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3-(4-Chlorobutyl)-2-oxazolidinone (1)

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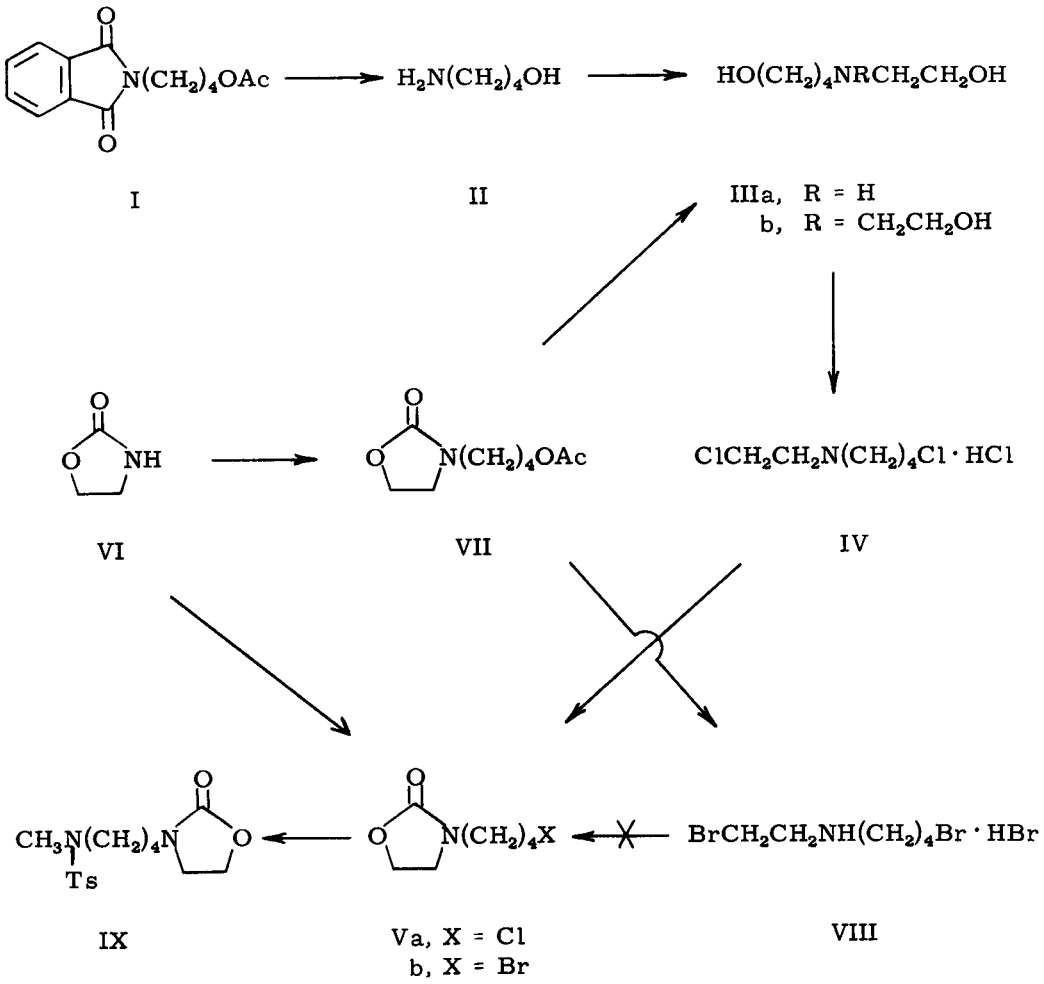
Expansion of homologous series of compounds advantageously derived from 3-(2-chloroethyl)-2-oxazolidinone and 3-(3-chloropropyl)-2-oxazolidinone, the utility of which in the synthesis of precursors to analogs of 2-aminoethanethiol and related radioprotective agents was recently described (2), requires the availability of other 3-(ω-haloalkyl)-2-oxazolidinones. The synthesis of one of these, 3-(4-chlorobutyl)-2-oxazolidinone (Va), has been achieved by routes involving both ring closure and alkylation of the preformed ring. The latter route has provided a practical source of Va for synthetic use.

