[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE UPJOHN COMPANY]

PYRROLIDYL ALKANOLS

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In connection with other work in this laboratory a variety of pyrrolidine substituted alcohols were needed. In recent communications from this laboratory the preparation of 3-(1-pyrrolidyl)propanol (1), 1-(1-pyrrolidyl)propanol-2 (2), 2-(2,5-dimethyl-1-pyrrolidyl)ethanol (2), 1-(2,5-dimethyl-1-pyrrolidyl)propanol-2 (2), 2-(2,4-dimethyl-1-pyrrolidyl)ethanol (2), and 1-(2,4-dimethyl-1-pyrrolidyl)propanol-2 (2) was reported. A search of the literature revealed that only the 2-(1-pyrrolidyl)ethanol (3) and 2-(2-ethyl-1-pyrrolidyl)ethanol (4) had previously been prepared.[1] In this communication a number of other pyrrolidyl alkanols are reported and their methods of preparation described.

Since no single method of preparation was suitable for all the compounds desired a variety of procedures was used. Some of these were modifications of well known methods for the preparation of tertiary amino alcohols, as, for example, the alkylation of pyrrolidine with the appropriate chlorohydrin (method I). A number of amino alcohols have previously been prepared by the reduction of amino esters, aldehydes, or ketones. For these reductions sodium and alcohol, catalytic hydrogenation, or aluminum isopropoxide have been used with varying degrees of success. It has now been found that lithium aluminum hydride (6) is very satisfactory for these reductions (method H). This reagent has also been found to be suitable for the reduction of N-alkanol substituted pyrrolidones[2] or N-alkanol substituted succinimides to the corresponding N-alkanolpyrrolidines. Heretofore similar reductions using active metals, catalytic, or electrolytic methods have given low yields.

Several attempts were made to prepare 2-(1-pyrrolidyl)-2-methylpropanol from α-(1-pyrrolidyl)isobutyronitrile, which is easily obtained from acetone cyanohydrin and pyrrolidine. It was planned to convert the nitrile to the corresponding ester and reduce this with lithium aluminum hydride; however the ester was obtained only in very small yield. This pyrrolidyl alcohol was finally prepared in good yield by closing the pyrrolidine ring on 2-amino-2-methylpropanol with tetramethylene dibromide (method J).

Table I lists the properties of a variety of intermediate compounds and Table II lists the pyrrolidyl alkanols. Each method of preparation is illustrated by one example in the experimental part. It will be noted that many of these compounds can exist in more than one stereoisomeric form; however no attempt was made to separate any of them, and it is therefore probable that some of the products

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[1] Blicke and Blake (5) prepared the benzoate of 1-(1-pyrrolidyl)-2-methylbutanol-2 but did not characterize the intermediate pyrrolidyl alcohol.

[2] Since the completion of this work the report of Karrer and Portmann (7) has appeared in which 2-carbethoxypyrrolidone-5 was reduced with lithium aluminum hydride to 2-hydroxymethylpyrrolidine.

