Novel Synthesis of 5-Chloropropyl- and 5-Chlorobutyl-2-oxazolidinones

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Abstract □ A novel synthesis of 5-chloroalkyl-2-oxazolidinones from cyclic ethers was demonstrated. Utilizing 5- and 6-membered cyclic ethers as examples, the α-methylaminomethylcyclic ethers were cyclized to 5-(3-chloropropyl)- and 5-(4-chlorobutyl)-3-methyl-2-oxazolidinone, respectively. Several derivatives of each are reported.

Keyphrases □ 5-Chloropropyl-2-oxazolidinones—synthesis □ 5-Chlorobutyl-2-oxazolidinones—synthesis □ NMR spectroscopy—structure, identity □ IR spectrophotometry—structure, identity

A number of methods of preparing 2-oxazolidinones from acyclic 2-aminoethanols or their equivalent have been reported and extensively summarized by Dyen and Swern (1) and Cornforth (2). In a recent reference, synthesis of 2-oxazolidinones from phosgene and 2-dialkylaminoalkanols was disclosed (3). Heterocyclic ring systems which have been utilized in the formation of 2-oxazolidinones include epoxides (1, 2), 2-phenylimino-1,3-dioxolanes (4), and 1-substituted 3-pyrrolidinols (5).

Cleavage of 2-aminoalkylfurans has been carried out employing catalytic hydrogenation conditions yielding alkylpyrroles (6), alkylpyrrolidines (6, 7), and α-pyrrolidyl-3-alkanols (8). Cyclic ethers such as tetrahydrofuran have been cleaved by acid halides to yield esters of 4-halo-1-pentanol and 5-halo-2-pentanol (9).

The present investigation has demonstrated that 5-haloalkyl-2-oxazolidinones (II) can be obtained by allowing 2-methylaminomethyltetrahydrofuran (*Ia*) or 2-methylaminomethyltetrahydropyran (*Ib*) to react with phosgene in the presence of triethylamine. The reaction sequence is postulated in Scheme I.

Elevation of the temperature to reflux was sufficient to effect cyclization to the 2-oxazolidinones when the cyclic ether was a tetrahydrofuran. With a 6-membered ring ether, *i.e.*, tetrahydropyran, the addition of a Lewis acid such as $ZnCl_2$ was required to effect formation of the 2-oxazolidinone. In compounds *Ia* and *Ib*, the nitrogen and oxygen atoms are in proper juxtaposition for formation of the 2-oxazolidinone ring system. This relationship is in agreement with the previously reported synthesis of 2-oxazolidinones from 3-pyrrolidinols (5). The 5-aminoalkyl-2-oxazolidinones (III) prepared from the corresponding halo-compounds are indicated in Table I.

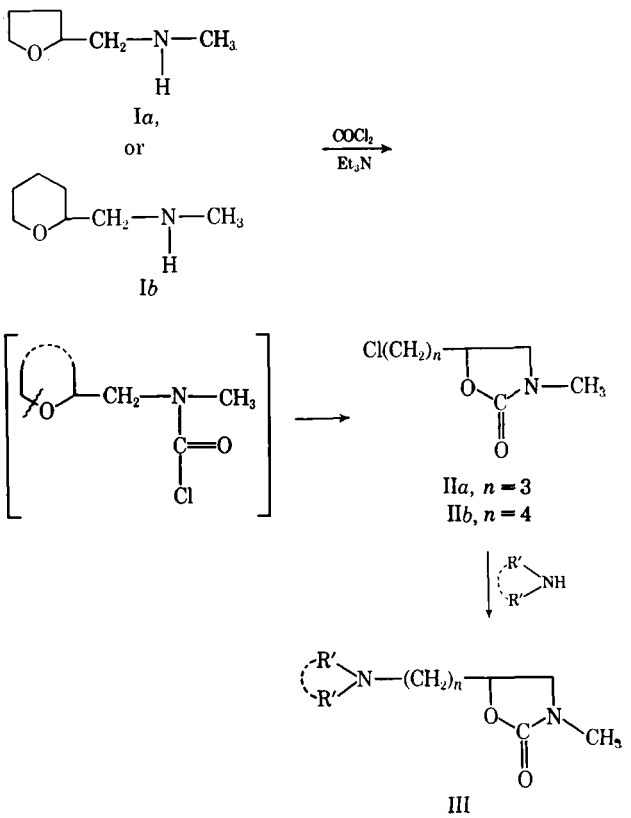
Several of the 5-substituted 2-oxazolidinones (III) possess anti-inflammatory activity.

