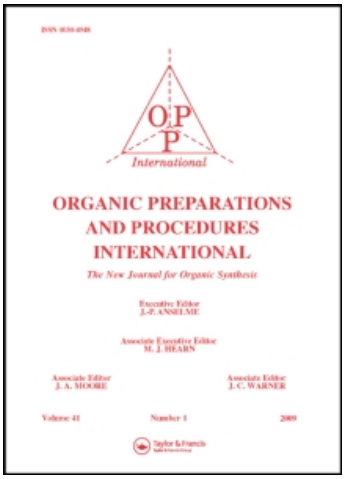

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INVESTIGATION OF THE ALKYLATION OF ALDOXIMES AND KETOXIMES WITH α-EPOXIDES

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INVESTIGATION OF THE ALKYLATION OF ALDOXIMES AND KETOXIMES WITH α-EPOXIDES

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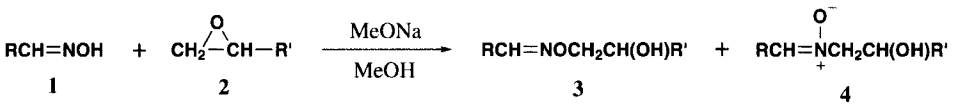
O- or N-alkyl derivatives of aldoximes and ketoximes display important biological[1,2] and physiological[3-5] properties and are useful as starting materials[6,7] in the pharmaceutical industry. Due to their versatility, the synthesis of aldoximes and ketoximes has been attracting much interest[8,9] in recent years. The most common approach for the preparation of O- or N-alkyl derivatives of oximes involves treatment of oximes with alkyl halides in the presence of base.[10-13] We recently reported[14] that the synthesis of O- or N-alkyl derivatives of aromatic and hydroaromatic aldoximes could be achieved from reaction of oximes with halohydrins. We now describe the preparation of various oxime derivatives from alkylation of aldoximes and ketoximes with α-epoxides under basic conditions.

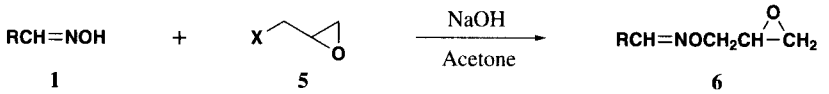
The alkylation of aldoximes with ethylene oxide, propylene oxide, 1,2-epoxy-3-phenoxypropane and (2,3-epoxypropyl)benzene yielded either O-alkyl or N-alkyl derivatives, while treatment of aldoximes and ketoximes with epi-halohydrins afforded to corresponding glycidic ethers in aprotic solvents. Reaction of aldoximes with 3-(β-chloroethoxy)-1,2-epoxypropane resulted in the formation of halohydrins that were converted into corresponding 1,4-dioxane derivatives. Oximes were prepared *via* following of literature procedure[15,16] from corresponding aldehydes or ketones. The reaction of **1a-f** with α-epoxides in protic solvents (MeOH, EtOH) afforded one major adduct **(3a-f)** in good yields whereas only minor amounts of adduct **4a-c** and **4f** were found; they were separated by fractional distillation under reduced pressure after an aqueous work-up. In all cases only the O-alkyl oximes were formed in aprotic solvents (acetone, benzene, toluene, DMSO, DMF).



1 2 3 4

1-12	R	R'
a	isobutyl-	methyl-
b	phenyl-	methyl-
c	3-cyclohexenyl-	methyl-
d	phenyl-	benzyl-
e	3-cyclohexenyl-	phenoxymethyl-
f	isobutyl-	H-
g	2-methyl-3-cyclohexenyl-	-
h	3,4-dimethyl-3-cyclohexenyl-	-
i	methyl-	-
j	ethyl-	-
k	2-furyl	-
l	6-methyl-3-cyclohexenyl	-
m	phenyl-	-
n	3-cyclohexenyl-	-

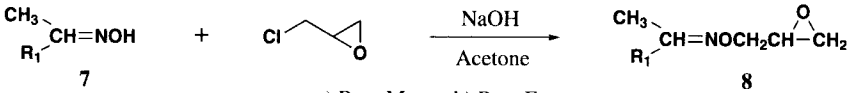
Aldoximes **1f-l** reacted with *epi*-chloro-, *epi*-bromo- and *epi*-iodohydrins under basic conditions to afford corresponding glycidic ethers **6f-l** exclusively in high yields.