TABLE I
INTERMEDIATE COMPOUNDS

No.	STRUCTURAL FORMULA	PREP. METHOD	YIELD %	B.P., °C.	MM	n_D^{25}	d_4^{25}	EMPIRICAL FORMULA	% NITROGEN[a]	
									Calc'd	Found
1	$CH_2CH_2CH_2CH_2NCH(CH_3)COOC_2H_5$	A	91.5	84	12	1.4450	0.9724	$C_9H_{17}NO_2$	8.18	8.21
2	$CH_2CH_2CH_2CH_2NCH_2CH(CH_3)COOCH_3$	B	79.5	86	13	1.4462	.9713	$C_9H_{17}NO_2$	8.18	8.12
3	$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2COOC_4H_9$	B[b]	77	71	0.05	1.4548	—	$C_{12}H_{23}NO_2$	6.59	6.53
4	$CH_2CH_2CH_2CH_2NCH(CH_3)COCH_3$	A[c]	81	73	14	1.4522	.9331	$C_8H_{15}NO$	9.92	9.80
5	$CH_2CH_2CH_2CH_2NC(CH_3)_2CN$	C	88.7	75	12	1.4511	.9267	$C_8H_{14}N_2$	20.28	20.10
6	$CH_2CH_2CH_2CH_2NC(CH_3)_2COOCH_3$	D	4.0	90	20	1.4518	—	$C_9H_{17}NO_2$	8.18	8.21
7	$CH_2CH_2CH_2CH_2NCH_2C(CH_3)_2CHO$	E	42.3	97	32	1.4565	—	$C_9H_{17}NO_2$	9.02	8.95
8	$CH(CH_3)CH_2CH_2C(O)NCH_2CH_2OH$[d]	F	95	167	12	1.4883[e]	1.1002	$C_7H_{13}NO_2$	9.78	9.36
9	$CH(CH_3)CH_2CH_2C(O)NCH_2CH_2CH_2OH$	F[f]	95.6	180	14	1.4855	—	$C_8H_{15}NO_2$	8.91	8.81
10	$CH(CH_3)CH_2C(CH_3)_2C(O)NCH_2CH_2OH$	F[g]	96.3	157	13	1.4727	1.0239	$C_9H_{17}NO_2$	8.18	8.16
11	$CH(CH_3)CH(CH_3)CH_2C(O)NCH_2CH_2OH$	F[h]	94.4	174	14	1.4850	—	$C_8H_{15}NO_2$	8.91	9.17
12	$C(O)CH_2CH(CH_3)C(O)NCH_2CH_2OH$	G	86.4	102	0.01	1.4970	—	$C_7H_{11}NO_3$	8.91	9.17
13	$C(O)CH(CH_3)CH(CH_3)C(O)NCH_2CH_2OH$	G[i]	92.2	167	12	1.4878	—	$C_8H_{13}NO_3$	8.18	8.54
14	$C(O)C(CH_3)_2CH_2C(O)NCH_2CH_2OH$	G[j]	87.6	167	14	1.4870	—	$C_8H_{13}NO_3$	8.18	8.38

[a] Nitrogen analyses by Mr. Harold Emerson and staff of our microanalytical laboratory. [b] Butyl crotonate was used in place of methyl methacrylate. The product distilled over considerable range (120–140° at 17 mm.), probably due to some dissociation during the distillation; yield 77% n_D^{25} 1.4535. This crude material was used for the reduction with lithium aluminum hydride. A small sample was redistilled under high vacuum through a short column giving a pure product, with the properties listed above. [c] 3-Bromobutanone-2 [Catch, Elliott, Hey, and Jones, *J. Chem. Soc.*, 272 (1948)] was used in place of ethyl α-bromopropionate and the reaction mixture was only refluxed for fifteen minutes after the addition and then allowed to stand over night. [d] Bachman and Mayheu, *J. Org. Chem.*, **10**, 243 (1945), report the preparation of this pyrrolidone by the alkylation of 5-methylpyrrolidone-2 with ethylene chlorohydrin giving b.p. 144–147° (7 mm.), n_D^{20} 1.4480, d_4^{20} 1.006. [e] n_D^{20} 1.4900. [f] Propanol amine [Schnider, *Jubilee Vol. Emil Barell*, 85–91 (1946)] was used in place of ethanol amine. [g] Mesitonic acid [Lapworth, *J. Chem. Soc.*, **85**, 1220 (1904)] was used in place of levulinic acid. [h] β-Methyllevulinic acid [Pauley, Gilmore, and Will, *Ann.*, **403**, 119 (1914)] was used in place of levulinic acid. [i] α,α'-Dimethylsuccinic anhydride was used in place of methylsuccinic acid. [j] α,α-Dimethyl succinic acid [Vogel, *J. Chem. Soc.*, 2020 (1928)] was used in place of methylsuccinic acid.

