TABLE II

PROPERTIES OF HETEROCYCLIC QUATERNARY AMMONIUM SALTS OF TYPE I

	R	C. K. D.[a] 1000 pts. H_2O *Staph. aureus*	*E. typhosa*	M.p., °C.[b]	Yield, %	Recrystn. solvent	Formula	Analyses, % Nitrogen Calcd.	Found	Carbon Calcd.	Found	Hydrogen Calcd.	Found
				Esters of N-carboxymethyl-N-methylmorpholinium chloride									
1	Lauryl	10-20	10-20	113-114 dec.	55	Me_2CO	$C_{19}H_{38}NO_4Cl$	3.85	3.71	62.70	62.90	10.52	10.25
2	Myristyl	1-10	10-20	118-119 dec.	67	Me_2CO	$C_{21}H_{42}NO_4Cl$	3.58	3.45	64.34	63.96	10.80	10.66
3	Cetyl	1	1-10	119-120 dec.	66	Me_2CO	$C_{23}H_{46}NO_4Cl$	3.34	3.38	65.76	65.74	11.04	10.74
				Esters of N,N'-dicarboxymethyl-N,N'-dimethylpiperazinium dichloride									
4	Lauryl	...	...	157-158	66	EtOH-Me_2CO	$C_{34}H_{68}N_2O_4Cl_2$	4.38	4.58	63.95	63.98	10.71	10.62
5	Myristyl	...	...	166-167	69	EtOH-Me_2CO	$C_{38}H_{76}N_2O_4Cl_2$	4.03	3.96	65.58	65.43	11.01	10.91
6	Cetyl	1.0	1-10	175-177 dec.	74	EtOH-Me_2CO	$C_{42}H_{84}N_2O_4Cl_2$	3.73	3.91	67.12	67.38	11.27	11.09
				Esters of carboxymethyldimethylbenzylammonium chloride									
7	Lauryl	1-10	20-30	120-121 dec.	89	Me_2CO	$C_{23}H_{40}NO_2Cl$	3.52	3.31	69.40	69.42	10.13	10.13
8	Myristyl	10-20	30	123-124	85	Me_2CO	$C_{25}H_{44}NO_2Cl$	3.29	3.30	70.47	70.73	10.41	10.17
9	Cetyl	1-10	1	121-122 dec.	79	Me_2CO	$C_{27}H_{48}NO_2Cl$	3.09	2.92	71.41	71.59	10.66	10.77
				Esters of N-carboxymethyl-N-(2-benzyloxy)-ethylmorpholinium chloride									
10	Myristyl	10-20	10-20	158-159	40	Me_2CO	$C_{29}H_{50}NO_4Cl$	2.74	2.76	68.00	68.25	9.84	9.93
				Esters of N-carboxymethyl-N-methyl-N'-carbethoxypiperazinium chloride									
11	Lauryl	24.0	20	125-127 dec.	40	Et_2O-Me_2CO	$C_{22}H_{43}N_2O_4Cl$	6.44	6.18	60.73	60.67	9.96	10.06
12	Myristyl	10-20	10-20	136-138 dec.	75	Et_2O-Me_2CO	$C_{24}H_{47}N_2O_4Cl$	6.06	5.79	62.27	61.80	10.16	10.22
				Esters of N-carboxymethyl-N-methylpiperidinium chloride									
13	Lauryl	20	40	156-157 dec.	87	Me_2CO	$C_{20}H_{40}NO_2Cl$	3.87	3.62	66.35	66.05	11.14	10.86
14	Myristyl	20	30	158-159 dec.	72	Me_2CO	$C_{22}H_{44}NO_2Cl$	3.60	3.42	67.74	67.62	11.37	11.41
15	Cetyl	1-10	10	160-161 dec.	74	Me_2CO	$C_{24}H_{48}NO_2Cl$	3.35	3.34	68.95	68.95	11.57	11.33

[a] Critical Killing Dilution—that concentration of the substance which will kill organisms of standard phenolic resistance in ten minutes but not in five minutes, at 37°, determined by the method described in Circular 198 of the U. S. Department of Agriculture. [b] Determined on a Fisher–Johns melting point apparatus.

Quaternary ammonium salts were prepared by adding the equivalent quantity of the alkyl chloroacetate to 0.05 mole of the tertiary amine in 20 ml. of acetone. This mixture was refluxed for from two to 30 hours on a steam-bath. The cooled mixture was then filtered and the solid recrystallized. Compounds 11 and 12 in Table II were best recrystallized from a mixture of acetone and ether containing a trace of alcohol. If the melting points of compounds 11 and 12 were taken in a capillary tube, they appeared to melt at 88 and 78°, respectively. If a Fisher–Johns melting point apparatus was used, much higher melting points were obtained; however, a change in crystalline structure was observed at the lower temperatures which seem to be the transition points for the compounds. Most yields were very good, but the primary objective was to obtain pure compounds rather than to determine the maximum yield attainable.

