NBS induced cyclisation with the succinimide acting as a proton scavaenger gave nitrone (**17**). The 1,3-dipolar cycloaddition of (**17**) using N-hydroxylmaleimide (NHM) as dipolarophile afforded cycloadduct (**18**) as a mixture of four isomer in 61% yield (scheme 4).



i. $NH_2OH.HCl$, CH_3COONa, CH_3CN/H_2O ii. NBS, CH_3CN, N_2
iii. NHM, PhH

Scheme 4

In summary, the technically simple, electrophile induced, oxime -> nitrone -> N-hydroxylamine and oxime ether -> iminium ion -> amine sequence occurs regio- and stereo-selectively and provides an major increase in molecular complexity.

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Experimental

General Technical Data: Nuclear magnetic resonance spectra and decoupling experiments were determined at 300 MHz. on a Q.E 300 instrument and at 400 MHz on a Bruker AM400 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad and brs= broad singlet. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF_{254} (Merck 7730). Petroleum ether refers the fraction with b.p 40-60 °C unless otherwise specified. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo - Erba Model 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. All calculations for selenium were based on its most abundant isotope ^{80}Se. Specific rotations were measured at ambient temperature with an Optical Activity Ltd., AA-1000 polarimeter. All solvents were purified according to procedures given in Purification of Laboratory Chemicals, D.D. Perrin, W.L.F. Armarego, D.R. Perrin, Permagon Press, 1980.

(+)-(1R)-2,2-3-Trimethyl-3-ene-1-acetaldehyde (Campholenal) (1). . Prepared by a modification of the literature method[20]. δ(300 MHz) , (C_6D_6): 9.8 (t, 1H, J 2.1Hz, CHO), 5.2 4(s, 1H, C=CH), 2.53 (m, 1H), 2.4 (m, 2H), 2.3 (m, 1H), 1.90 (m, 1H) , 1.63 (s, 3H, Me), 1.01 (s, 3H, Me) and 0.8 (s, 3H, Me).m/z(%): 152 (M^+, 2), 137 (3), 105 (10), 108 (100), 93 (62), 67 (27) and 41 (20).

(+)-(1R)-2,2-3-Trimethyl-3-ene-1-acetaldoxime (2). A solution of aldehyde (1) (2 g, 13mmol) in acetonitrile (75 ml) was added to a solution of hydroxylamine hydrochloride (1 g, 1.1 equiv.) and sodium acetate (1.29 g, 1.2 equiv.) in water (75 ml). The resulting solution was stirred at ambient temperature for 3 h. then extracted with chloroform (2x200 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduce pressure. The residue was subjected to column chromatography on silica eluting with 1:1 v/v petroleum ether-ether to afford the product (2.1 g, 95%) as a colourless liquid, b.p. 66-68 °C /0.1 mmHg which comprised a 1:1 mixture of *E*- and *Z*- isomers. $[\alpha]_D$ = +11.2 (c.1.5 g/100 ml, $CHCl_3$).
(Found: C, 71.6; H, 10.5; N, 8.4 ; $C_{10}H_{17}NO$ requires: C, 71.8; H, 10.25; N, 8.4 %.; δ(300 MHz): 9.86 and 9.32 (br, 1H, OH, isomers), 7.46 (t, 1H, E-CH=N), 6.75 (t, 1H, *Z*-CH=N), 5.21 (brs, 1H, C=CH, isomers), 2.54 -1.66 (m, 5H, alphatics-H, isomers), 1.66 and 1.60 (s, 3H, CH=CH-Me, isomers), 1.03 and 1.00 (s, 3H, Me, isomers) and 0.8 and 0.7 (s, 3H, Me, isomers); m/z(%): 167 (M^+, 6), 150 (7), 134 (21), 108 (100), 93 (52), 67 (11) and 41(18).