1 5 6

X = Cl, Br, I

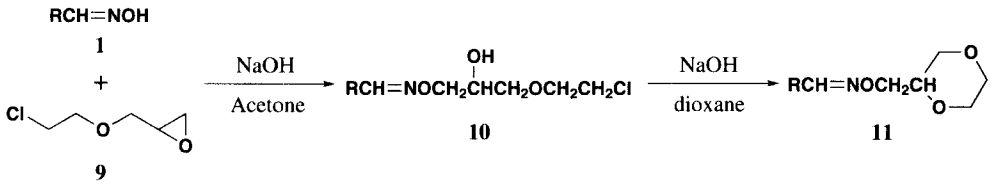
Glycidic ethers **8a,b,** derived from ketoximes **7a,b** were also obtained with *epi*-chlorohydrin under the same conditions.



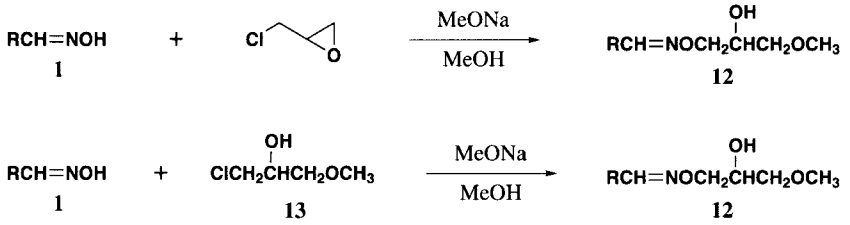
7 8

a) R_1 = Me b) R_1 = Et

Alkylation of oximes **1f,m** with a long-chain epoxide such as 3-(β-chloroethoxy)-1,2-epoxypropane **(9)** afforded **10f,m** instead of glycidic ethers and were converted to their 1,4-dioxane derivatives **11f,m** by heating in the presence of powdered NaOH and dioxane.



Treatment of aldoximes **1m,n** with *epi*-chlorohydrin yielded methoxy- or ethoxy-derivatives **12m,n** in protic solvents, such as methanol. The structure of **12m,n** was also confirmed by synthesis from **1m,n** with 3-chloro-1-methoxy-2-propanol **(13).**



The structure of all compounds synthesized was confirmed by microanalyses, IR, ^1H NMR (Table 1 and 2).

Table 1. Physical Data of the New Compounds

Cmpd.	Yield (%)	bp. (°C/mmHg)	n_4^{20}	Elemental Analyses (Found) C	H	N
3a	65	90/0.5	1.4445	60.35(60.12)	10.76(10.48)	8.80(8.66)
3b	69	108/0.5	1.5418	67.02(66.84)	7.31(7.18)	7.82(7.54)
3c	72	122/0.5	1.4986	65.54(65.38)	9.35(9.18)	7.64(7.48)
3d	78	184/1	1.5475	75.27(75.02)	6.71(6.60)	5.49(5.32)
3e	74	197/0.5	1.5515	69.79(69.73)	7.69(7.52)	5.09(6.88)
3f	65	85/0.5	1.4415	57.90(57.72)	10.41(10.28)	9.65(9.44)
4a	3.8	124/0.5	1.4725	60.34(60.46)	10.76(10.56)	8.80(8.92)
4b	3.5	135/0.5	1.5742	67.02(67.24)	7.31(7.26)	7.82(7.78)
4c	3.7	147/0.5	1.5108	65.54(65.42)	9.35(9.26)	7.64(7.54)
4f	3.8	117/0.5	1.4930	57.90(57.72)	10.41(10.20)	9.65(9.38)
6f	68	110/2	1.4985	61.12(61.34)	9.62(9.77)	8.91(8.83)
6g	70	99/0.5	1.4973	67.66(67.72)	8.78(8.70)	7.17(7.28)
6h	58	66/5	1.4462	68.87(68.76)	9.15(9.32)	6.69(6.58)
6i	55	65/1	1.4450	52.16(52.22)	7.88(7.72)	12.17(12.33)
6j	65	132/2	1.5595	55.80(55.72)	8.59(8.48)	10.85(10.74)
6k	57	63/1.5	1.4472	57.48(57.62)	5.43(5.57)	8.38(8.21)
6l	74	99/0.5	1.5848	67.66(67.90)	8.78(8.66)	7.17(7.02)
8a	52	157/2.5	1.5420	55.36(55.24)	9.29(9.36)	10.76(10.68)
8b	54	137/2.5	1.4866	58.31(58.44)	9.79(9.64)	9.72(9.58)

