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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of *N*-Substituted Oxazolidines and Morpholines

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Abstract—A series of *N*-substituted oxazolidines and morpholines were prepared and characterized.

Among synthetic antioxidants, amine and diamine derivatives are the most similar to natural antioxidants in the antiradical activity [1]. Therefore, it was of interest to prepare new oxazolidine and morpholine derivatives and to study their antioxidant properties.

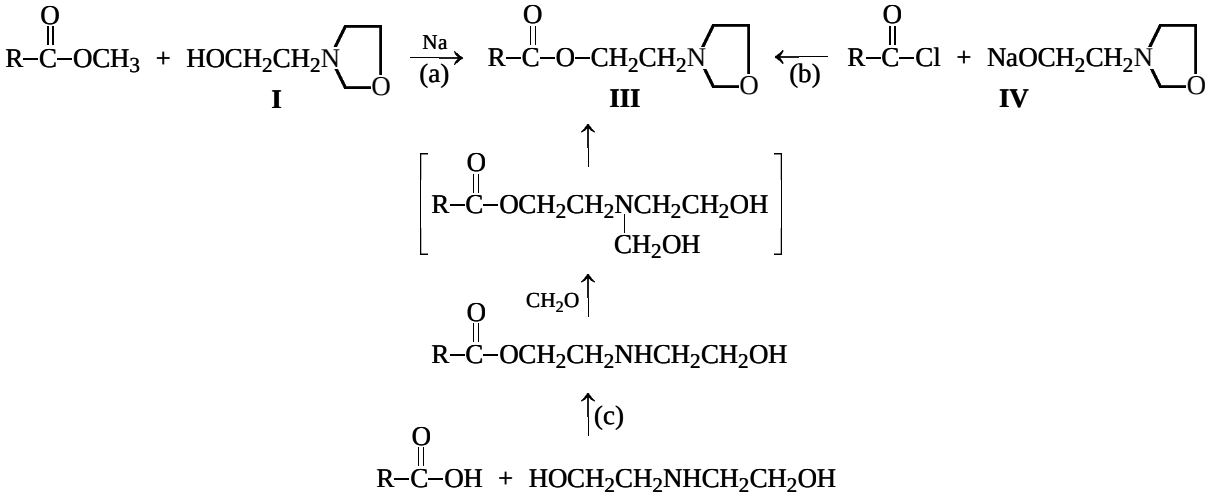
Condensation of *N*-methylethanolamine with aldehydes yielded *N*-methyloxazolidines [2]. Among *N*-substituted morpholine derivatives, 4-(2-hydroxyethyl)-, 2-methyl-4-(2-hydroxyethyl)-, and 2,2-dimethyl-4-(2-hydroxyethyl)morpholines and 4-benzyl-4-(2-benzyloxyethyl)morpholinium chloride are known [3].

In this study, we prepared new nitrogen-containing compounds, *N*-(2-alkanoyloxyethyl), *N*-(halobenzyl), and *N*-(halobenzyloxyethyl) derivatives of 1,3-oxazolidine and morpholine by reacting carboxylic acids and halobenzyl chlorides with ethanolamine, diethanolamine, ethylene chlorohydrin, morpholine, *N*-(2-hydroxyethyl)-1,3-oxazolidine, and *N*-(2-hydroxyethyl)-1,3-morpholine.

As a route to *N*-(2-alkanoyloxyethyl) derivatives of 1,3-oxazolidine and morpholine, we first examined the thermal esterification of carboxylic acids with *N*-(2-hydroxyethyl)oxazolidine **I** and *N*-(2-hydroxyethyl)morpholine **II**. Oxazolidine **I** was prepared by condensation of diethanolamine with formaldehyde [4], and morpholine **II**, by the reaction of morpholine with ethylene chlorohydrin.