TABLE II

Pyrrolidyl Alkanols

FORMULA	k	PREP. METHOD	YIELD %	B.P., °C	MM.	n_D^{25}	d_4^{25}	FORMULA	NEUT. EQUIV.		% NITROGEN[a]	
									Calc'd	Found	Calc'd	Found
$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2OH$	1	H	79.0	80	11	1.4758	0.9733	$C_7H_{15}NO$	129.20	128.8	10.84	10.96
$CH_2CH_2CH_2CH_2NCH_2CH_2CH_2CH_2OH$	—	I	72.1	113	12	1.4705	.9463	$C_8H_{17}NO$	143.23	144.3	9.78	9.71
$CH_2CH_2CH_2CH_2NCH_2CH_2CH(CH_3)OH$	—	H[b]	51.7	87	13	1.4611	.9350	$C_8H_{17}NO$	143.23	150.8	9.78	9.34
$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2CH_2OH$	3	H	74.6[c]	114	21	1.4742	.9596	$C_8H_{17}NO$	143.23	146.1	9.78	9.66
$CH_2CH_2CH_2CH_2NCH_2CH(CH_3)CH_2OH$	2	H[d]	89.7	91	12	1.4620	.9332	$C_8H_{17}NO$	143.23	146.3	9.78	9.61
$CH_2CH_2CH_2CH_2NCH(CH_3)CH(CH_3)OH$	4	H	92.6	79	13	1.4610	.9367	$C_8H_{17}NO$	143.23	147.2	9.78	9.67
$CH_2CH_2CH_2CH_2NC(CH_3)_2CH_2OH$	—	J	75.5	87	12[e]	1.4720[f]	.9624[f]	$C_8H_{17}NO$	143.23	143.3	9.78	9.80
$CH_2CH_2CH_2CH_2NCH_2C(CH_3)_2CH_2OH$	7	K	41.7	111	26	1.4609	.9248	$C_9H_{19}NO$	157.25	166.0	8.91	8.61
$CH_2CH_2CH_2CH_2N(CH_2)_3CH(CH_3)OH$	—	L[g]	85	111	12	1.4652	.930	$C_9H_{19}NO$	157.25	160.2	8.91	9.06
$CH_2CH_2CH_2CH_2NCH_2CH_2OCH_2CH_2OH$	—	[h]	—	122	13	1.4691	1.0064	$C_8H_{17}NO_2$	159.23	161.4	8.80	8.73
$CH_2CH_2CH_2CH(CH_3)NCH_2CH_2OH$	8	H[i]	76.0	81	16	1.4680	0.9537	$C_7H_{15}NO$	129.20	130.9	10.84	10.51
$CH_2CH_2CH_2CH(CH_3)NCH_2CH_2CH_2OH$	9	H[i]	91.0	100	18	1.4672	.9384	$C_8H_{17}NO$	143.23	144.0	9.78	9.64, 9.86
$CH_2CH_2CH(CH_3)CH_2NCH_2CH_2OH$	12	H[j]	68.1[c]	105	45	1.4640	.9466	$C_7H_{15}NO$	129.20	132.5	10.84	10.20
$CH_2CH_2CH(CH_3)CH(CH_3)NCH_2CH_2OH$	11	H[i]	89.4	86	13	1.4661	.9411	$C_8H_{17}NO$	143.23	144.0	9.78	9.60, 9.93
$CH_2CH_2C(CH_3)_2CH_2NCH_2CH_2OH$	14	H[j]	—	81	13	1.4580	.9209	$C_8H_{17}NO$	143.23	147.0	9.78	9.68
$CH_2CH(CH_3)CH(CH_3)CH_2NCH_2CH_2OH$	13	H[j]	61.6	86	12	1.4594	.9248	$C_8H_{17}NO$	143.23	146.3	9.78	9.15
$CH_2C(CH_3)_2CH_2CH(CH_3)NCH_2CH_2OH$	10	H[i]	88.2	84	14	1.4535	.9042	$C_9H_{19}NO$	157.25	159.8	8.91	8.74, 9.09

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[a] Footnote [a] Table I. [b] Equimolar quantities of methyl vinyl ketone and pyrrolidine were mixed and reduced with lithium aluminum hydride without isolating the intermediate methyl β-(1-pyrrolidyl)ethyl ketone. The yield is the over-all yield. [c] This yield is based on the crude intermediate which was used for the lithium aluminum hydride reduction. [d] This same compound was also prepared in 17.4% yield, by the addition of pyrrolidine (1 mole) to methallyl alcohol (3.55 moles) in which 1 mole of sodium had been dissolved. [e] This amino alcohol is a solid, freezing point 30°. [f] Taken at 30° on the liquid. [g] This compound was prepared by Dr. Robert H. Reitsema in this Laboratory. [h] This compound was isolated by Dr. Wm. Bradley Reid, Jr. in this Laboratory as a by-product, in about 10% yield, during the preparation of 2-(1-pyrrolidyl)ethanol from pyrrolidine and ethylene oxide. [i] Prepared by the reduction of the corresponding N-alkanolpyrrolidone. [j] Prepared by the reduction of the corresponding N-alkanol succinimide. [k] Number refers to compound in Table I used as starting material.

described represent mixtures of diastereoisomers and *cis-trans* forms as well as racemic mixtures.

EXPERIMENTAL

Method A. Ethyl α-(1-pyrrolidyl)propionate. To a solution of 181 g. (1 mole) of ethyl α-bromopropionate in 200 ml. of benzene was slowly added 148 g. (2.1 moles) of pyrrolidine with stirring. The reaction was exothermic and the solvent refluxed. After the addition was complete the mixture was heated under reflux for one hour, cooled, poured into ice-water, and acidified with dilute hydrochloric acid. The aqueous solution was separated, washed with ether, and made basic with cold sodium hydroxide. The basic ester was extracted with four 200-ml. portions of ether, washed with water, and dried over potassium carbonate. After removal of the solvent the product was distilled through a short column, giving 156.7 g. of a colorless liquid with the properties listed in Table I.

