Summary

1. Ten aliphatic tertiary alcohols containing *n*-butyl groups have been prepared and some of their properties have been determined.

2. Ethylpropylbutyl, ethyldibutyl, dipropylbutyl and propyldibutyl carbinols have been prepared for the first time.

3. The ten corresponding tertiary chlorides have been prepared and studied. All except one of these are new.

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Alkamine Esters: Novocaine Analogs. III

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In accord with the statement in a previous communication:[2] "In the absence of any considerable number of trustworthy generalizations that relate chemical structure and physiological activity, the only means of learning of the effects of such relationships are to prepare compounds of slight structural differences and study the effects of such changes," the data herewith accumulated from further studies of anesthetic compounds are presented.

The anesthetic properties of the compounds that have been prepared and are herein described were determined by the use of goldfish as detailed by Adams and co-workers[3] with this slight modification, that the water used in the tests was in all cases aerated to avoid any possible effect on the fish from lack of oxygen in the water in which they were submerged.

The compounds synthesized and studied are listed below. The hydrochlorides of the esters formed by esterification of β-4-morpholinoethanol with benzoic acid, phenylacetic acid, β-phenylpropionic acid, cinnamic acid and tetrahydropyran-4-carboxylic acid, respectively; a second series of these same acids with β-N-piperidinoethanol; and a third series of esters from β-menthylethylaminoethanol with benzoic acid and tetrahydropyran-4-carboxylic acid.

Experimental

Preparation of the Alkaminoethanols.—Menthylamine was synthesized by means of the following series of reactions: menthol (U. S. P.) ⟶ menthone ⟶ menthone oxime ⟶ menthylamine. Reduction of the oxime and its recovery were carried out in accordance with the procedure detailed by Wallach and others.[4] The amine, distilled in an

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[1] Honors Student in Chemistry at Miami University, 1932.

[2] Brill, THIS JOURNAL, **54,** 2484 (1932).

[3] Adams, Ridea, Burnett, Jenkins and Dreger, *ibid.*, **48,** 1758 (1926).

[4] Wallach, *Ann.*, **276,** 293 (1893); Read and Story, *J. Chem. Soc.*, 2221 (1926); Read and Robertson, *ibid.*, 2209 (1926); Mailhe, *Bull. soc. chim.*, **33,** 83 (1923).

atmosphere of hydrogen, boiled at 97° at a pressure of 56 mm.; yield, 75%. A mixture of equivalent amounts of menthylamine and of ethyl bromide dissolved in dry benzene was heated on a steam-bath for two hours. Precipitation of the hydrobromide began almost immediately, so that a solid mass of crystals resulted. The free menthylethylamine distilled at 70.5° at a pressure of 4 mm.; yield 74%. β-Menthylethylaminoethanol prepared in a manner similar to the preceding synthesis was obtained in a 62% yield, boiling point 79° at 4 mm. pressure. β-N-Piperidinoethanol is best prepared by warming equivalent amounts of piperidine and ethylene chlorohydrin in the absence of a solvent in order to increase the yield of the nitrogen substituted derivative of piperidine.[5]

A number of methods were tried in the preparation of β-4-morpholinoethanol[6] with varying yields of morpholine and the ethanol derivative. The results obtained are not distinctly different from those reported by Gardner and Haenni[7a] and will not be reported in detail, except to state that none were so satisfactory as the method described by the investigators just cited.

Preparation of Acids.—Tetrahydropyrancarbonic acid is the only acid used in this study that needs any statement in regard to its preparation. The method announced by Gibson and Johnson[8] gave the best yields of those tried.[9] An attempt was made to prepare this acid by substitution of acetoacetic ester for the malonic ester with unsatisfactory results. β,β′-Dichlorodiethyl ether had not condensed completely with acetoacetic ester after refluxing for thirty-five hours and the cleavage of the condensation product did not go smoothly, consequently the effort was discontinued.