The first route proceeded through five steps: alkylation of potassium phthalimide with 4-chlorobutyl acetate to give *N*-(4-acetoxybutyl)phthalimide (I); basic hydrolysis of I to give 4-amino-1-butanol (II); hydroxyethylation of II with ethylene oxide to give 4-(2-hydroxyethylamino)-1-butanol (IIIa); treatment of the preformed hydrochloride of IIIa with thionyl chloride to give *N*-(2-chloroethyl)-4-chlorobutylamine hydrochloride (IV); and cyclization of IV with sodium carbonate, as in the reported (3) preparation of the chloroethyl homolog, to give Va. Hyrolysis of I was first attempted in refluxing hydrochloric acid; but, although nearly the theoretical amount of phthalic acid separated from the cooled solution, none of the desired II could be liberated from the remaining reaction mixture. The troublesome purification and low yield of IIIa in the hydroxyethylation step limits the usefulness of the entire sequence as a preparative route; IIIa was separated



from unchanged II and appreciable co-product, 4-[bis(2-hydroxyethylamino)]-1-butanol (IIIb). The yield of Va from the final ring-closure step was also low.

The second route that led to Va involved a direct, preferential alkylation of 2-oxazolidinone (VI) with 1-bromo-4-chlorobutane. Two exploratory experiments were unsuccessful: an attempted alkylation in *N,N*-dimethylformamide (DMF) at 75° with potassium carbonate as base led only to a high recovery of unchanged VI; but treatment of the sodium derivative of VI (formed *in situ* with sodium hydride) with an equivalent amount of the dihalide in DMF resulted in an exothermic reaction, which apparently produced 3,3'-tetramethylenebis-2-oxazolidinone (2) as the major product. A procedural refinement in which a solution of VI in DMF was added to a mixture of the dihalide and sodium hydride produced, on a small scale, a 38% yield of twice-distilled Va; but attempts to adapt this procedure to a larger scale failed apparently because of the formation of the bis-2-oxazolidinone. The use of benzene as solvent instead of DMF on the same small scale gave a 27% yield of Va, but this procedure and variations of it also failed on a larger scale. An alternative approach, which would circumvent the formation of the troublesome bis-2-oxazolidinone, was then pursued. Alkylation of the sodium derivative of VI with 4-chlorobutyl acetate produced 3-(4-acetoxybutyl)-2-oxazolidinone (VII), hydrolysis of which in refluxing hydrochloric acid conveniently afforded the hydrochloride of IIIa, the key intermediate in the initial synthesis of Va. The action of an acetic acid solution of hydrogen bromide on VII afforded *N*-(2-bromoethyl)-4-bromobutylamine hydrobromide (VIII), but an attempt to cyclize VIII to the bromo analog Vb failed possibly because of pyrrolidine-ring formation from the reactive bromobutylamine group.

Although analytically pure samples of Va were prepared by the methods described above, procedural and yield limitations forced a re-examination of the direct chlorobutylation of VI. Slow addition of a solution of VI and excess 1,4-dichlorobutane in DMF to a mixture of sodium hydride and DMF led to a high yield of undistilled Va as a yellow oil pure enough for many synthetic uses. Furthermore, the procedure was found to be reproducible on a larger scale. The utility of Va produced in this manner was demonstrated by its conversion, for example, to *N*-methyl-*N*-[4-(2-oxo-3-oxazolidinyl)butyl]-*p*-toluenesulfonamide (IX), a homolog of recently reported (2) oxazolidinone derivatives.

EXPERIMENTAL (4)

N-(4-Acetoxybutyl)phthalimide (I).

A solution of 4-chlorobutyl acetate (5) (182 g., 1.21 moles) in DMF (200 ml.) was added dropwise to a stirred mixture of potassium phthalimide (218 g., 1.18 moles) in DMF (400 ml.) at 90-100°. Heating with stirring at 90-100° was continued for 3 hours. The mixture was allowed to cool, diluted with water (3 l.), and extracted with three 600-ml. portions of chloroform. Removal of the solvent from the water-washed and dried (magnesium sulfate) chloroform solution left I as a colorless oil, which subsequently crystallized. The crystalline mass was pulverized under ethanol and dried *in vacuo* over phosphorus pentoxide; yield 244 g. (79%), m.p. 60-61° [lit. (6a) m.p. 59.5°, lit. (6b) m.p. 58-60°].