The esterification was performed by the procedure described in [5]. We found that, in the reactions of carboxylic acids with oxazolidine **I**, the oxazolidine ring is cleaved first, yielding a complex mixture of products; in esterification of propionic acid, we isolated a product identified by ^{1}H NMR spectroscopy as $(CH_3CH_2COOCH_2CH_2)_2NCH_3$.

We succeeded in preparation of *N*-(2-alkanoyloxyetyhyl)-1,3-oxazolidines **III** by three routes: ester interchange of carboxylic acid methyl esters with *N*-(2-hydroxyethyl)-1,3-oxazolidine **I** (route a), reaction of carboxylic acid chlorides with *N*-(2-hydroxyethyl)-1,3-oxazolidine sodium derivative **IV** (route b), and esterification of carboxylic acids with diethanolamine, followed by condensation of the resulting ester with formaldehyde (route c):



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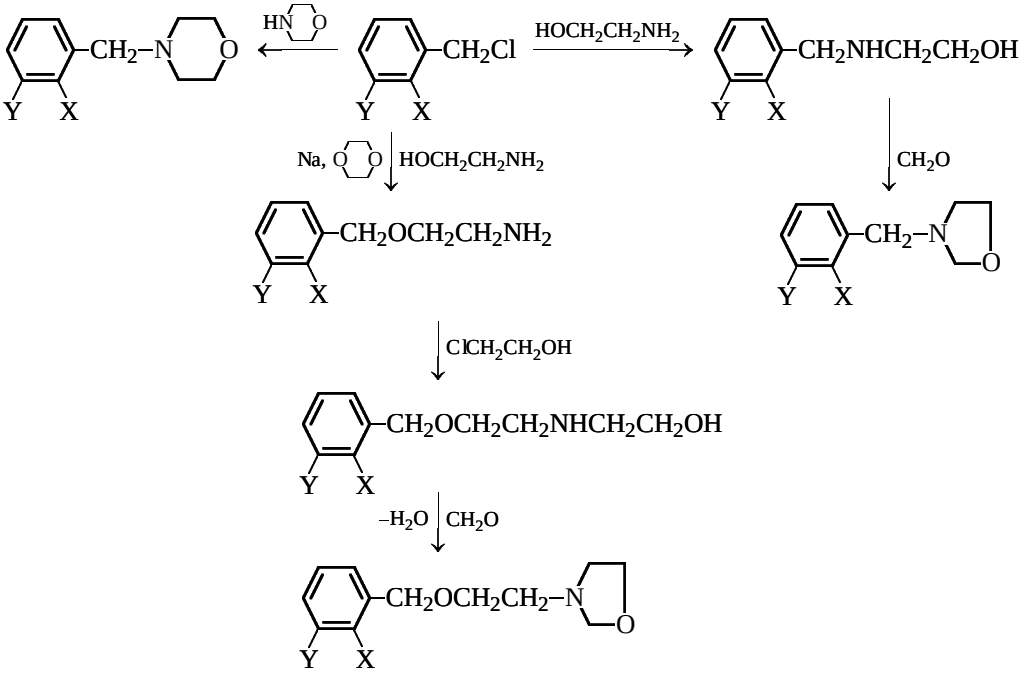
Synthesis of esters **III** by the reaction of carboxylic acids with diethanolamine is complicated by formation of a minor amount of *N*-acyldiethanolamine, which is difficult to separate.

In contrast to oxazolidine **I**, thermal esterification of carboxylic acids with morpholine **II** occurs without complications and yields *N*-(2-alkanoyloxyethyl)morpholines **V** in high yield (80–90%).

Then we prepared new *N*-substituted 1,3-oxazolidine and morpholine derivative by the reactions of halobenzene chlorides with ethanolamine or morpholine:



where Y = H, X = F: Y = Cl, X = H.