10f	86	92	1.4659	50.52(50.39)	8.48(8.61)	5.89(6.03)
10m	78	198/0.5	1.5290	55.93(55.84)	6.26(6.34)	5.44(5.38)
11f	58	145/3	1.5280	59.68(59.42)	9.51(9.72)	6.96(7.14)
11m	82	142	1.5374	65.14(65.02)	6.83(6.74)	6.33(6.18)
12m	56	121/1	1.4935	63.14(63.28)	7.23(7.14)	6.70(6.56)
12n	65	112/1	1.4860	61.95(62.18)	8.98(8.86)	6.57(6.44)

Table 2. Spectroscopic Data of the New Compounds

Cmpd.	IR (ν_{max} / cm^{-1})				^{1}H NMR (δ_H / ppm)
	C=N	N-O	OH	Other	
3a	1670	965	1080 3500	-	1.27 (3H, t, CH_3), 1.50 (1H, m, C<u>H</u>$(CH_3)_2$), 1.10-1.25 (6H, m, CH(C<u>H</u>$_3)_2$), 3.82-4.15 (1H, m, CH), 1.30-1.40 (2H, m, $CH_3)_2$CHC<u>H</u>$_2$), 3.52 (1H, br, OH), 3.22 (2H, m, OCH_2), 6.60 (1H, s, HC=N, anti), 7.12 (1H, d, HC=N, syn).
3b	1665	940	1070 3450	-	1.30 (3H, t, CH_3), 3.58 (1H, s, OH), 4.38 (1H, q, CH-R'), 3.18 (2H, m, OCH_2), 6.65 (1H, s, HC=N, anti), 7.15 (1H, d, HC=N, syn), 7.55 (5H, m, Ar).
3c	1690 1685	930 920	1070 3500	-	1.25 (3H, t, CH_3), 3.95 (2H, m, CH_2), 2.55 (4H, d, CH_2), 5.62 (2H, m, CH=CH), 1.48 (!H, m, CH), 3.55 (1H, br, OH), 4.10 (1H, m, CH-R'), 3.24 (2H, m, OCH_2), 6.68 (1H, s, HC=N, anti), 7.18 (1H, d, HC=N, syn).
3d	1670	940	1080 3450		2.74 (2H, m, CH_2), 3.45 (1H, br, OH), 3.95 (1H, m, CH-R'), 3.18 (2H, m, OCH_2), 6.67 (1H, s, HC=N, anti), 7.20 (1H, d, HC=N, syn), 7.25-7.51 (10H, m, Ar).
3e	1680 1675	960	1075 3500	-	2.62-2.80 (6H, m, CH_2), 5.66 (2H, m, CH=CH), 1.48 (1H, m, CH), 3.48 (1H, br, OH), 4.87 (1H, m, CH-R'), 3.18-3.28 (4H, m, OCH_2), 6.60 (1H, s, HC=N, anti), 7.16 (1H, d, HC=N, syn), 7.42 (5H, m, Ar).
3f	1660 1655	970	1080 3450	-	1.55 (1H, m,^{o}H$_3)_2$C<u>H</u>), 1.12 (6H, d,^{o}<u>H</u>$_3)_2$CH), 1.34-1.45 (2H, m,^{o}H$_3)_2$CHC<u>H</u>$_2$), 2.35 (1H, s, OH), 3.72 (2H, t, CH_2O), 4.18 (2H, t, OCH_2), 6.62 (1H, d, HC=N anti), 7.23 (1H, d, HC=N syn).
4a	1670 1665	-	1075 3500	1180[a]	1.24 (3H, t, CH_3), 1.51 (1H, m, C<u>H</u>$(CH_3)_2$), 1.16-1.25 (6H, m, CH(C<u>H</u>$_3)_2$), 1.38-1.43 (2H, m,^{o}H$_3)_2$CHC<u>H</u>$_2$), 2.38 (1H, s, OH), 3.87-4.10 (1H, m, CH-R'), 3.64 (2H, t, NCH_2), 7.08 (1H, t, HC=N, anti).
4b	1680	-	1075 3500	1175[a]	1.28 (3H, t, CH_3), 2.37 (1H, s, OH), 4.02-4.14 (1H, m, CH-R'), 3.68 (2H, t, NCH_2), 7.12 (1H, t, HC=N, anti), 7.43-7.55 (5H, m, Ar).
4c	1685	-	1070 3500	1185[a]	1.22 (3H, t, CH_3), 1.59 (2H, m, CH_2), 2.61 (4H, d, CH_2), 5.70 (2H, m, CH=CH), 1.46 (1H, m, CH), 2.42

