[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

N-(2-LEPIDYL) SUBSTITUTED AMINO ALCOHOLS

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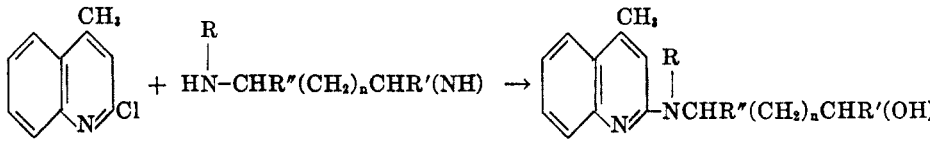
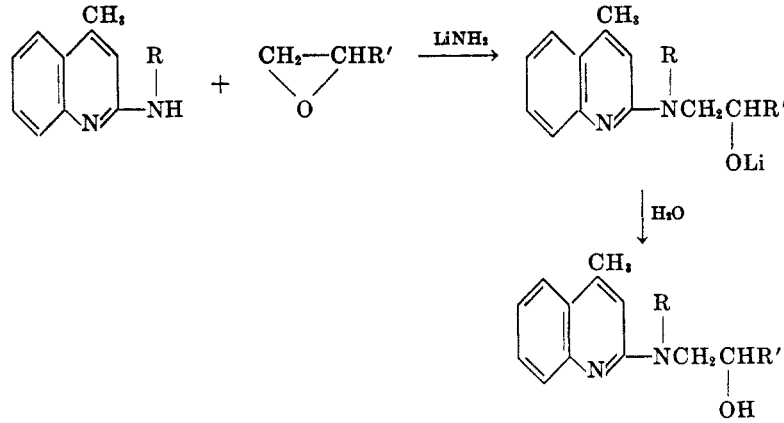
As an extension of a previous investigation involving the synthesis of some N-2-pyridylalkanolamines (1), the preparation of several N-(2-lepidyl) substituted amino alcohols was undertaken.

Although seven of the desired compounds were obtained in good yield by heating 2-chlorolepidine with an excess of the requisite amino alcohols (Method A) only tarry decomposition products resulted from the reaction of the heterocyclic halide with N-benzylethanolamine. The product was subsequently prepared in excellent yield by heating a xylene solution of 2-benzylaminolepidine and ethylene oxide with lithium amide at 100° (Method B); in the absence of lithium amide no

METHOD A



METHOD B



reaction occurred. N-[2-(2-Lepidyl)aminoethyl]-morpholine, when treated similarly with either propylene or styrene oxide, gave no evidence of reaction although the diamine, as well as several other N-substituted 2-aminolepidines, gave the expected amino alcohol with ethylene oxide. That a steric factor may be involved may be inferred from the fact that the homologous N,N-diethyl-N′-(2-lepidyl)-trimethylenediamine was successfully condensed with both propylene and styrene oxides.

[1] From a thesis submitted by Herman Horn to the Graduate Faculty of Brooklyn College, February 1953, in partial fulfillment of the requirements for the Master of Arts degree.

The availability of the hydroxyethylating reagent, ethylene carbonate, prompted an investigation into the possibility of substituting it for ethylene oxide in this reaction (Method B), thus eliminating the necessity of conducting the reaction under pressure. Under conditions, and modifications thereof, wherein N-methyl-N-phenylethanolamine was formed (5), none of the expected product could be isolated from the reaction of 2-benzylaminopyridine with this reagent.

The hydrochloride of N-(2-lepidyl)ethanolamine as well as 2-chlorolepidine, 2-benzylaminolepidine, and N-ethyl-N-(2-lepidyl)ethanolamine, were inactive in retarding the growth of Sarcoma 180 in mice.[2a] The latter caused convulsions in mice, showed no curariform activity, and offered no protection against electric shock, metrazol, or strychnine.[2b]

Acknowledgment. The authors wish to thank the Research Corporation for financial support of this project and Mr. Irving C. Kogon for the initial preparations of 2-(3-hydroxybutyl)aminolepidine and 2-(3-isopropoxypropyl)aminolepidine.

EXPERIMENTAL

All melting points are corrected, boiling points are not. The preparations of 2-chlorolepidine, 2-aminolepidine, N-[2-(2-lepidyl)aminoethyl]-morpholine, and N,N-diethyl- and N,N-di-*n*-butyl-N'-(2-lepidyl)trimethylenediamines were described in previous publications (2–3). 2-Benzylaminolepidine (2), m.p. 70–73°, was obtained in 84% yield by Method A. 3-Aminopropanol and 3-isopropoxypropylamine were generously donated by the American Cyanamid Co., 4-amino-2-butanol, N-ethyl- and N-butyl-ethanolamines, 3-diethyl- and 3-di-*n*-butyl-aminopropylamines, and N-hydroxyethylmorpholine by Sharples Chemicals, Inc., 2-amino-1-butanol by the Commercial Solvents Corporation, ethylene carbonate by the Jefferson Chemical Co., Inc., and monoisopropanolamine and N-aminoethylmorpholine by the Carbide and Carbon Chemicals Co. N-Benzylaminoethanol was prepared by the method of Rumpf and Kwass (4).