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Quaternary Carbon Compounds. V. Trisubstituted Carbinylcarbamates

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Although the majority of compounds synthesized as antispasmodics are basic esters of alicyclic and/or aromatic acids,[1] a limited number of diversified structures have also shown this interesting pharmacological action. Of the latter group, carbamic acid derivatives may be viewed as intermediate in structure between the basic esters and the non-ester type of antispasmodic compounds. Only one series of carbamic acid esters has been reported to exhibit antispasmodic activity.[2] Of a number of derivatives of carbamylcholine, the dibutylcarbamate of dimethylethyl-β-hydroxyethylammonium sulfate, the most active member of this series, exhibited a quick-acting atropine-like action. Two other series of carbamates, the alkamine esters of disubstituted methylcarbamic acids, $R_1R_2CHNHCOO(CH_2)_nNR_2$ where R_1 and R_2 are either aliphatic or aromatic radicals[3] and the dialkylaminoalkyl esters of α-naphthylphenylcarbamic acid[4] have been reported to possess local anesthetic activity.

In continuation of studies on quaternary carbon compounds,[5] it appeared of interest to investigate the pharmacological action of carbamic acid derivatives of the general formula $RR'R''CNHCOO(CH_2)_nR'''$ (I)[6] where R is an alkyl, diethylaminomethyl or a N-piperidinomethyl group, R' and R'' are alkyl groups containing two to five carbon atoms, R''' is a dialkylamino group, and *n* is two or three (Table I). In addition, the tributylcarbinylcarbamates from β-(2-pyridyl)-ethanol and β-(N-piperidino)-ethanol were prepared as examples of cyclic amino alcohols. The carbamates were prepared by refluxing the trisubstituted carbinylisocyanate and the amino alcohol in xylene. Upon removal of the solvent, and fractionation of the residual oil *in vacuo*, the carbamates were obtained as viscous, yellow liquids.

The *in vitro* antispasmodic activity of the carbamates was determined on isolated rabbit intestinal muscle by measuring the relaxation produced by the test compound against Doryl and barium chloride-induced spasms using atropine and papaverine as standards. The most active compounds were those in which R, R' and R'' were butyl or amyl, R''' was dimethylamino, diethylamino or

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(5) For paper IV in this series, see N. Sperber, D. Papa and E. Schwenk, *ibid.*, **72**, 2012 (1950).

(6) U. S. Patent 2,536,079, Jan. 2, 1951.

TABLE I

TRISUBSTITUTED CARBINYLCARBAMATES OF FORMULA RR'R''C–NHCOO$(CH_2)_n$R'''

R	R'	R''	R'''	n	B.p., °C.	Mm.	n_D	t, °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
C_2H_5	C_2H_5	C_2H_5	$N(C_2H_5)_2$	2	128–129	1	1.4560	25	62	$C_{14}H_{30}O_2N_2$	10.85	10.85
C_2H_5	C_4H_9	C_4H_9	$N(C_2H_5)_2$	2	164–166	2.5	1.4568	25	83	$C_{18}H_{38}O_2N_2$	8.91	8.87
C_4H_9	C_4H_9	C_4H_9	$N(CH_3)_2$	2	175–176	5	1.4570	22	83	$C_{18}H_{38}O_2N_2$	8.91	9.31
C_4H_9	C_4H_9	C_4H_9	$N(C_2H_5)_2$	2	164–165	2	1.4567	25	87	$C_{20}H_{42}O_2N_2$	8.18	8.31
C_4H_9	C_4H_9	C_4H_9	$N(C_4H_9)_2$	2	181–183	2	1.4550	22	83	$C_{24}H_{50}O_2N_2$	7.03	7.17
C_4H_9	C_4H_9	C_4H_9	$N(C_4H_9)_2$	3	185–190	3	1.4531	24	80	$C_{25}H_{52}O_2N_2$	6.79	6.78
C_4H_9	C_4H_9	C_4H_9	$N(C_2H_5)_2$	3	175–177	2	1.4558	22	75	$C_{21}H_{44}O_2N_2$	7.86	7.78
C_4H_9	C_4H_9	C_4H_9	$CH_2CH(CH_3)N(C_2H_5)_2$	0	164–165	1.5	1.4548	23	46	$C_{21}H_{44}O_2N_2$	7.86	8.06
C_4H_9	C_4H_9	C_4H_9	$CH_2CH_2NC_5H_{10}$[a]	0	185–188	3	1.4682	25	64	$C_{21}H_{42}O_2N_2$	7.90	8.04
C_4H_9	C_4H_9	C_4H_9	$CH_2CH_2C_5H_4N$[b]	0	198-200	2	1.4877	24	61	$C_{21}H_{36}O_2N_2$	8.04	8.05
C_5H_{11}	C_5H_{11}	C_5H_{11}	$N(C_2H_5)_2$	2	180–183	2.5	1.4564	25	82	$C_{23}H_{48}O_2N_2$	7.29	7.17
$(C_2H_5)_2NCH_2$	C_4H_9	C_4H_9	$N(C_2H_5)_2$	2	186–187	4.5	1.4603	25	85	$C_{21}H_{45}O_2N_3$	11.32	11.10
$C_5H_{10}NCH_2$[c]	C_4H_9	C_4H_9	$N(C_2H_5)_2$	2	186-188	4	1.4720	22	32	$C_{22}H_{45}O_2N_3$	10.96	10.84