Method B. Methyl β-(1-pyrrolidyl)isobutyrate. A mixture of 100 g. (1 mole) of methyl methacrylate (stabilized with 0.006% hydroquinone) and 71 g. (1 mole) of pyrrolidine was refluxed for three hours and then distilled *in vacuo*. After removing a small forerun the product was collected giving 136.4 g. of a colorless liquid with the properties listed in Table I.

Method C. α-(1-Pyrrolidyl)isobutyronitrile. To 170 g. (2 moles) of acetone cyanohydrin was slowly added 142 g. (2 moles) of pyrrolidine. The mixture was cooled slightly to keep the temperature below the boiling point. The water which separated was saturated with sodium sulfate by shaking. The aqueous layer was removed, and the organic solution was dried over calcium sulfate and distilled through a short column, giving 245 g. of colorless liquid with the properties listed in Table I.

Method D. Methyl α-(1-pyrrolidyl)isobutyrate. To 69.1 g. (0.5 mole) of crude (undistilled) α-(1-pyrrolidyl)isobutyronitrile was added 400 ml. of concentrated hydrochloric acid, and the mixture was heated on a steam-bath for twenty hours. The solution was distilled to dryness, the residue was boiled with absolute methanol and filtered from ammonium chloride. The solvent was removed *in vacuo* and the residue was again taken up in 500 ml. of absolute methanol and saturated with hydrogen chloride gas with cooling. After standing at about 25° for four days the mixture was distilled to dryness *in vacuo*. The residue was diluted with water, made basic with sodium hydroxide solution, and continuously extracted with ether for six hours. The ether solution was dried over potassium carbonate and distilled, giving only 3.4 g. of colorless liquid with the properties listed in Table I.

Method E. 2,2-Dimethyl-3-(1-pyrrolidyl)propionaldehyde. A mixture of 71.1 g. (1 mole) of pyrrolidine, 81 ml. (1 mole) of concentrated hydrochloric acid, and 81 ml. (1 mole) of 37% aqueous formaldehyde was heated to the boiling point and then 79.3 g. (1.1 moles) of isobutyraldehyde was slowly added with stirring during three-fourths hour. The refluxing was continued for one hour and then 50 ml. more formaldehyde solution was added. After refluxing for one and one-fourth hours more and standing three days the mixture was made basic with cold 40% sodium hydroxide and extracted five times with ether. The ether solution was dried over potassium carbonate and distilled through a short column giving 65.7 g. of nearly colorless liquid with the properties listed in Table I.

Method F. 1-(2-Hydroxyethyl)-5-methylpyrrolidone-2. A suspension of 0.2 g. of platinum oxide catalyst in 25 ml. of absolute ethanol was hydrogenated to platinum and then a solution of 34.8 g. (0.3 mole) of levulinic acid and 37.8 g. (0.62 mole) of ethanolamine in 75 ml. of absolute alcohol was added and the mixture was hydrogenated at about 50 lbs. pressure and room temperature. Approximately the theoretical quantity of hydrogen was absorbed in less than four hours. After distilling off the alcohol and the excess ethanolamine the pyrrolidone was distilled twice through a short column giving a liquid with the properties listed in Table I.

Method G. N-(2-Hydroxyethyl)-α-methylsuccinimide. A mixture of 66 g. (0.5 mole) of methylsuccinic acid[3] and 73.4 g. (1.2 moles) of ethanolamine in a Claisen flask was placed in an oil-bath, the temperature of which was gradually raised to 260° and kept at about this temperature until the distillation practically ceased (about one-half hour). The residue was distilled *in vacuo*, giving a viscous oil which was redistilled through a short column giving 67.8 g. of light yellow liquid which contained a small amount of solid impurity. The physical properties are listed in Table I.