Compound (4). Phenylselenyl bromide (0.141g, 1.2equiv.) was added to a solution of oxime (2) (0.1 g, 0.6 mmol) in dry acetonitrile (5ml). The resulting solution was stirred at ambient temperature for 2h, Acetonitrile was removed under reduced pressure and the residue was taken up in DCM:MeOH (1:1 v/v) (10 mL), $NaBH_4$ (0.045 g, 1.2 mmol) added and the mixture was stirred at room temperature for 2 h. The solvent was then evaporated under reduced pressure and the residue was subjected to column chromatography on silica, eluting with 9:1 v/v chloroform methanol to afford the product (0.67g, 69 %) as a colourless prisms, m.p.115-117 °C. $[\alpha]_D$ = + 6.4 (0.5 g/100 ml, $CHCl_3$), Found: C, 59.25; H,7.3; N, 4.4, $C_{16}H_{23}NOSe$ requires: C, 59.25; H, 7.15; N, 4.3 %., δ(300 MHz): 8.22(br, 1H, OH), 7.61 and 7.21(2xm, 5H, ArH), 4.19(t, 1H, J 8.1 Hz, Hd), 3.16 and 2.74 (2xm, 2H, NCH_2), 2.3(m, 1H), 2.01(m, 2H), 1.72(m, 1H), 1.34(s, 3H, Me), 1.24(m, 1H), 1.08 and

1.06(2xs, 6H, Me)., m/z(%): 325(M^+, 28), 308(99), 168(100), 157(46), 126(94), 109(46), 91(42), 83(67), 77(64), 67(40), 55(91) and 41(97).

Compound (5). A solution of aldehyde (1) (3g, 19.71mmol) in acetonitrile (150ml) was added to a solution of O-benzylhydroxylamine hydrochloride (3.46g, 21.68 mmol) and sodium acetate (1.94g, 23.65mmol) in water (100ml). The resulting solution was stirred at ambient temperature for 8h and then extracted with chloroform (2x250ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography on slica. Eluting with 1:1 v/v petroleum ether - ether. The product (4.4g, 88%) was obtained as a colourless oil, which comprised a 2:1 mixture of E- and Z- isomers. Found: C, 79.15; H, 8.8; N, 5.4, $C_{17}H_{23}NO$ requires: C, 79.3; H, 9.0; N, 5.4%. δ(300 MHz): 7.47 and 6.71 (t, 1H, J 6.4 and J 5.0 Hz, CH=N, isomers), 7.34-7.20(m, 5H, aromatic-H, isomers), 5.20(brs, 1H, C=CH, isomers), 5.10-5.03(m, 2H, OCH_2, isomers), 2.36-1.63(m, 3H, aliphatic-H) and 1.90 and 0.96(2xs, 6H, Me). m/z(%) 257(M^+, 6), 242(3), 166(6), 149(52), 117(28), 107(17), 91(100) and 77(18).

(1R)-2,2-Dimethyl-3-methylidene cyclopentane-1-acetaldehyde (8) was prepared by the literature procedure[20].

Compound (9). A solution of aldehyde (8) (3.01g, 19.72mmol) in acetonitrile (150ml) was added to a solution of O-benzylhydroxylamine hydrochloride (3.50g, 21.68 mmol) and sodium acetate (1.94g, 23.65mmol) in water (100ml). The resulting solution was stirred at ambient temperature for 8h and then extracted with chloroform (2x250ml). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography on slica. Eluting with 2:1 v/v petroleum ether - ether. The product (4.0g, 80%) was obtained as a colourless oil, which comprised a 2:1 mixture of E- and Z- isomers. Found: C, 79.15; H, 8.8; N, 5.4, $C_{17}H_{23}NO$ requires: C, 79.3; H, 9.0; N, 5.4%. δ(300 MHz): 7.47 and 6.71 (t, 1H, J 6.4 and J 5.0 Hz, CH=N, isomers), 7.34-7.20 (m, 5H, aromatic-H, isomers), 5.10-5.03(m, 2H, OCH_2, isomers), 4.70(brs, 2H, $C=CH_2$, isomers), 2.60 -1.1 (m, 7H, aliphatic-H) and 0.94 and 0.90(2xs, 6H, Me). m/ (%): 257(M^+, 28), 149(100), 119(24), 91(67) and 71(26).