N-(2-Lepidyl) substituted amino alcohols. Method A. A mixture of 0.20 mole of 2-chlorolepidine and 0.80 mole of the aminoalcohol was heated at a bath temperature of 160–165° for 20–24 hours. The reaction mixture, while still warm, was dissolved in 150 ml. of chloroform or ethylene chloride and shaken with 25 ml. of a saturated aqueous potassium carbonate solution. Sufficient anhydrous potassium carbonate was added to remove the water and after standing overnight, the mixture was filtered, the solvent removed, and the product obtained by distillation under diminished pressure.

Method B. A mixture consisting of 0.10 mole of the 2-lepidylamine, 0.15 mole of ethylene oxide dissolved in 25 g. of xylene, and 0.12 mole of lithium amide was heated in a pressure vessel, with vigorous shaking, at 100° for 15 hours. At the end of this time the reaction mixture was washed several times with water and then distilled under diminished pressure.

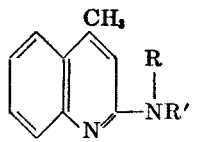
In the absence of lithium amide there was obtained from a reaction between 2-benzylaminolepidine and ethylene oxide almost a quantitative recovery of the original secondary amine, isolated as its hydrochloride, m.p. 239–241° (2). The melting point was not depressed on admixture with an authentic sample.

Method C. A mixture of 0.10 mole of the 2-lepidylamine, 0.12 mole of either styrene oxide or 0.15 mole of propylene oxide, 0.12 mole of lithium amide, and 100 ml. of benzene, which had been dried over calcium hydride, was heated under reflux for 24 hours. The reaction-

[2] The authors wish to thank (a) Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research and (b) Dr. Irwin H. Slater of the School of Medicine and Dentistry at the University of Rochester for this information.

TABLE I

N-(2-LEPIDYL) SUBSTITUTED AMINO ALCOHOLS



R	R'	METHOD	B.P. °C.	B.P. Mm.	YIELD, %	M.P., °C.	Formula	ANALYSES Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
H	CH_2CH_2OH	A	164	0.11	77–86	107.5–108.5[a]	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.26	7.09	13.85
						237.5–239.5[b]	$C_{12}H_{14}N_2O \cdot HCl$	60.37	6.33		60.46	6.54	
H	$CH_2CH_2CH_2OH$	A	185–190	.08	84	100–100.5[c]	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.41	7.44	12.79
						250–251[d]	$C_{13}H_{16}N_2O \cdot HCl$	61.75	6.78		61.92	6.91	
H	$CH_2CH(OH)CH_3$	A	148	.05	84–87		$C_{13}H_{16}N_2O$	72.19	7.46		72.18	7.67	
						208–209	$C_{13}H_{16}N_2O \cdot HCl$	61.75	6.78		61.94	6.43	
H	$-CH(C_2H_5)CH_2OH$	A	166	.17	85	133–134.5[a]	$C_{14}H_{18}N_2O$	73.01	7.88		72.84	7.79	
						170–172[d]	$C_{14}H_{18}N_2O \cdot HCl$	63.01	7.18		63.09	7.39	
						231–232[d]	$C_{14}H_{18}N_2O \cdot \frac{1}{2}H_2SO_4$			10.03			9.85
H	$CH_2CH_2CH(OH)CH_3$	A	165	.03	84	98.5–99.5[a]	$C_{14}H_{18}N_2O$	73.01	7.88		72.69	7.67	
						222–223[b]	$C_{14}H_{18}N_2O \cdot HCl$	63.01	7.18		62.86	7.10	
C_2H_5	CH_2CH_2OH	A	139–141	.10	70–73		$C_{14}H_{18}N_2O$	73.01	7.88	12.17	72.96	7.92	12.22
						219.5–221[b]	$C_{14}H_{18}N_2O \cdot HCl$	63.01	7.18		63.06	7.25	
$n\text{-}C_4H_9$	CH_2CH_2OH	A	156–162	.16	60–65		$C_{16}H_{22}N_2O$	74.38	8.58		74.39	8.81	
						198.5–199[b]	$C_{16}H_{22}N_2O \cdot HCl$	65.17	7.86	9.50	65.48	7.97	9.42
$CH_2C_6H_5$	CH_2CH_2OH	B	201–202	.01	87		$C_{19}H_{20}N_2O$	78.05	6.90		77.94	6.72	
						176–176.5[d]	$C_{19}H_{20}N_2O \cdot HCl$	69.39	6.44	10.78[e]	69.26	6.53	10.98[e]
$(CH_3)_2OCH(CH_3)_2$	CH_2CH_2OH	B	175–185	.04	83		$C_{18}H_{26}N_2O_2$	71.49	8.67		71.36	8.77	
						157–158[d]	$C_{18}H_{26}N_2O_2 \cdot HCl$	63.79	8.03		63.67	8.17	
$(CH_2)_2NC_4H_8O$[f]	CH_2CH_2OH	B	185–188	.04	51		$C_{18}H_{28}N_2O_2$	68.54	7.99		69.02	8.40	
						228–229[g]	$C_{24}H_{32}N_6O_3$	52.94	5.18		52.82	5.38	