Among the compounds synthesized, *N*-(2-ethanoyloxyethyl)-1,3-oxazolidine was tested as antioxidant in studying the photosynthetic activity of *Synechococcus sp*. PCC 7942 (*Cyanophyceae*) cells as influenced by various doses of UV-C radication and the effect of various chronic doses of UV-C radiation on the duplication cycles of the population density of these cells. We found that the antioxidant deactivates the radicals generated in the cell throughout the experiment and thus increases the relative contribution from stimulation of cell fission by small doses of UV-C radiation; upon a single introduction into the cultural medium, the antioxidant restores the suppression of the fission rate of the irradiated cells by chronically high UV-C radiation doses to the level of the control population.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker-300 spectrometer.

***N*-(2-Hydroxyethyl)-1,3-oxazolidine I**. a. A 55-g portion of diethanolamine was added dropwise over a period of 20 min to a stirred mixture of 15 g of paraform and 50 ml of benzene, heated to 80°C. After that, the stirring was continued for an additional 1.5 h. After the reaction completion, the solvent was distilled off; by distillation of the residue in a nitrogen flow under reduced pressure, we isolated 53 g (87%) of *N*-(2-hydroxyethyl)oxazolidine **I**, bp 79–80°C (4 mm Hg), d_4^{20} 1.1236, n_D^{20} 1.4764. ^{1}H NMR spectrum, δ, ppm: 2.68 (2H, NCH_2), 2.98 (2H, NCH_2), 3.61 t (2H, OCH_2), 3.75 t (2H, OCH_2), 4.25 s (2H, NCH_2O), 4.7 s (H, OH). ^{13}C NMR spectrum, δ_C, ppm: 52.5, 57.0, 62.0, 66.0, 87.0.

Di(2-propanoyloxyethyl)methylamine. b. A mixture of 11.7 g of oxazolidine **I** and 22.2 g of propionic acid was stirred at 130°C for 6 h. After the reaction completion, the mixture was neutralized with KOH and filtered to remove the potassium propionate precipitate. By distillation in a nitrogen flow under re-

duced pressure, we isolated 4 g (25%) of di(2-propanoyloxyethyl)methylamine, bp 102–103°C (2 mm Hg), d_4^{20} 1.0202, n_D^{20} 1.4400. ^{1}H NMR spectrum, δ, ppm: 1.18 t (6H, $2CH_3$), 2.32 q (4H, $2CH_2$), 2.4 s (3H, CH_3), 2.71 t [4H, $N(CH_2)_2$], 4.15 t (4H, $2OCH_2$). ^{13}C NMR spectrum, δ_C, ppm: 9.9, 27.0, 43.0, 56.0, 62.0, 172.5.

***N*-(2-Alkanoyloxyethyl)oxazolidines**. c. A solution of 0.09 ml of **I** in *m*-xylene was added dropwise to 0.005 mol of finely divided Na in 20 ml of *m*-xylene. After the completion of the initially vigorous reaction, the mixture was heated to 60°C, and the stirring was continued at this temperature until the sodium fully dissolved. Then 0.08 mol of appropriate carboxylic acid methyl ester was added dropwise at 120°C to the alcoholate, and the released methanol was distilled off. After cooling, the organic matter was separated, the residue was washed with benzene, and, after common work-up, the target products were isolated by distillation in a nitrogen flow under reduced pressure.

N-(2-Butanoyloxyethyl)-, *N*-(2-pentanoyloxyethyl)-, *N*-(2-hexanoyloxyethyl)-, and *N*-(2-octanoyloxyethyl)-1,3-oxazolidines were prepared (see table).