[a] β-(N-Piperidyl)-ethyl. [b] β-(2-Pyridyl)-ethyl. [c] N-Piperidylmethyl.

dibutylamino and n was two. β-Diethylaminoethyl tributylcarbinylcarbamate, the most active member of the series, was twenty times more active than papaverine and possessed one-thirtieth the activity of atropine. In general, the structural requirements for antispasmodic activity observed in the quaternary carbon compounds described previously[5] apply to the dialkylaminoalkyl trisubstituted carbinylcarbamates.

Experimental

The synthesis of the trialkylcarbinylisocyanates has been described.[7] The dialkylaminoalkanols were obtained either from commercial sources or were prepared by standard procedures.

Dialkylaminoalkyl Trialkylcarbinylcarbamates.—The preparation of β-diethylaminoethyl tributylcarbinylcarbamate will illustrate the general method: A solution of 11.3 g. (0.05 mole) of tributylcarbinylisocyanate and 8.2 g. (0.07 mole) of β-diethylaminoethanol in 50 ml. of dry xylene was refluxed for 48–72 hours. The xylene was removed *in vacuo* and the residue was fractionated. After a small forerun, the carbamate was collected as a yellow, viscous oil. The methiodide melted at 118–118.5° after two recrystallizations from benzene–petroleum ether.

Anal. Calcd. for $C_{21}H_{44}O_2N_2I$: N, 5.78; I, 26.8. Found: N, 5.50; I, 27.2.

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The Gentiobiose Heptaacetates

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Bergmann and W. Freudenberg[2] prepared a substance designated α-gentiobiose heptaacetate, m.p. 178° (cor.), $[\alpha]^{20}D$ + 35.1° → +31.6° (pyridine), from amygdalin. We wish to report the synthesis of β-gentiobiose heptaacetate, m.p. 113–115°, $[\alpha]^{28}D$ + 2.9° (chloroform), $[\alpha]^{28}D$ − 7.0° (initial, extrapolated) +34.1° (5 hr., pyridine), together with evidence that the "alpha" form previously reported is a crystalline molecular compound containing both anomers in a ratio α:β = 3:1. When held at a temperature of 135–140° the liquid beta isomer is converted to a crystalline solid which after recrystallization from suitable solvents appears to be identical with that reported by Bergmann and Freudenberg; m.p. 175–178°, $[\alpha]^{28}D$ + 36° (chloroform), $[\alpha]^{28}D$ + 35° (pyridine). The rotation data in pyridine indicate that this material is approximately an equilibrium mixture of the alpha and beta anomers. Applying Hudson's[3] rules of isorotation, the rotational value of α-gentiobiose heptaacetate can be calculated from values for β-gentiobiose heptaacetate and the anomeric forms of gentiobiose octaacetate.

α-Gentiobiose octaacetate, $A + B = 35{,}500$
β-Gentiobiose octaacetate, $-A + B = -3{,}600$
$2B = 31{,}900$

A represents the rotational contribution of the carbonyl group and B that of the remainder of the molecule.

α-Gentiobiose heptaacetate, $A' + B = x$
β-Gentiobiose heptaacetate, $-A' + B = 1{,}800$

Then it follows that the value of x, the molecular rotation of α-gentiobiose heptaacetate, is 30,100° ($[\alpha]D$ + 47.4°, chloroform). The molecular rotation of 23,000° ($[\alpha]D$ + 36.1°, chloroform) found for the equilibrium mixture would indicate the presence of approximately three parts of the alpha to one of the beta anomer. The specific reaction constant of the mutarotation in pyridine of the beta anomer was first order, indicating the presence of essentially only alpha and beta anomers in solution. However, X-ray powder diffraction diagrams showed that the material isolated from the equilibrium mixture contained no admixed crystalline β-gentiobiose heptaacetate. This equilibrium material must therefore be a crystal compound from the two isomers. Similar molecular compounds between anomers have been reported by Hockett and Hudson for methyl D-xyloside and for lactose.[4]

Experimental

β-Gentiobiose Heptaacetate.—Five grams of β-gentiobiose octaacetate was converted to heptaacetyl-α-gentiobiosyl bromide by the method of Zemplén[5]; yield 3.9 g.

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