$(CH_3)_2N(n\text{-}C_4H_9)_2$	CH_3CH_2OH	B	175–180	.03	71		$C_{23}H_{37}N_3O$	74.35	10.04		73.97	9.66	
						176–177[h]	$C_{35}H_{43}N_9O_{14}$	50.65	5.22		50.23	5.07	
$(CH_3)_2N(C_2H_5)_2$	$CH_3CH(OH)CH_3$	C	175–180	.04	62		$C_{20}H_{31}N_3O$	72.90	9.48	12.76	73.42	9.23	12.90
						180–181[d, i]	$C_{33}H_{37}N_9O_{14}$	48.79	4.73	16.00	48.73	4.47	16.12
$(CH_3)_2N(C_2H_5)_2$	$CH_3CH(OH)C_6H_5$	C	165–168	.03	55		$C_{22}H_{29}N_3O$	76.68	8.50	10.73	76.55	8.64	10.85
						130–131[d, i]							
H	$(CH_3)_2OCH(CH_3)_2$[j]	A	123–124	.06	89		$C_{16}H_{23}N_3O$	74.38	8.58	10.84	74.42	8.95	10.95
						126–127[d]	$C_{16}H_{22}N_3O \cdot HCl$	65.20	7.53	9.51	64.92	7.72	9.56

[a] Recrystallized from benzene. [b] Recrystallized from ethanol. [c] Recrystallized from benzene-hexane. [d] Recrystallized from isopropyl alcohol. [e] Ionizable chlorine. [f] NC_4H_8O i[g] N-morpholino. [g] Monopicrate recrystallized from acetone-dioxane. [h] Dipicrate recrystallized from isopropyl alcohol-acetone. [i] Dipicrate. The picrate of the starting diamine, N,N'-diethyl-N-(2-lepidyl)trimethylenediamine, melted at 171–172° after two recrystallizations from isopropyl alcohol. *Anal.* Calc'd for $C_{29}H_{31}N_9O_{14}$: C, 47.73; H, 4.28; N, 17.28. Found: C, 47.88; H, 4.29; N, 17.22. [j] Intermediate used in the preparation of the amino alcohol.

mixture was washed thoroughly with water and then dried over potassium carbonate. After removing the benzene by distillation, the residual liquid was distilled under diminished pressure. In the reaction of N-[2-(2-lepidyl)aminoethyl]morpholine with propylene and styrene oxides, 70–80% of the starting diamine (2) was recovered, b.p. 172–175° (0.05 mm.). A small amount of tarry residue remained in the distillation flask.

Anal. Calc'd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80.
Found: C, 70.37; H, 7.75.

The *picrate*, m.p. 226–227° after three recrystallizations from acetone, showed no depression in melting point when admixed with picrate prepared from N-[2-(2-lepidyl)aminoethyl]-morpholine.

Anal. Calc'd for $C_{22}H_{24}N_6O_8$: C, 52.80; H, 4.83.
Found: C, 52.31; H, 4.65.

Reactions of amines with ethylene carbonate (5). A mixture of 21.4 g. (0.2 mole) of monomethylaniline, 19.4 g. (0.22 mole) of ethylene carbonate, and 0.25 g. of lithium amide was heated at a bath temperature of 145° until the evolution of carbon dioxide had ceased. Heating was then continued at 160° for one hour and at 190° for two hours. The cooled reaction mixture was dissolved in about 75 ml. of benzene and washed well with water. After removing the benzene by distillation, there was obtained 16.2 g. (53.5%) of a yellow oil distilling at 126–132° (5 mm.).

Repetition of this reaction using benzylaminopyridine in place of the monomethylaniline resulted in a 98% recovery of starting material. Conducting the reaction in refluxing *sec*-butylbenzene gave similar unsatisfactory results.

SUMMARY

Several N-(2-lepidyl) substituted amino alcohols were prepared by heating a mixture of 2-chlorolepidine with an excess of an aminoalcohol or by treating a 2-lepidylamine with an epoxide in the presence of lithium amide.

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