Yields, constants, and NMR spectra of the compounds synthesized

Compound	Yield, %	bp, °C (*P*, mm Hg)	n_D^{20}	d_4^{20}	NMR spectrum, δ, ppm
N-(2-Butanoyloxyethyl)oxazolidine	50	90–92 (2)	1.4540	1.0560	^{1}H NMR: 1.02 (3H, CH_3), 1.69 m, (2H, CH_2), 2.31 t, (2H, CH_2), 2.78 t, (2H, OCH_2), 3.72 t, (2H, OCH_2), 4.16 t, (2H, OCH_2), 4.22 s, (2H, NCH_2O). ^{13}C NMR: 12, 18, 37, 52, 62, 88, 172
N-(2-Pentanoyloxyethyl)oxazolidine	53	97–98 (2)	1.4534	1.0372	^{1}H NMR: 0.99 (3H, CH_3), 1.41 m, (2H, CH_2), 1.62 m, (2H, CH_2), 2.3 m, (2H, CH_2), 2.7 t, (2H, NCH_2), 3.0 t, (2H, OCH_2), 3.72 t, (2H, NCH_2), 4.15 t, (2H, OCH_2), 4.25 s, (2H, NCH_2O). ^{13}C NMR: 14, 22, 24, 33.5, 53.5, 54, 62.8, 63.2, 86.75, 173
N-(2-Hexanoyloxyethyl)oxazolidine	55	108–109 (2)	1.4490	1.0023	–
N-(2-Octanoyloxyethyl)oxazolidine	54	125 (2)	1.4520	0.9841	–
N-(2-Ethanoyloxyethyl)morpholine	70	69–70 (3)	1.4560	1.0723	–
N-(2-Propanoyloxyethyl)morpholine	75	80–81 (2)	1.4553	1.0439	–
N-(2-Butanoyloxyethyl)morpholine	90	108–109 (4)	1.4540	1.0231	^{1}H NMR: 1.08 t, (3H, CH_3), 1.75 m, (2H, CH_2), 2.37 t, (2H, CH_2), 2.58 t, (4H, $N(CH_2)_2$), 2.68 t, (2H, NCH_2), 3.71 t, (4H, $O(CH_2)_2$), 4.28 t, (2H, OCH_2). ^{13}C NMR: 14, 18, 37, 54, 58, 62, 67, 172
N-(2-Pentanoyloxyethyl)morpholine	80	115–116 (3)	1.4540	1.0072	–
N-(2-Hexanoyloxyethyl)morpholine	66	122–123 (3)	1.4555	0.9922	–
N-(2-Octanoyloxyethyl)morpholine	78	128–129 (2.5)	1.4560	0.9786	–
N-(*o*-Fluorobenzyl)morpholine	67	98–99 (5)	1.5140	1.1213	^{1}H NMR: 2.32 t, (4H, $N(CH_2)_2$), 3.45 s, (2H, $C_6H_4CH_2$), 3.54 t, (4H, $O(CH_2)_2$), 6.86–7.34 m, (4H, C_6H_4). ^{13}C NMR: 53, 57, 67, 115, 123, 129, 132, 159.9, 163
N-(*m*-Chlorobenzyl)morpholine	64	134 (3)	1.5180	1.1477	–
N-(*o*-Fluorobenzyl)-ethanolamine	60	120–122 (3)	1.5140	1.1449	–

Table (Contd.)