EXPERIMENTAL[1]

Ethyl 2-Tetrahydropyranomethylcarbamate—A solution of ethyl chloroformate (33.5 g., 0.31 mole) in anhydrous ether (100 ml.) was added dropwise to a stirred solution of 2-aminomethyltetrahydropyran (34.6 g., 0.3 mole) in anhydrous ether (150 ml.). After about one-fourth of the ethyl chloroformate solution had been added, a solution of sodium hydroxide (12.4 g., 0.31 mole) in water (100 ml.) was added at such a rate that both additions were completed simultaneously. The temperature of the reaction mixture was maintained at 0 to 7°. The mixture was allowed to warm to room temperature. The ether layer was separated and the aqueous portion was washed with ether (3 × 100 ml.). The combined ether solutions were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was distilled, 51 g., b.p. 90–93°/0.6 mm. On redistillation, a yield of 43.0 g. (77%), b.p. 153–156°/1.5 mm., was obtained. IR and NMR spectral data are consistent with the proposed structure.

Anal.—Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 56.46; H, 9.03; N, 7.32.

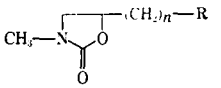
2-Methylaminomethyltetrahydropyran Hydrochloride (Ib)—A solution of ethyl 2-tetrahydropyranomethylcarbamate (37.4 g., 0.2 mole) in tetrahydrofuran (20 ml.) was added dropwise with stirring to a refluxing suspension of lithium aluminum hydride (15.2 g., 0.4 mole) in tetrahydrofuran (500 ml.). On completing the addition of the ester, the mixture was stirred and refluxed for 2 hr. and then allowed to cool to room temperature. The excess hydride and metal salts were decomposed with saturated magnesium sulfate solution and the reaction mixture filtered. The residue was washed with tetrahydrofuran (200 ml.) and the filtrate was stripped on a flash evaporator, yielding an oil. Vacuum distillation gave 9.8 g. of material, b.p. 70–72°/30 mm. The free base was converted to the salt with ethereal hydrogen chloride. The salt was recrystallized from methylethylketone, m.p. 159–162° (3.8 g., 11.5%).

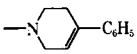
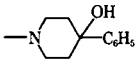
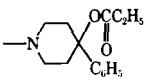
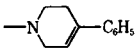
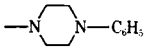
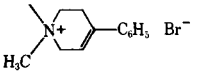


Scheme I

[1] Melting points are corrected. The NMR and IR spectra are consistent with the proposed structures based on analogous spectral data as reported by Fielden *et al.* (5). Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Table I—5-Substituted-3-methyl-2-oxazolidinones



Compd.	*n*	R	M.p., °C.	Anal. Calcd.	Anal. Found
II*a*	3	Cl	134–144 (1 mm.)[a]	C, 47.33 H, 6.81 N, 7.88	C, 46.88 H, 6.89 N, 7.89
II*b*	4	Cl	140–141 (0.5 mm.)[a]	C, 50.13 H, 7.36 N, 7.31	C, 49.85 H, 7.39 N, 7.22
III*a*	3		205–7[b,c]	C, 64.18 H, 7.48 N, 8.32	C, 63.97 H, 7.47 N, 8.23
III*b*	3		154.5–156[b,d]	C, 49.90 H, 7.99 N, 10.58	C, 49.98 H, 8.18 N, 10.62
III*c*	3		212–214[b,c]	C, 60.92 H, 7.67 N, 7.89	C, 60.97 H, 7.77 N, 7.61
III*d*	3		184.5–187[b]	C, 61.38 H, 7.60 N, 6.82	C, 61.25 H, 7.51 N, 6.82
III*e*	4		159–161[b,e]	C, 65.04 H, 7.76 N, 7.98	C, 64.79 H, 7.80 N, 7.94
III*f*	4		166.5–169[b,d]	C, 51.70 H, 8.32 N, 10.05	C, 51.53 H, 8.28 N, 9.93
III*g*	4		82.5–84[f]	C, 68.11 H, 8.57 N, 13.24	C, 67.71 H, 8.50 N, 13.29
III*h*	4		163–165	C, 58.68 H, 7.14 N, 6.84	C, 58.79 H, 7.24 N, 6.63

[a] Boiling point. [b] Hydrochloride salt. [c] Recrystallized from absolute ethanol. [d] Recrystallized from isopropyl alcohol. [e] Recrystallized from a mixture of methylethylketone and methanol. [f] Recrystallized from isopropyl ether.

Anal.—Calcd. for $C_7H_{15}NO \cdot HCl$: C, 50.75; H, 9.74; N, 8.45. Found: C, 51.17; H, 9.74; N, 8.60.

5-(3-Chloropropyl)-3-methyl-2-oxazolidinone (IIa)—A solution of *N*-methyltetrahydrofurfurylamine (57.6 g., 0.5 mole) and triethylamine (50.5 g., 0.5 mole) in toluene (200 ml.) was added to a stirred solution of phosgene (99 g., 1.0 mole) in toluene (400 ml.) with cooling while maintaining the temperature of the reaction mixture below 20°. The mixture was then filtered and the residue washed with toluene. The combined filtrates were heated to reflux for approximately 10 min. The toluene was removed with a flash evaporator and the residue purified by fractional distillation under reduced pressure; b.p. 134–144°/1–3 mm. (61.5 g., 69%).