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.78; N, 5.36. Found: C, 64.43; H, 5.87; N, 5.49.

4-Amino-1-butanol (II).

A stirred mixture of I (159 g., 0.609 mole) and 20% potassium hydroxide solution (1 l.) was refluxed for 1 hour under a 30-cm. Vigreux column. The extent of heating was then increased to cause distillation, and 600 ml. of distillate was collected and discarded. The column was replaced by a Claisen head, and the remaining solution was distilled to near-dryness as evidenced by a drop in distilling vapor temperature from a maximum of 110°. The distillate, an aqueous solution of II, was set aside. More water (100 ml.) was added to the distillation residue, and the mixture was again distilled to near dryness or until 100 ml. of distillate had been collected; this process was repeated twice more. The Claisen head distillates were combined and fractionally distilled through a 30-cm. Vigreux column. The yield of II, b.p. 197-200° [lit. (7) b.p. 202°], was 30.5 g. (56%). This procedure is adapted from that described by Kremer (8) for the conversion of *N*-(3-bromopropyl)phthalimide to 3-amino-1-propanol.

4-(2-Hydroxyethylamino)-1-butanol (IIIa).

Liquid ethylene oxide (12.4 g., 0.281 mole; cylinder gas condensed in chilled flask) was added to a cold (0-5°) solution of II (30.0 g., 0.337 mole) in ethanol (80 ml.) contained in a glass-lined stainless steel pressure vessel. The sealed vessel was heated at 100° for 1 hour. The ethanol was removed under reduced pressure (water aspirator, rotary evaporator), and the residue was fractionally distilled *in vacuo* through a Vigreux column. Three fractions were collected: unchanged II, 9.8 g., b.r. 87-95° (6 mm.); crude IIIa, 17.4 g., b.r. 158-188° (6 mm.); and 4-[bis(2-hydroxyethyl)amino]-1-butanol (IIIb), 9.6 g., b.r. 182-194° (1.5 mm.), n_D^{24} 1.4867. Redistillation of the second fraction gave pure IIIa, 12.2 g., b.p. 160-163° (6 mm.), n_D^{23} 1.4768; the yield of twice-distilled IIIa based on unrecovered II was 40%.

Anal. Calcd. for $C_6H_{15}NO_2$: C, 54.10; H, 11.35; N, 10.51. Found: C, 54.40; H, 11.48; N, 10.58.

The yield of once distilled IIIb, which was analytically pure as such, was 24% based on unrecovered II.

Anal. Calcd. for $C_8H_{19}NO_3$: C, 54.21; H, 10.80; N, 7.90. Found: C, 54.37; H, 10.79; N, 7.96.

The above-described procedure was modeled after that reported by Brown (9) for preparation of a lower homolog of IIIa.

N-(2-Chloroethyl)-4-chlorobutylamine Hydrochloride (IV). Method A. From IIIa.

A solution of IIIa (11.2 g., 84.0 mmoles) in ethanol was treated with an excess of an ethanolic solution of hydrogen chloride. The ethanol was removed by evaporation under reduced pressure (rotary evaporator, water aspirator), the last traces being removed at less than 1 mm. (oil pump). A stirred solution of the residual oil in chloroform (100 ml.) was treated with a solution of thionyl chloride (22.0 g., 0.185 mole) in the same solvent (50 ml.), refluxed for 4 hours and cooled. Slow addition of ether precipitated crystalline IV, which was washed with ether and dried *in vacuo*; yield 14.8 g. (86%), m.p. 164-167°.

Anal. Calcd. for $C_6H_{13}Cl_2N\cdot HCl$: C, 34.91; H, 6.83. Found: C, 35.05; H, 6.79.

Method B. From VII via IIIa·HCl.

A solution of VII (32.0 g., 0.159 mole) in concentrated hydrochloric acid (500 ml.) was slowly heated to boiling, refluxed for 3 hours, and distilled at atmospheric pressure until 335 ml. of distillate had been collected. The remaining solution was evaporated to dryness under reduced pressure. A solution of the residual oil (IIIa·HCl) in chloroform (250 ml.) was treated with a solution of thionyl chloride (38.8 g., 0.326 mole) in the same solvent (150 ml.) in the manner described under A to give IV, m.p. 162-165°, in 59% yield (based on VII) following recrystallization from chloroform-ether.