Compound	Yield, %	bp, °C (*P*, mm Hg)	n_D^{20}	d_4^{20}	NMR spectrum, δ, ppm
N-(*m*-Chlorobenzyl)-ethanolamine	60	138–140 (3)	1.5310	1.1709	–
N-(*o*-Fluorobenzyl)-oxazolidine	77	87–88 (2)	1.5240	1.1680	–
N-(*m*-Chlorobenzyl)-oxazolidine	87	108–110 (3)	1.5470	1.2010	^{1}H NMR: 2.8 t, (2H, NCH_2), 3.55 s, (2H, $C_6H_4CH_2$), 3.64 t, (2H, OCH_2), 4.1 s, (2H, NCH_2O), 7.08–7.3 m, (4H, C_6H_4). ^{13}C NMR: 52, 57.5, 86, 126.5, 127.5, 128.5, 129.5, 134, 141.5
N-(*o*-Fluorobenzyl)-ethylamine	50	86–87 (2)	1.5000	1.1012	–
N-(*m*-Chlorobenzyl)-ethylamine	50	110–112 (2)	1.5330	1.1489	–
N-(*o*-Fluorobenzyl-oxyethyl)ethanol-amine	30	150–151 (2)	1.5110	1.1418	–
N-(*m*-Chlorobenzyl-oxyethyl)ethanol-amine	30	170–172 (2)	1.5340	1.1683	^{1}H NMR: 1.72 s, (2H, NH_2), 2.7 t, (2H, NCH_2), 3.35 t, (2H, OCH_2), 4.35 s, (2H, $C_6H_4CH_2$), 7.0–7.25 m, (4H, C_6H_4), ^{13}C NMR: 42, 72, 73, 125, 127, 129, 134, 142
N-(*o*-Fluorobenzyl-oxyethyl)oxazolidine	76	134–135 (2)	1.5070	1.1349	–
N-(*m*-Chlorobenzyl-oxyethyl)oxazolidine	72	148–149 (2)	1.5370	1.1786	^{1}H NMR: 2.66 t, (2H, NCH_2), 2.86 t, (2H, NCH_2), 3.49 t, (2H, OCH_2), 3.61 t, (2H, OCH_2), 4.15 s, (2H, NCH_2O), 4.4 s, (2H, $C_6H_4CH_2$), 7.0–7.3 m, (4H, C_6H_4). ^{13}C NMR: 53, 54, 62, 71, 73, 87, 125, 129, 134, 141

***N*-(2-Ethanoyloxyethyl)-1,3-oxazolidine**. A solution of 5.7 g of **I** in benzene was added dropwise to 1.124 g of finely crushed Na in 20 ml of benzene. After the completion of the initially vigorous reaction, the mixture was heated to 60°C, and the stirring was continued at this temperature until the sodium fully dissolved. Then 3.82 g of acetyl chloride was added dropwise to the alcoholate at 20–22°C over a period of 2 h, after which the mixture was stirred for an additional 4 h. After the reaction completion, the organic phase was filtered to remove NaCl, the solvent was distilled off, and the residue was distilled in a nitrogen flow under reduced pressure to obtain 4 g (40%) of *N*-(2-ethanoyloxyethyl)-1,3-oxazolidine, bp 90°C (2 mm Hg), d_4^{20} 1.0998, n_D^{20} 1.4520. ^{1}H NMR spectrum, δ, ppm: 2.1 t (3H, CH_3), 2.75 t (2H, NCH_2), 3.0 t (2H, NCH_2), 3.72 t (2H, OCH_2), 4.15 t (2H, OCH_2), 4.21 s (2H, NCH_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.0, 54.0, 62.5, 87.0, 170.0.

***N*-(2-Pentanoyloxyethyl)-1,3-oxazolidine**. A mixture of 10.5 g of diethanolamine, 10.2 g of valeric acid, and 30 ml of toluene was refluxed until the release of water was complete, after which the mixture was neutralized with KOH and filtered to remove KCl; the solvent was distilled off, and distillation of the residue in a nitrogen flow under reduced pressure gave 5 g (26%) of 2-(2-hydroxyethyl)aminoethyl valerate, bp 135–137°C (2 mm Hg), d_4^{20} 1.0816, n_D^{20} 1.4730.

The condensation of 2-(2-hydroxyethyl)aminoethyl valerate was performed by procedure a. The yield and physicochemical constants of *N*-(2-pentanoyloxyethyl)-1,3-oxazolidine coincided with those of the same product obtained by method c.

***N*-(2-Hydroxyethyl)morpholine**. To a mixture of 34.8 g of morpholine and 32.2 g of ethylene chlorohydrin, we added dropwise at 40–45°C over a period of 1.5 h 32 g of a 50% NaOH solution. After the reaction completion, the organic layer was separated and dried over sodium sulfate; by distillation in a nitrogen flow under reduced pressure, we isolated 35 g (67%)

of *N*-(2-hydroxyethyl)morpholine, bp 104°C (10 mm Hg), d_4^{20} 1.0742, n_D^{20} 1.4766. ^{1}H NMR spectrum, δ, ppm: 2.52 t (2H, NCH_2), 2.53 t [4H, $N(CH_2)_2$], 3.66 t [4H, $O(CH_2)_2$], 4.23 s (H, OH). ^{13}C NMR spectrum, δ, ppm: 54.0; 58.0, 61.0, 66.5.