5-(4-Chlorobutyl)-3-methyl-2-oxazolidinone (IIb)—To a stirred, cooled solution of phosgene (100 g., 1 mole) in toluene (450 ml.) was added dropwise a solution of 2-methylaminomethyltetrahydropyran, *Ib*, (61.7 g., 0.475 mole) and triethylamine (150 ml.) at such a rate as to maintain the temperature of the reaction between −3 and 10°. After the addition was complete, toluene (200 ml.) was added to facilitate stirring while allowing the temperature of the mixture to rise to 25°. The mixture was filtered and the residue washed with toluene (300 ml.). The combined filtrates were refluxed for 2 hr. and then allowed to cool to room temperature. Approximately 1 g. of finely-divided anhydrous zinc chloride was added and the mixture was refluxed with stirring for 15 min. An additional amount of anhydrous zinc chloride (*ca.* 0.5 g.) was added and the mixture was refluxed for 10 min. The cooled reaction mixture was decanted and the decantate stripped to a red oil. Purification of the product was carried out by fractional distillation under reduced pressure, b.p. 120–200°/0.5 mm. (63.5 g., 69.5%). The product was redistilled twice and 59.6 g., b.p. 138–144°/0.5 mm. was collected (a center cut for an analytical sample taken at b.p. 140–141°/0.5 mm.).

Preparation of IIIa, IIIb, IIIc, IIIe, IIIf, and IIIg—The aminoalkyl-2-oxazolidinones were prepared by conventional methods (5). Except for the morpholine derivatives, an equimolar mixture of II, the appropriate amine, and an excess of potassium carbonate in 50–75 ml. of 1- or 2-butanol was refluxed for 2–24 hr. For the preparation of III*b* and III*f*, a 5-molar excess of morpholine was used in place of a solvent and potassium carbonate. Typically, the hot reaction mixture was filtered and the filtrate concentrated *in vacuo*. The free base was purified by recrystallization or converted to the hydrogen chloride salt and recrystallized from the appropriate solvent. Analytical data, recrystallization solvents, and melting points are reported in Table I.

3-Methyl-5-[3(4-phenyl-4-propionoxypiperidino)-propyl]-2-oxazolidinone Hydrochloride (IIId)—A solution of 3-methyl-5-[3(4-hydroxy-4-phenylpiperidino)propyl]-2-oxazolidinone hydrochloride, III*c*, (10.1 g., 0.028 mole) in chloroform (100 ml.) containing anhydrous potassium carbonate (6.9 g., 0.05 mole) was stirred for 30 min. and propionyl chloride (2.7 g., 0.028 mole) in chloroform (20 ml.) was added with stirring over a period of 30 min. The mixture was stirred for 2 hr. at room temperature and a mixture of 50 g. of ice and 5 ml. of saturated sodium carbonate solution was added. The chloroform layer was separated and dried over magnesium sulfate, filtered, and stripped to an oil which was crystallized by the addition of ether. The salt was formed from ethereal hydrogen chloride and recrystallized twice from absolute ethanol with the aid of charcoal, m.p. 184.5–187° (4 g., 34.5%).

1-Methyl-1-[4-(3-methyloxazolidin-2-on-5-yl)butyl]-3,6-dihydro-4-phenyl-(2H)-pyridinium Bromide (IIIh)—An aqueous solution of 3-methyl-5-[4-(4-phenyl-1,2,5,6-tetrahydro-1-pyridyl)-butyl]-2-oxazolidinone hydrochloride, III*e* (11.7 g., 0.037 mole) was made alkaline with saturated sodium carbonate solution and the mixture filtered. The residue was washed with water. The dried residue was then dissolved in methylethylketone (50 ml.) and added to a solution of methyl bromide (22.6 g., 0.24 mole) in methylethylketone (50 ml.) and the mixture was stirred at room temperature for 1 hr. The recovered viscous residue was crystallized from acetone and recrystallized twice from a mixture of methanol and methylethylketone with the aid of activated charcoal, m.p. 163–165° (6.7 g., 44%).

REFERENCES

(1) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197(1967).