Method H. 2-(1-Pyrrolidyl)propanol. A 1-l. three-necked flask was fitted with a reflux condenser, stirrer, and dropping-funnel. In it was placed 21.3 g. (0.56 mole) of lithium aluminum hydride (6),[4] and 250 ml. of absolute ether. The mixture was refluxed until most of the hydride was dissolved and then a solution of 157.3 g. (0.92 mole) of ethyl α-(1-pyrrolidyl)propionate in 100 ml. of dry ether was slowly added with vigorous stirring at such a rate that the ether refluxed smoothly. When the addition was complete the mixture was refluxed for one-half hour longer and then decomposed by very cautiously adding dropwise, with vigorous stirring, 50 ml. of water. Sufficient dilute hydrochloric acid was cautiously added to dissolve the precipitated aluminum hydroxide and the aqueous layer was separated and washed with ether. A large excess of strong sodium hydroxide solution was added to the acid solution giving a milky suspension which was continuously extracted with ether for six hours. After drying over potassium carbonate the ether was removed and the product distilled through a short column giving a colorless liquid with the properties listed in Table II.

Method I. 4-(1-Pyrrolidyl)butanol. A 1-l. three-necked flask was fitted with a stirrer and two efficient condensers. In the flask was placed 142.2 g. (2 moles) of pyrrolidine and then 108.6 g. (1 mole) of tetramethylene chlorohydrin was added all at once with stirring. The exothermic reaction caused vigorous reflux for a few minutes, and then the mixture was heated on a steam-bath for one hour. After cooling 140 ml. of 40% sodium hydroxide solution was added. The amine layer was separated and saturated with potassium carbonate. The aqueous layers and precipitated salts were extracted with ether which was added to the amine layer and dried with potassium carbonate. After removal of the ether and excess pyrrolidine the product was distilled through a short column giving a colorless liquid with the properties listed in Table II.

Method J. 2-(1-Pyrrolidyl)-2-methylpropanol. In a flask fitted with a reflux condenser and an efficient stirrer was placed 44.6 g. (0.5 mole) of 2-amino-2-methylpropanol,[5] 108 g. (0.5 mole) of tetramethylene dibromide, and 200 ml. of toluene. After refluxing for three hours with stirring, 84 g. (1 mole) of sodium bicarbonate was added and the mixture was refluxed with vigorous stirring for an additional fifteen hours. After cooling 80 ml. of 50% sodium hydroxide solution was added. The organic layer was separated, enough water was added to the aqueous layer to dissolve the salt, and the solution was continuously extracted with ether for nine hours. The ether extract was added to the toluene solution, dried over potassium carbonate and distilled. The product solidified in the receiver, f.p. 27.5°. This was treated in acid solution with nitrous acid to remove any primary amine. The solution was extracted with ether, made basic, again extracted with ether, dried and redistilled. The freezing point was raised only 2.5°. The properties are listed in Table II.

Method K. 3-(1-Pyrrolidyl-2,2-dimethylpropanol. A mixture of 61.5 g. (0.396 mole) of 3-(1-pyrrolidyl),2,2-dimethylpropionaldehyde, 350 ml. of isopropanol, and 40.8 g. (0.2 mole) of aluminum isopropoxide was slowly distilled through an efficient column for six hours. By this time the test for acetone in the distillate was nearly negative and the mixture had become very dark. After cooling, 200 ml. of 10% sodium hydroxide solution was added. The upper layer was removed and saturated with potassium carbonate. The two aqueous layers

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[3] The methylsuccinic acid was prepared by a procedure similar to that described by Brown (8) except that methyl methacrylate was used in place of ethyl crotonate. The yield was 47%.

[4] Obtained from Metal Hydrides Incorporated, Beverly, Mass.

[5] From Commercial Solvents Corp., Terre Haute, Ind.

were combined and extracted six times with ether. The ether solution was combined with the isopropanol solution and dried over potassium carbonate. After removal of the solvent the product was distilled twice through a short column giving a colorless liquid with the properties listed in Table II.

Method L. 5-(1-Pyrrolidyl)pentanol-2. A solution of 65.5 g. (0.422 mole) of 5-pyrrolidylpentanone-2 (9) in 60 ml. of methanol was hydrogenated in the presence of 5 g. of Raney nickel catalyst at 1100 lbs. pressure and 100° for three hours. Approximately the theoretical quantity of hydrogen was absorbed and after filtration from catalyst and distillation a yield of 57.2 g. (85%) of the amino alcohol was obtained. A sample was redistilled giving a colorless liquid with the properties listed in Table II.

SUMMARY

1. Seventeen new pyrrolidyl alkanols have been prepared. Many different straight- and branched-chain alkanol groups have been attached to the nitrogen of pyrrolidine rings, some of which have been substituted with methyl groups in various positions.

2. Lithium aluminum hydride has been found to be very satisfactory for the reduction of pyrrolidyl substituted esters or ketones to pyrrolidyl alcohols, and for the reduction of substituted pyrrolidones and succinimides to pyrrolidines.

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