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SYNTHESIS OF N-ALKYLDIMETHYL DERIVATIVES OF ω-AMINO ACIDS

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Received February 17, 1953

In several diverse series of quaternary ammonium compounds containing a lipophilic alkyl group, antibacterial activity has been shown to increase with increasing length of the alkyl chain to an optimum at about 16 carbon atoms (1). There are no similar studies of compounds containing an alkyldimethylammonium group separated from a carboxylic acid group by an alkylene chain in which the lengths of alkyl and alkylene chains are varied over a wide range.

Laboratory and clinical studies have shown that the salts of certain fatty acids possess useful antifungal properties (2). This activity shows no apparent correlation with structure; examples of active compounds are found among saturated acids such as caprylic, unsaturated acids such as hendecenoic, and acids of lower molecular weight like propionic.

In this work syntheses are reported for alkyl (carboxyalkyl) dimethylam-

$$[CH_3(CH_2)_mN^+(CH_3)_2(CH_2)_nCOOH]X^-$$

I. m = 7, 9, 11, 13 or 15
n = 1, 5, 7, or 10

monium halides (I), combining in one molecule the antibacterial alkyldimethylammonium group and the antifungal fatty acid group. In addition a few related compounds in which the carboxyl function of I has been replaced by an ester, amide, or nitrile group are also reported, as well as some alkylaminocaproic and caprylic acids, esters and lactams.

Three routes to the quaternary ammonium compounds (Table I) were employed: A, methylation of an alkylamino acid or ester; B, reaction of a bromo acid or ester with an alkyldimethylamine; or C, reaction of a dimethylamino acid or nitrile with an alkyl bromide.

Alkylaminocaproic acids were prepared by reaction of the sodio derivative of caprolactam with alkyl bromides, followed by acid hydrolysis. Reaction of the alkylaminocaproic acids or esters with two moles of methyl iodide or methyl bromide furnished the quaternary ammonium compounds in good yield (method A).

Caprylic acid derivatives were obtained by two routes. Carboxyheptyldimethylhexadecylammonium bromide was obtained from cycloöctanone via caprylolactam; the corresponding methyl ester resulted from conversion of silver methyl azelate to methyl bromocaprylate, followed by reaction with dimethylhexadecylamine (method B). Over-all yields were about equal by the two routes (20%) but the necessity of preparing cycloöctanone from cyclohexanone and diazomethane would make the azelaic acid method preferable for large runs.

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The remaining compounds listed in Table I (the glycine derivatives, the propionitrile, and the hendecanoic acid derivatives) were prepared from easily obtained intermediates by methods B and C.

In general the compounds of formula I show a bactericidal activity which increases with increasing lengths of both the alkylene and the alkyl chains. The hendecanoic acid derivatives are at least 15 times as active as the corresponding acetic acid compounds, and the hexadecyl members are the most active in the acetic, caproic, and hendecanoic acid series. Bacteriostatic and antifungal activities are less clearly related to structure. The most active compounds in the group show antibacterial and antifungal activities of the same order as those of benzyldimethylhexadecylammonium chloride. Details of these studies have been reported elsewhere (3).