Tetrahydropyrancarbonyl chloride was prepared by heating 20 g. of the acid on the water-bath with 30 cc. of thionyl chloride. The product distilled at 85–86° at a pressure of 16 mm.

Preparation of Esters.—In all cases the esters were produced by warming dry benzene solutions of the various alcohols with 5% excess of like solutions of the acid chlorides until the reactions appeared to be completed.

The hydrochlorides of the esters of β-menthylethylaminoethanol apparently lose a molecule of hydrogen chloride so readily that recrystallization from alcohol and solution in water result in the production of the free base. The hydrochlorides of these esters are precipitated by the customary reactions in benzene solution; when recrystallized from alcohol–ether mixture it was found that their solubilities have changed, they are markedly more soluble in ether and hydrocarbon solvents and hardly at all soluble in water than when precipitated from the benzene solutions of the reacting base and acid chlorides. Their melting points have changed and they give no test for chlorine. A portion of the ester of tetrahydropyran-4-carbonic acid was recrystallized from dry ether before this sensitiveness to alcohol and water had been observed. The melting point of this is reported in Table II. As this melting point is lower than that for the free base and the

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[5] Powell and Dehn, THIS JOURNAL, **39**, 1717 (1917).

[6] Kamm and Waldo, *ibid.*, **43**, 2223 (1921); Cretcher and Pittenger, *ibid.*, **47**, 163 (1925).

[7] (a) Gardner and Haenni, *ibid.*, **53**, 2763 (1931). (b) The authors wish to express their appreciation to the Carbide and Carbon Chemicals Corporation for their gift of the triethanolamine used in this investigation.

[8] Gibson and Johnson, *J. Chem. Soc.*, 2525 (1930).

[9] V. Braun and Koehler, *Ber.*, 50, 1657 (1917).

TABLE I

SOME DATA ON CERTAIN ALKAMINE ESTERS

	Hydrochlorides	Formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Chlorine, % Found
A.	β-4-Morpholinoethylbenzoate	$C_{13}H_{17}NO_3HCl$	48	205	13.06	12.85
B.	β-4-Morpholinoethylphenylacetate	$C_{14}H_{19}NO_3HCl$	45	131	12.42	12.26
C.	β-4-Morpholinoethyl-β-phenylpropionate	$C_{15}H_{21}NO_3HCl$	73	139	11.84	11.63
D.	β-4-Morpholinoethylcinnamate	$C_{15}H_{19}NO_3HCl$	65	211	11.92	11.68[a]
E.	β-4-Morpholinoethyl-tetrahydropyran-4-carbonate	$C_{12}H_{17}NO_4HCl$	75	145	12.68	12.53
F.	β-N-Piperidinoethyl benzoate	$C_{14}H_{19}NO_2HCl$	64	176	13.15	13.02
G.	β-N-Piperidinoethyl phenylacetate	$C_{15}H_{21}NO_2HCl$	95	139	12.50	12.39
H.	β-N-Piperidinoethyl-β-phenylpropionate	$C_{16}H_{23}NO_2HCl$	65	116	11.91	11.79
I.	β-N-Piperidinoethylcinnamate	$C_{16}H_{21}NO_2HCl$	76	158	11.99	11.76
J.	β-N-Piperidinoethyl-tetrahydropyran-4-carbonate	$C_{13}H_{23}NO_3HCl$	50	103	12.78	12.69

[a] A Dumas nitrogen determination gave 4.78% found, 4.71% calculated. These esters have the usual solubility in water and alcohol with less solubility in ether, acetone and chloroform and decidedly less solubility in benzene and petroleum ether. They were recrystallized from a mixture of alcohol and ether.

TABLE II

DATA ON CERTAIN MENTHYLAMINE DERIVATIVES

	B. p., °C.	M. p., °C.
Menthylamine	97 (56 mm.)	
Menthylethylamine	70.5 (4 mm.)	(HBr) 306 (decomp.)
β-Menthylethylaminoethanol	79 (4 mm.)	(HCl) 274 (decomp.)