3-(4-Chlorobutyl)-2-oxazolidinone (Va). A. From IV.

Compound IV (13.8 g., 66.7 mmoles) was added all at once to a cold (0-5°), stirred solution of sodium bicarbonate (5.61 g., 66.7 mmoles) and sodium hydroxide (2.66 g., 66.7 mmoles) in water (70 ml.) with

immediate separation of an oil. The stirred mixture was allowed to warm to room temperature and then was kept at 35-40° (water bath) for 20 minutes. The resultant clear solution was extracted several times with dichloromethane, and *in vacuo* evaporation of the water-washed and dried (sodium sulfate) dichloromethane solution left an oily residue, vacuum distillation of which afforded 1.36 g. (12%) of Va, b.r. 180-210° (0.4 mm.), n_D^{24} 1.4841, infrared absorption (film) at 2930, 2865, 1745, 1645, 1520, 1485, 1430, 1370, 1260, 1155, 1095, 1050, 970, 800, 760, 720, 695, 640, 620 cm^{-1}.

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.34; H, 6.81; Cl, 19.96. Found: C, 47.76; H, 6.93; Cl, 20.0.

B. From VI (in DMF).

A solution of VI (10) (2.00 g., 23.0 mmoles) in DMF (5 ml.) was added dropwise to a stirred mixture of sodium hydride [1.12 g., 50% oil dispersion (11); 23.3 mmoles], 1-bromo-4-chlorobutane (5) (3.94 g., 23.0 mmoles), and DMF (20 ml.). The resultant mixture was stirred overnight at room temperature, the solvent removed by vacuum distillation, and the residue extracted with chloroform. Distillation of the water-washed and dried (magnesium sulfate) chloroform solution led to a distillate [b.r. 146-162° (0.3 mm.)] that separated immediately into two layers (mineral oil from the sodium hydride dispersion co-distilled with Va). The distillate was washed with 30-60° ligroin to remove mineral oil and redistilled; the yield of Va, b.p. 137-142° (0.2 mm.) and n_D^{20} 1.4876, was 1.58 g. (38%). The infrared spectra of Va from A and B are identical.

C. From VI (in Benzene).

The reaction described under B was repeated on the same scale but in benzene (total of 40 ml.) instead of DMF and with dry oil-free sodium hydride. (The 50% sodium hydride oil dispersion was washed several times with 30-60° ligroin, each portion of clear supernatant being carefully withdrawn with a pipette. The sodium hydride was then dried in a stream of nitrogen with warming by water bath). A 64-hour reflux period, removal of the solvent, extraction of the residue with chloroform, and distillation afforded 1.10 g. (27%) of Va, b.p. 144-148° (0.2 mm.) and n_D^{20} 1.4862. The infrared spectrum was identical with those of samples from A and B.

D. Practical Synthesis from VI and 1,4-Dichlorobutane.

A solution of VI (17.4 g., 0.200 mole), 1,4-dichlorobutane (132 g., 1.04 moles), and DMF (100 ml.) was added dropwise during 2.5 hours to a stirred suspension of oil-free sodium hydride (0.200 mole, see under C) and DMF (10 ml.), the temperature being maintained at 25-30° by moderate cooling. The resultant mixture was stirred 0.5 hour longer, then filtered from sodium chloride, and the solvent was removed from the filtrate by distillation *in vacuo* (final pressure less than 1 mm. with bath temperature 75°). The residual orange oil (33.2 g.) was dissolved in absolute ethanol (100 ml.), and the solution was treated with Norit and filtered through Celite. Removal of the ethanol afforded 32.0 g. (90%) of Va as a pale-orange oil, n_D^{25} 1.4838, with infrared spectrum practically identical with that of the sample from A.

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.34; H, 6.81; Cl, 19.96; N, 7.89. Found: C, 47.37, 47.24; H, 7.34, 7.34; Cl, 17.50, 17.54; N, 8.35.