TABLE I

QUATERNARY AMMONIUM HALIDES

$[RN^+(CH_3)_2(CH_2)_nR']X^-$

R *n*-alkyl	n	R′	X	M.P., °C.	NITROGEN	
					Calc'd	Found
C_8H_{17}	1	—COOH	Br	150.5–151.5	4.73	4.62
$C_{10}H_{21}$	1	—COOH	Br	155–156	4.32	4.42
$C_{12}H_{25}$	1	—COOH	Br	179 dec.	3.98	3.95
$C_{14}H_{29}$	1	—COOH	Br	193 dec.	3.68	3.65
$C_{16}H_{33}$	1	—COOH	Br	201 dec.	3.43	3.34
$C_{16}H_{33}$	1	—COO^-	[a]	205–206	4.29	3.97
$C_{16}H_{33}$	2	—CN	Br	152–154	6.94	7.01
$C_{12}H_{25}$	5	—COOH	I	75–79	3.07	2.89
$C_{14}H_{29}$	5	—COOH	I	76–78	2.90	2.96
$C_{16}H_{33}$	5	—COOH	I	92.5–94.0	2.74	2.70
$C_{16}H_{33}$	5	—$COOCH_3$	Br	66–68	2.93	2.90
$C_{16}H_{33}$	5	—$CONH_2$	Br	95.5–96.5	6.04	5.70
$C_{16}H_{33}$	7	—COOH	Br	123–124	2.84	2.85
$C_{16}H_{33}$	7	—$COOCH_3$	Br	58–62	2.76	2.76
$C_{10}H_{21}$	10	—COOH	Br	109–110	3.11	3.12
$C_{16}H_{33}$	10	—COOH	Br	149–140.5	2.62	2.62

[a] *N-Hexadecylbetaine*. See *Chem. Abstr.*, **45**, 5099[i] (1951).

EXPERIMENTAL

Melting points. All melting points were determined with a calibrated 400° thermometer in an aluminum block like that described by Fieser (4).

Analysis. Nitrogen was determined by a semimicro Kjeldahl procedure (5).

Alkyldimethylamines. The tertiary amines were obtained by reaction of alkyl halides with dimethylamine.

Dimethylamino acids. Dimethylglycine was prepared from glycine by the Sommelet reaction (6) or from chloroacetic acid and dimethylamine (7). β-Dimethylaminopropionitrile was a commercial product.

Bromo acids and esters. Methyl η-bromocaprylate was prepared from silver methyl azelate

by the Hunsdiecker reaction (8). 11-Bromohendecanoic acid was obtained from 10-hendecenoic acid by the procedure of Ashton and Smith (9).

Cyclic ketones. Cyclohexanone was a commercial product. Cycloöctanone was obtained by ring enlargement from cyclohexanone in two stages (10).

Oximes and lactams. The oximes were prepared from the ketones by standard procedures. They were converted to the lactams by a procedure which permitted rearrangement of any desired amount in a single batch (11) and which afforded higher yields than do older methods (12).

N-Alkyl lactams. The lactams were alkylated by reaction of their sodio derivatives with alkyl bromides, as illustrated for hexadecylcaprolactam. The method is a modification of the methylation procedure described by Ruzicka (13).

N-Hexadecylcaprolactam. 1-(n-Hexadecyl)-2-oxohexamethyleneimine. To 5 g. (0.22 mole) of sodium sand prepared in 175 ml. of xylene was added, at 65–70° with stirring, 25 g. (0.22 mole) of 2-oxohexamethyleneimine dissolved in 75 ml. of xylene. After the addition of 67 g. (0.22 mole) of *n*-hexadecyl bromide the mixture was refluxed for 40 hours and then filtered.

TABLE II

HYDROHALIDES OF ω-ALKYLAMINO ACIDS AND ESTERS

$RNH(CH_2)_nR' \cdot HX$

R *n*-alkyl	n	R′	X	M.P., °C.	NITROGEN	
					Calc'd	Found
C_8H_{17}	5	—COOH	Cl	83–84	5.01	5.27
$C_{12}H_{25}$	5	—COOH	Cl	140–141	4.17	4.26
$C_{14}H_{29}$	5	—COOH	Br	171.5–172.5	3.43	3.40
$C_{16}H_{33}$	5	—COOH	Br	169–171	3.21	3.23
$C_{16}H_{33}$	5	—$COOCH_3$	Br	195–196	3.11	3.05
$C_{16}H_{33}$	7	—COOH	Br	183–185	3.02	2.86

Xylene was removed from the filtrate and the residue was distilled to give 46 g. (62%) of a thick oil, b.p. 215–223° at 2–3 mm.