Compound (11). Phenylselenyl bromide (0.183 g, 0.78 mmol) was added to a solution of oxime ether **9** ((0.2 g, 0.78 mmol) in dry acetonitrile (10 mL). The resulting solution was stirred at room temperature for 16 h. Acetonitrile was removed under reduced pressure and the residue was taken up in DCM:MeOH (1:1 v/v) (10 mL), $NaBH_4$ (0.06 g, 1.59 mmol) added and the mixture was stirred at room temperature for 2 h. The solvent

was then evaporated under reduced pressure and the residue was subjected to column chromatography on silica, eluting with 95:5 v/v chloroform methanol to afford a pale yellow oil (0.08 g, 34 %).
δ(300 MHz): 7.60-7.50 (m, 2H, ArH), 7.35-7.25 (m, 3H, ArH), 5.45 (br, 1H, NH), 3.75 (brd, 2H, $PhSeCH_2$), 2.62-1.02 (m, 9H) and 0.98 and1.20 (2xs, 6H, 2xMe); **m/z(%):** 310 (M+1, 6), 309 (M^+, 3), 220 (12), 205 (40), 109 (100), 91 (74) and 55 (28).

6-Oxoundeca-1,10-diene oxime (12). The product (81%) was a colourless liquid which comprised a 3:2 mixture of E- and Z- isomers, identical to that reported previously[18,19].

N-Hydroxy-2-iodomethyl-6-(pent-4'-enyl) piperidine (14). A solution of oxime (12) (0.23 g, 1.27 mmol) was added to a solution of iodine (0.321 g, 1 equiv.) in dry dichloromethane (5 ml). The resulting solution was stirred at 40 °C for 16 h. and the solvent was then removed under reduced pressure . The residue was disolved in 1:1 v/v dichloromethane-methanol (20 ml) and then solid sodium borohydride (0.096 g, 2 equiv) added. The resulting solution was stirred at room temperature for 1h then poured into water (10ml), and extracted with diethylether (2x30). The combined organic layer were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromotography on slica gel eluting with 3:2 v/v, petroleum ether-ether. The product (0.22 g, 57%) crystallized from petroleum ether-ether as colourless prisms, mp. 59-61 °C. (Found : C, 42.7; H, 6.7; N, 4.25 ; $C_{11}H_{20}NOI$ requires : C, 42.75; H, 6.5; N, 4.55 %). δ(300 MHz): 5.85 (m, 1H, $C\underline{H}=CH_2$), 5.07-4.93 (m, 2H, $CH=C\underline{H_2}$), 3.55-3.39 (m, 2H, CH_2I), 2.82-2.50 (br, 1H, OH), 2.02-2.12 (m, 3H, NCH and aliphatic-H) and 2.0-1.2 (m, 12H, aliphatic-H). m/z(%): 310(M+1, 100), 182 (28), 55 (22) and 240 (17).

Compound (18). A solution of 2-(Cyclopent-2-en)-1-acetaldoxime (16) (0.2g, 1.6 mmol) and NBS(recrystallised) (0.29g, 1.6 mmol) in dry DCM (40 ml) was stirred at room temperature for 3h. The DCM was removed under reduced pressure and the residue was taken up in benzene (40 ml), N-hydroxymaleimide (NHM) (0.181 g, 1.6 mmol) added and the mixture heated at 60 °C for 13h. After cooling the benzene was evaporated under reduce pressure to leave a yellow brown oil which comprised a 1:1 mixture of isomers. Flash column chromatographyeluting with 9:1 v/v ether-ethanolm afforded the title compound (0.32g, 61% yield. mp. 159-163 °C. (Found : C, 41.7; H, 4.3; N, 8.75 ; $C_{11}H_{13}N_2O_4Br$ requires C, 41.65; H, 4.15; N, 8.85 ; %). δ (400 MHz): 5.01 (br, N-OH)), 4.66(m, 1H), 4.31 (m, 1H), 4.1 (m, 1H), 3.85 (m, 1H), 3.50 (m, 2H), 3.2-1.04 (m, 5H). m/z(%): 318 (M^+ , 4), 316 (4), 237 (6), 203(19), 188 (16), 149(11), 99(100), 56(83) and 43(30).

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