(2) J. W. Cornforth, in "Heterocyclic Compounds," Vol. 5,

R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp. 396–400.
(3) K. C. Murdock, *J. Org. Chem.*, **33**, 1367(1968).
(4) K. Gulbins and K. Hamann, *Angew. Chem.*, **73**, 434(1961).
(5) M. L. Fielden, W. J. Welstead, and C. D. Lunsford, *Abstracts, 152nd National Meeting of the American Chemical Society*, New York, N. Y., 1966, p. 5P.
(6) W. I. Shuikin, A. D. Petrov, V. G. Glukhovtsov, I. F. Bel'skii, and G. E. Skobtsova, *Izvest. Akad. Nauk SSSR, Ser. Khim.*, **9**, 1682(1964).
(7) F. Sorm and Z. Arnold, *Coll. Czech. Chem. Commun.*, **12**, 444(1947); through *Chem. Abstr.*, **43**, 2988*c*(1949).
(8) A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, *Khim. Geterots. Soed.*, **1966**, 923.
(9) S. A. Morrell, U. S. pat. 2,424,184 (July 15, 1947); through *Chem. Abstr.*, **41**, P7411*e*(1947).

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Solubility of the Parabens in Ethanol–Water Mixtures

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Abstract □ The solubilities of *n*-alkyl parabens have been determined in binary mixtures of ethanol and water. The profiles showed a dielectric requirement value of about 29–32 for the subject compounds. The butyl derivative formed a two-phase system over a certain composition range of ethanol and water. These phases were analyzed and found to be approximately invarient with respect to the concentration of the three components indicating the formation of a solvate. The ratio of the solubility of these compounds relative to the methyl derivative is considered over the polarity range studied.

Keyphrases □ Paraben solubility—ethanol-water mixtures □ Dielectric requirements—parabens □ Dielectric constants—ethanol-water mixtures □ Polarity—paraben solubility

Previous studies on the *n*-alkyl esters of *p*-hydroxybenzoic acid have indicated cosolvency maxima at dielectric requirements (DR) (1, 4) of about 14 and 30 in a pure solvent scan and about 10 in dioxane–water mixtures (2). This study was conducted in order to substantiate the probable DR of 30 from previous work. The solvent system used, alcohol and water, provided a convenient span of dielectric constant values, *i.e.*, 24–78 and would also aid in the isolation of the solubility distribution curve in this dielectric constant range. Although a previous study utilized a solvent system encompassing the value expected, two liquid systems were formed over a wide range of composition (2).

EXPERIMENTAL

Reagents—The reagents used in this study have been previously given in recent studies (1, 2).

Procedures and Apparatus—The methodology used in determining solubility was by a gravimetric procedure which has been described previously (3). The results shown are the averages from at least three solubility runs over the total composition range.

RESULTS AND DISCUSSION

In Figs. 1 and 2 the solubilities of the parabens in milligrams per milliliter are plotted *versus* the dielectric constant of the respective binary mixture used. As can be easily seen, the parabens show a dielectric requirement at a dielectric constant value of 30. This value substantiates the value of about 30 found for the pure solvent scan (1). It should also be noted that results are being compared utilizing the same concentration notation. The solubility profiles have been presented in the manner shown for convenience and ease of observation. For the first three members of this series of esters, a fairly linear curve is observed over a range of dielectric constants for these mixtures. This range of dielectric constants spans values of about 35–60, with slight differences in the slopes of the linear positions of these profiles. The slopes, *i.e.*, the rate of change in solubility in milligrams per milliliter per dielectric constant unit is summarized in Table I. It can be seen that as the magnitude of

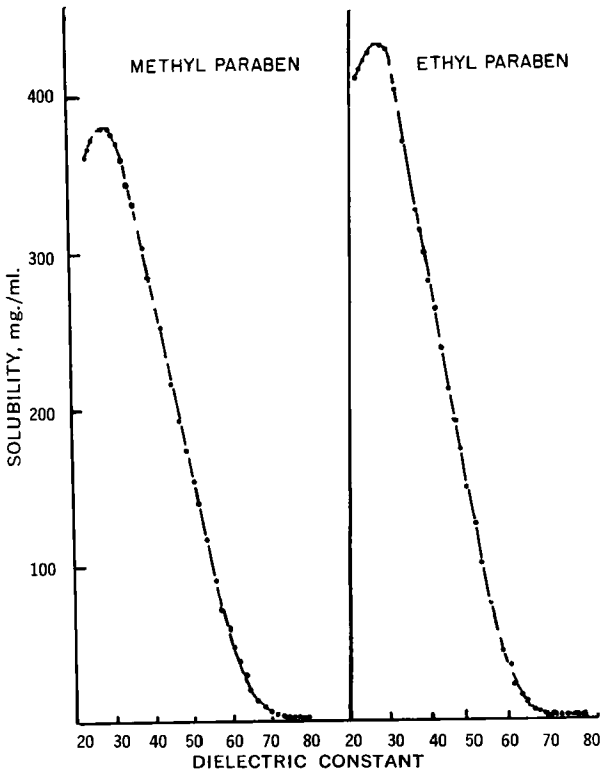

Figure 1—*A plot of the solubility at 25° in mg./ml. for methyl and ethyl parabens* versus *the dielectric constant of the binary mixtures.*