		Formula			Calcd., %	Found, %
K.	β-Menthylethylaminoethylbenzoate	$C_{21}H_{33}NO_2$	155	N	4.23	4.26
L.	β-Menthylethylaminoethyltetrahydropyran-4-carbonate	$C_{20}H_{37}NO_3$	166	N	4.13	4.25
M.	Hydrochloride	$C_{20}H_{37}NO_3HCl$	142[a]	Cl	9.73	8.23

[a] The melting point and the chlorine content of this ester indicate that a small portion of hydrogen chloride has been lost even though this compound has been recrystallized from dry ether and has been protected from moisture and alcohol.

TABLE III

ANESTHETIC EFFECTS ON GOLDFISH AND *P*H VALUES

Compound hydrochlorides	*P*H[a] 0.006 mol. concn.	Mole concn., used	Time in soln., min.	Observed effect	Fate after removal
β-4-Morpholinoethylbenzoate	4.4	0.006	45	Sluggish, incomplete anesthesia	Recovered
		.024	25	Irritated, evidences of toxicity	Died
β-4-Morpholinoethylphenylacetate	4.4	.024	25	Irritated, evidences of toxicity	Died
β-4-Morpholinoethylphenylpropionate	4.3	.012	60	Sluggish, incomplete anesthesia	Recovered
β-4-Morpholinoethylcinnamate	4.4	.006	45	Very sluggish, incomplete anesthesia	Recovered
		.012	11	Complete anesthesia	Recovered
β-4-Morpholinoethyltetrahydropyran-4-carbonate	4.4	Not tested			
β-N-Piperidinoethylbenzoate	6.4	.006	45	Sluggish, incomplete anesthesia	Recovered
		.024	25	Sluggish, evidences of toxicity	Recovered
β-N-Piperidinoethylphenylacetate	5.9	.006	31	Very sluggish, incomplete anesthesia	Recovered
		.012	45	Very sluggish, no marked increase in effect	Recovered
β-N-Piperidinoethyl-β-phenylpropionate	4.8	.012	45	Very sluggish, incomplete anesthesia	Recovered
β-N-Piperidinoethylcinnamate	6.4	.003	69	Very sluggish, incomplete anesthesia	Recovered
		.005	54	Complete anesthesia	Recovered
		.006	10	Complete anesthesia	Recovered
		.007	9	Complete anesthesia	Recovered
		.008	10	Complete anesthesia	Recovered
		.012	7	Complete anesthesia	Recov. with difficulty
β-N-Piperidinoethyltetrahydropyran-4-carbonate	4.8	.008	30	Slight sluggishness	Recovered
		.012	30	Greater sluggishness	Recovered

K, L and M could not be tested for reasons already noted.

[a] The *P*H values were found by means of a Hellige comparator.

percentage of chlorine found is likewise low, it is apparently a mixture of the hydrochloride and the basic ester free of hydrogen chloride. Solutions of these basic esters in dry benzene or ether did not form precipitable hydrochlorides or hydrosulfates when dry hydrogen chloride and sulfuric acid, respectively, were added under the conditions used.

Their study is being continued and they will be reported upon in more detail later.

Surface Tension Relationships.—The surface tensions of three of these esters, namely, the hydrochlorides of β-N-piperidinoethylcinnamate (the most active anesthetic of those studied), β-4-morpholinoethylcinnamate (ot intermediate activity) and β-N-piperidinoethyl-β-phenylpropionate (of low activity) were determined. The results of these tests show so little differences in values that no conclusion can be drawn as to the influence of surface tension on the anesthetic powers of the compounds. The compound with the highest anesthetic effect has the highest surface tension instead of the lowest as would be expected from Traube's theory. Certainly the chemical constitution appears to be one of the more important factors in the establishment of physiological activity as Adams has noted in his study of the relationships between surface tension and bactericidal activity.[10]