***N*-(2-Alkanoyloxyethyl)morpholines** were prepared by esterification of carboxylic acids with morpholine **II**. The reactions were performed similarly to the preparation of *N*-(2-pentanoyloxyethyl)-1,3-oxazolidine. *N*-(2-Ethanoyloxyethyl)-, *N*-(2-propanoyloxyethyl)-, *N*-(2-butanoyloxyethyl)-, *N*-(2-pentanoyloxyethyl)-, *N*-(2-hexanoyloxyethyl)-, and *N*-(2-octanoyloxyethyl)morpholines were prepared (see table).

***N*-(Halobenzyl)morpholines**. To a stirred solution of 0.125 mol of morpholine in 60 ml of benzene, heated to 80°C, we added dropwise over a period of 1 h 0.125 mol of halobenzyl chloride, after which the mixture was stirred for an additional 3 h. After the reaction completion, the mixture was neutralized with a 5% $NaHCO_3$ solution, washed with water to neutral reaction, and dried over sodium sulfate. After distilling off the solvent, the desired compounds were isolated by distillation in a nitrogen flow under reduced pressure.

***N*-(*o*-Fluorobenzyl)- and *N*-(*m*-chlorobenzyl)morpholines** were prepared (see table). Data on *N*-(halobenzyl)-1,3-oxazolidines are listed in the table.

***N*-(*m*-Chlorobenzyl)- and *N*-(*o*-fluorobenzyl)ethanolamines**. Halobenzyl chloride (0.12 mol) was added dropwise to a stirred mixture of 1 mol of ethanolamine and 30 ml of benzene, after which the mixture was refluxed with stirring for 4 h, neutralized after cooling with KOH, and filtered to remove KCl. The benzene was distilled off, and the target products were isolated by distillation in a nitrogen flow under reduced pressure.

***N*-(*m*-Chlorobenzyl)- and *N*-(*o*-fluorobenzyl)oxazolidines** were prepared similarly to *N*-(2-hydroxyethyl)-1,3-oxazolidine. Data on *N*-(halobenzyloxyethyl)-1,3-oxazolidines are listed in the table.

β-(*m*-Chlorobenzyloxy)- and β-(*o*-fluorobenzyloxy)ethylamines. Ethanolamine (0.1 mol) was added dropwise to 0.25 mol of finely divided Na in 25 ml of dioxane. After the completion of the initially vigorous reaction, the mixture was heated to reflux and stirred at this temperature until the sodium fully dissolved. Then, while cooling below 15°C, 0.19 mol of halobenzyl chloride was added dropwise, and the resulting mixture was stirred for 5 h. After the reaction completion, the mixture was filtered to remove NaCl, the dioxane was distilled off, and the desired products were isolated by distillation in a nitrogen flow under reduced pressure.

***N*(*m*-Chlorobenzyloxyethyl)- and *N*-(*o*-fluorobenzyloxyethyl)ethanolamines** were prepared similarly to *N*-(*m*-chlorobenzyl)- and *N*-(*o*-fluorobenzyl)-1,3-oxazolidines.

***N*-(*m*-Chlorobenzyloxyethyl)- and *N*-(*o*-fluorobenzyloxyethyl)oxazolidines** were prepared similarly to *N*-(2-hydroxyethyl)-1,3-oxazolidine.

CONCLUSION

Thermal esterification of carboxylic acids with *N*-(2-hydroxyethyl)morpholine gives *N*-(2-alkanoyloxyethyl)morpholines in high yield (80–90%). With *N*-(2-hydroxyethyl)-1,3-oxazolidine, a complex mixture of products is formed; the desired products were obtained in 50–80% yield by indirect procedures.

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