					(1H, br, OH), 4.07 (1H, m, CH-R'), 3.70 (2H, t, NCH_2), 7.15 (1H, t, HC=N, anti),
4f	1660 1650	-	1080 3400	1180[a]	1.48-1.54 (1H, m,$^oH_3)_2C\underline{H}$), 1.12-1.18 (6H, m,$^o\underline{H}_3)_2CH$), 1.30-1.40 (2H, m,$^oH_3)_2CHC\underline{H}_2$), 2.35 (1H, s, OH), 3.62 (2H, t, CH_2O), 4.18 (2H, t, NCH_2), 7.19 (1H, d, HC=N anti).
6f	1685 1670	980	-	850[b] 1255[b]	1.45 (1H, m, $C\underline{H}(CH_3)_2$), 1.08-1.20 (6H, m, $CH(C\underline{H}_3)_2$), 1.35-1.41 (2H, m,$^oH_3)_2CHC\underline{H}_2$), 2.90 (1H, m, CH-epoxy), 2.68 (2H, d, CH_2-epoxy), 3.87 (2H, d, OCH_2), 6.61 (1H, d, HC=N, anti), 7.38 (1H, t, HC=N, syn).
6g	1690 1660	945	-	850[b] 1260[b]	0.92 (3H, d, CH_3), 1.30-2.20 (4H, m, CH_2), 5.65 (d, CH=CH), 1.46 (2H, m, CH), 2.92 (1H, m, CH-epoxy), 2.70 (2H, d, CH_2-epoxy), 3.85 (2H, d, OCH_2), 6.65 (1H, d, HC=N, anti), 7.40 (1H, t, HC=N, syn).
6h	1685	970	-	1255[b]	1.28 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.38 (2H, m, CH_2), 3.25 (4H, m, CH_2), 1.44 (1H, m, CH), 2.92 (1H, m, CH-epoxy), 2.68 (2H, d, CH_2-epoxy), 3.85 (2H, d, OCH_2), 6.58 (1H, d, HC=N, anti), 7.38 (1H, t, HC=N, syn).
6i	1690 1660	980 935	-	820[b] 1260[b]	1.26 (3H, d, CH_3), 3.02 (1H, m, CH-epoxy), 2.70 (2H, d, CH_2-epoxy), 3.82 (2H, d, OCH_2), 6.65 (1H, d, HC=N, anti), 7.45 (1H, t, HC=N, syn).
6j	1690 1660	960 940	-	755[b] 1265[b]	1.10 (3H, t, CH_3), 1.25 (2H, q, CH_2), 2.95 (1H, m, CH-epoxy), 2.65 (2H, d, CH_2-epoxy), 3.85 (2H, d, OCH_2), 6.60 (1H, d, HC=N, anti), 7.40 (1H, t, HC=N, syn).
6k	1690 1665	970	-	855[b] 1260[b]	4.72 (1H, d, CH), 5.62 (1H, t, CH), 6.45 (1H, d, CH), 2.94 (1H, m, CH-epoxy), 2.69 (2H, d, CH_2-epoxy), 3.88 (2H, d, OCH_2), 6.62 (1H, d, HC=N, anti), 7.50 (1H, t, HC=N, syn).
6l	1670	960	-	1260[b]	0.96 (3H, d, CH_3), 1.22-2.25 (4H, m, CH_2), 5.63 (d, CH=CH), 1.44 (2H, m, CH), 2.94 (1H, m, CH-epoxy), 2.63 (2H, d, CH_2-epoxy), 3.82 (2H, d, OCH_2), 6.60 (1H, d, HC=N, anti), 7.42 (1H, t, HC=N, syn).
8a	1675 1660	935 920	-	830[b] 1260[b]	1.20 (6H, s, CH_3), 3.00 (1H, m, CH-epoxy), 2.70 (2H, d, CH_2-epoxy), 3.87 (2H, d, OCH_2), 6.65 (1H, d, HC=N, anti), 7.45 (1H, t, HC=N, syn).
8b	1685 1680	940 935	-	750[b] 1260[b]	1.15 (3H, t, CH_3), 1.18 (3H, s, CH_3), 1.22 (2H, q, CH_2), 2.95 (1H, m, CH-epoxy), 2.65 (2H, d, CH_2-epoxy), 3.82 (2H, d, OCH_2), 6.60 (1H, d, HC=N, anti), 7.40 (1H, t, HC=N, syn).
10f	1650	990	3400	-	4.31-4.38 (1H, m, CH), 3.78-3.92 (4H, m, OCH_2), 4.08 (2H, d, CH_2O), 3.17 (2H, t, CH_2-Cl), 3.55 (1H, br, OH), 6.62 (1H, d, HC=N, anti), 7.32 (1H, t, HC=N, syn), 1.42 (1H, m, $C\underline{H}(CH_3)_2$), 1.15 (6H, m, $CH(C\underline{H}_3)_2$), 1.38-1.42 (2H, m,$^oH_3)_2CHC\underline{H}_2$).