TABLE IV

SURFACE TENSIONS AND DENSITIES (0.006 MOLAR CONCENTRATIONS), 25°

Compound, hydrochlorides	Density of solution	Surface tension, dynes/cm.
β-N-Piperidinoethylcinnamate	0.9965	71.96
β-4-Morpholinoethylcinnamate	.9969	69.30
β-N-Piperidinoethyl-β-phenylpropionate	.9969	69.00
Redistilled water	.9970	71.80

Discussion and Conclusions.—The menthyl derivatives were included in this investigation in the hope that they might show marked surface penetration because of their high radical weight and favorable configuration. Rather convincing evidence of this relationship is furnished by the marked surface penetrating power of cocaine and of the greater activity of Butyn[11] over Novocaine in this regard. The former two are more penetrating and of higher molecular weight than the last named anesthetic.

The morpholine esters are not as active anesthetics as the piperidine esters. This structure appears to have no advantage over other basic groups in endowing compounds with anesthetic powers. They are likewise somewhat more acid in properties, and high acidity in local anesthetics appears to be undesirable and unfavorable to the best results. For this same reason the esters of tetrahydropyran-4-carboxylic acid are likely to possess low activity. This configuration apparently has no pronouncedly unfavorable toxic effect on compounds.

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[10] Stanley and Adams, THIS JOURNAL, **54,** 1548 (1932).

[11] Schmitz and Loevenhart, *J. Pharmacol.*, **24,** 167 (1924).

The cinnamates are the most active of all studied, which is evidence of the favorable effect of a double bond in enhancing the anesthetic powers of compounds.

Summary

1. Esters of β-4-morpholinoethanol with benzoic, phenylacetic, β-phenylpropionic, cinnamic and tetraphydropyran-4-carboxylic acids; a second series of β-N-piperidinoethanol with these same acids; and a third series of β-menthylethylaminoethanol with benzoic and tetrahydropyran-4-carboxylic acids are described under the following heads: (a) preparation, (b) physical properties, (c) *P*H values, (d) anesthetic activities, (e) surface tension.

2. The cinnamates are the most active physiologically of those studied.

3. No apparent relationship between surface tension and surface penetration was indicated.

4. The menthylethylamino derivatives differ from the others studied in the ease with which hydrogen chloride is lost.

OXFORD, OHIO

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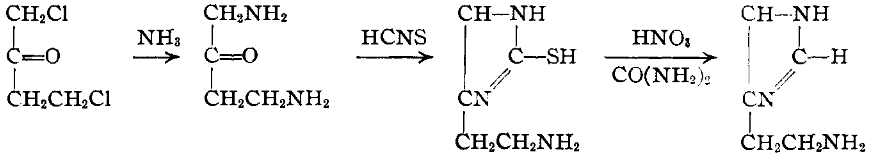
α′,β-Dichloromethylethyl Ketone (1,4-Dichlorobutanone-2)[1]

BY R. H. CARROLL AND G. B. L. SMITH

Introduction

The preparation of α′,β-dichloromethylethyl ketone is not recorded in the literature, and this relatively simple substance is important because of the possibility of using it as an intermediate in the synthesis of compounds of biological and pharmacological interest. For instance it might be employed in the synthesis of histamine, as follows[2]



The present paper describes two methods for the preparation of α′,β-dichloromethylethyl ketone.

The Nierenstein Reaction.—In 1915, Clibbens and Nierenstein[3] reported that acid chlorides react with diazomethane to produce α-chloro

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[1] This paper is constructed from part of the thesis submitted by Mr. Carroll to the faculty of the Polytechnic Institute of Brooklyn in June, 1932, in partial fulfilment of the requirements for the degree of Master of Science in Chemistry.

[2] Now being investigated in this laboratory.

[3] Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915).