Thin-layer chromatograms [Silica gel H (Merck), ethyl acetate] of crude Va revealed an immobile contaminant, which was diminished in a partially purified sample of Va obtained in 96% recovery following clarification (Norit, Celite) of the cloudy solution resulting from dissolving crude Va in ethyl acetate. Distillation *in vacuo* proved an ineffective means for purification of Va because of partial decomposition.

N-Methyl-*N*-[4-(2-oxo-3-oxazolidinyl)butyl]-*p*-toluenesulfonamide (IX).

A stirred mixture of crude Va (4.08 g.), *N*-methyl-*p*-toluenesulfonamide (3.70 g., 20.0 mmoles), potassium carbonate (3.44 g., 25.0 mmoles) and DMF (10 ml.) was maintained at 110-120° for 3 hours. Dilution of the cooled mixture with water (100 ml.) caused separation of an orange oil from which the supernatant was removed by decantation. The oil was stirred with two 100-ml. portions of water, which were also removed and combined with the original decantate. The oil was then dissolved in ethanol (25 ml.). Crystalline IX separated from the chilled ethanol solution, and the mixture was diluted with cold water; further chilling afforded a crystalline mass. More IX crystallized from the seeded and chilled aqueous decantate. The total yield of IX, dried *in vacuo* (phosphorus pentoxide), was 5.00 g. (77%), m.p. 63-65°. An analytical sample, which crystallized from cold ethanol, had m.p. 64-66°. Its infrared spectrum in potassium bromide disc revealed *N,N*-disubstituted sulfonamide bands at 1340 and 1155 cm^{-1} and two narrow carbonyl bands at 1745 and 1725 cm^{-1}; in chloroform solution the 1725 cm^{-1} band was not present.

Anal. Calcd. for $C_{15}H_{22}N_2O_4S$: C, 55.19; H, 6.79; N, 8.58; S, 9.83. Found: C, 54.96; H, 6.60; N, 8.47; S, 10.05.

In two subsequent preparations IX with m.p. 63-65° separated from the seeded, water-diluted reaction mixture in yields of 81 and 90%.

3-(4-Acetoxybutyl)-2-oxazolidinone (VII).

An oil dispersion of sodium hydride (11) (48.1 g., 50% sodium hydride; 1.00 mole) was stirred with several portions of ligroin and dried as under C. DMF (300 ml.) was added, and the stirred mixture was treated dropwise with a solution of VI (10) (87.1 g., 1.00 mole) in DMF (100 ml.) at such a rate that frothing was not excessive and the temperature did not exceed 60°. After 0.5 hour, the resulting suspension was heated to 70° and treated dropwise with a solution of 4-chlorobutyl acetate (5) (155 g., 1.03 mole) in DMF (50 ml.) during 1 hour. The mixture was stirred at 85-90° for 64 hours. Removal of the solvent *in vacuo*, extraction of the residue with chloroform, and fractionation of the water-washed and dried (magnesium sulfate) chloroform solution afforded VII as a colorless oil, b.r. 150-160° (0.07 mm.) in 36% yield (72.2 g.). The infrared spectrum is identical with that of an analytical sample, b.r. 140-150° (0.1 mm.), obtained in a pilot experiment; infrared absorption (film) at 2940, 2865, 1740, 1520, 1480, 1430, 1365, 1240, 1120, 1050, 970, 880, 800, 760, 690, 630, 600 cm^{-1}.

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.71; H, 7.51; N, 6.96. Found: C, 54.15; H, 7.75; N, 7.10.

N-(2-Bromoethyl)-4-bromobutylamine Hydrobromide (VIII).

A solution of VII (72.0 g., 0.358 mole) in 30% hydrogen bromide in acetic acid solution (5) (800 ml.) was stirred overnight at room temperature, gradually heated to boiling, and refluxed for 72 hours. Dilution of the cooled solution with ether (2 l.) precipitated VIII, which was washed with ether, dried *in vacuo*, and purified by two recrystallizations from chloroform; yield 100 g. (83%), m.p. 164-166°.

Anal. Calcd. for $C_6H_{13}Br_2N \cdot HBr$: C, 21.20; H, 4.15; Br, 70.52. Found: C, 21.46; H, 4.51; Br, 70.3.

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