10m	1670	930	3450	-	4.29-4.34 (1H, m, CH), 3.82-3.90 (4H, m, OCH_2), 4.12 (2H, d, CH_2O), 3.22 (2H, t, CH_2-Cl), 3.51 (1H, br, OH), 6.58 (1H, d, HC=N, anti), 7.28 (1H, t, HC=N, syn), 7.40-7.48 (5H, m, Ar).
11f	1670	985	-		1.48 (1H, m, $C\underline{H}(CH_3)_2$), 1.10 (6H, m, $CH(C\underline{H}_3)_2$), 1.33-1.40 (2H, m, $^{a}H_3)_2CHC\underline{H}_2$), 4.24 (1H, m, CH), 3.49-3.98 (8H, m, OCH_2), 6.60 (1H, d, HC=N, anti), 7.34 (1H, t, HC=N, syn).
11m	1645	970	-	-	4.18 (1H, m, CH), 3.51-3.95 (8H, m, OCH_2), 6.59 (1H, d, HC=N, anti), 7.36 (1H, t, HC=N, syn), 7.45-7.52 (5H, m, Ar).
12m	1670	985	3400	-	4.24-4.29 (1H, m, CH), 4.22 (2H, t, OCH_2), 3.65 (2H, t, CH_2O), 3.45 (1H, br, OH), 6.56 (1H, d, HC=N, anti), 7.23 (1H, t, HC=N, syn), 3.29 (3H, s, CH_3), 7.45-7.52 (5H, m, Ar).
12n	1665	960	3450	-	4.22-4.25 (1H, m, CH), 4.20 (2H, t, OCH_2), 3.68 (2H, t, CH_2O), 3.38 (1H, br, OH), 6.62 (1H, d, HC=N, anti), 7.24 (1H, d, HC=N, syn), 1.78-1.83 (2H, m, CH_2), 2.44-2.49 (4H, m, CH_2), 5.65 (2H, m, CH=CH), 3.31 (3H, s, CH_3).

[a]: C-N, [b]: epoxy

EXPERIMENTAL SECTION

Infrared spectra were obtained on a Pye Unicam SP1025 spectrometer. ^{1}H nmr spectra were recorded on a Varian T100-A spectrometer at 100 MHz. All spectra used TMS as the internal standard and were carried out in $CDCl_3$. Elemental analyses were determined using a Carlo Erba 1106 automatic elemental analysis instrument. Melting points were recorded on an Electrothermal digital melting point apparatus and are uncorrected. Thin layer chromatography was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates.

Synthesis of Oximes. General Procedure.- Hydroxylamine hydrochloride (0.1 mol) and Na_2CO_3 (0.1 mol) in 100 mL of benzene were stirred at 60° for 45 min. The aldehyde (0.1 mol) was then added dropwise and stirring was continued at 80° for 4-5 hrs, after which time organic phase was separated from salts by filtration. The filtrate was neutralized with 2M acetic acid. The separated organic phase was dried over $MgSO_4$ and solvent evaporated in *vacuo*. The residue was fractionally distilled under reduced pressure to give **1a-n.**

Alkylation of Oximes with α-Epoxides. General Procedure.- The oxime (0.3 mol) was dissolved in acetone (120 mL) and a solution of NaOH (5N, 60 mL) was added. Ethylene oxide was passed through the reaction mixture for 2.5 hrs. at 60°. The solution was neutralized with 2M acetic acid, extracted with diethyl ether (3x50 mL) before the extraction with chloroform (3x50 mL) and the extracts were dried over Na_2SO_4. **3a-f** were obtained from ethereal phase after evaporation of the solvent and subsequent fractional distillation. Compounds **4a-c,** and **4f** were

obtained from the chloroform extract following the same procedure.

Alkylation of Aldoximes and Ketoximes with *epi*-Halohydrins. General Procedure.- A mixture of oxime (0.25 mol) and NaOH (5N, 50 mL) in acetone (75 mL) was stirred at 40-45° for 40 min. and *epi*-halohydrin (0.25 mol) was added. The reaction mixture was heated to 60-65°, and stirred for 3 hrs. The solution was neutralized with 2M acetic acid, extracted with ether (3x50 mL) dried over $MgSO_4$. After evaporation of the solvent in *vacuo,* the residue was fractionally distilled under reduced pressure to afford **6f-l** and **8a,b.**

Synthesis of 10f,m.- A mixture of **1f** or **1m** (0.25 mol) and NaOH (5N, 70 mL) in acetone (75 mL) was stirred at 55-60° for 45 min. After the reaction mixture was heated to 60°, 3-(β-chloroethoxy)-1,2-epoxypropane (34.13g, 0.25 mol) was added and the mixture was stirred for 4.5 hrs. The organic phase was separated from precipitated salts, extracted with diethyl ether (3x50 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by fractional distillation under reduced pressure, gave **10f** or **10m**.

Synthesis of 11f,m.- A mixture of **10f** or **10m** (0.25 mol) and NaOH (12g, 0.3 mol) in dioxane (75 mL) was stirred at 70° for 8 hrs. The organic phase was separated from precipitated salts, washed with distilled water (2x50 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by fractional distillation under reduced pressure, afforded **11f** or **11m**.

Synthesis of 12m,n.- To a solution of sodium methoxide prepared dissolving metallic Na (5.75 g, 0.25 mol) in 75 mL of dry MeOH, **1m** or **1n** (0.25 mol) was added at r.t. and the mixture was stirred at 30-40° for 20 h. Then *epi*-chlorohydrin (0.25 mol) was added to the solution and the mixture was stirred at the same temperature. The reaction mixture was allowed to stand overnight and the organic phase was separated from the salts. Half of the solvent was evaporated and water was added. The solution was extracted with diethyl ether (3x50 mL), dried over Na_2SO_4, and the solvent was evaporated in *vacuo.* Fractional distillation of the residue under reduced pressure gave **12m,n**.

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