Anal. Calc'd for $C_{22}H_{43}NO$: N, 4.15. Found: N, 4.06.

This product and the remaining caprolactams (octyl, b.p. 150–160° at about 5 mm.; dodecyl, b.p. 188–201° at about 5 mm.; and tetradecyl, b.p. 205–213° at 2–3 mm.) were used in the next step without further purification. N-Hexadecylcaprylolactam was not distilled before hydrolysis.

N-Alkyl amino acid hydrohalides. The N-alkyl lactams were hydrolyzed by the method illustrated for ε-hexadecylaminocaproic acid hydrobromide. The octyl and dodecylcaprolactams were hydrolyzed in 37% hydrochloric acid instead of 48% hydrobromic acid.

ε-Hexadecylaminocaproic acid hydrobromide. To 45.5 g. (0.136 mole) of 1-(*n*-hexadecyl)-2-oxohexamethyleneimine was added 100 ml. of 48% hydrobromic acid. The mixture was refluxed for 65 hours. On cooling a solid formed and was collected. Two crystallizations from acetone gave 38 g. (79%), m.p. 169–171°.

Anal. Calc'd for $C_{22}H_{46}BrNO_2$: N, 3.21. Found: N, 3.23.

The *methyl ester* of this compound (Table II) was prepared from it by refluxing in methanolic hydrogen bromide. Melting points and analytical data for the remaining alkylamino acid hydrohalides appear in Table II.

Quaternary ammonium halides. A. Methylation of an alkylamino acid. The conditions of Enz and Leuenberger (14) were used, as illustrated for *carboxypentyldimethylhexadecylammonium iodide.* A mixture of 10 g. (0.023 mole) of ε-hexadecylaminocaproic acid hydro-

bromide, 6.5 g. (0.046 mole) of methyl iodide, 7.3 g. (0.069 mole) of sodium carbonate, and 100 ml. of methanol was refluxed for 17 hours. After filtration the solvent was removed and the residue was dissolved in 100 ml. of water. Hydrobromic acid (24%) was added until about *p*H 2 was obtained. The precipitate was separated, dried over phosphorus pentoxide, and crystallized from acetone and ether to give 8.6 g. (74%) of *(5-carboxypentyl)dimethylhexadecylammonium iodide*, m.p. 92.5–94°. That this compound is the iodide and not the bromide was shown by qualitative tests.

Anal. Calc'd for $C_{24}H_{50}INO_2$: N, 2.74. Found: N, 2.70.

The other caproic acid derivatives were prepared similarly. Methyl ε-hexadecylaminocaproate hydrobromide was converted to the quaternary ammonium compound by reaction with methyl bromide. Reaction of the product, (5-carbomethoxypentyl)dimethylhexadecylammonium bromide, with methanolic ammonia by the procedure of Zoss and Hennion (15) gave the amide (Table I).

B. Reaction of a bromo acid derivative with an alkyldimethylamine. A mixture of 7.2 g. (0.027 mole) of 11-bromohendecanoic acid, 7.3 g. (0.027 mole) of dimethylhexadecylamine, 4 g. (0.038 mole) of sodium carbonate, and 60 ml. of methanol was refluxed for 72 hours. The residue obtained by filtration and removal of the solvent was worked up in a manner similar to that described under method *A*. Crystallization from acetone gave 5.4 g. (37%) of *(10-carboxydecyl)dimethylhexadecylammonium bromide*, m.p. 140–140.5°.

Anal. Calc'd for $C_{29}H_{60}BrNO_2$: N, 2.62. Found: N, 2.62.

C. Reaction of a dimethylamino acid with an alkyl halide. A mixture of 25 g. (0.18 mole) of dimethylglycine hydrochloride, 34.5 g. (0.18 mole) of *n*-octyl bromide, 47.5 g. (0.45 mole) of sodium carbonate, and 175 ml. of methanol was refluxed for 60 hours. The insoluble inorganic salts were removed and the filtrate was concentrated to ⅓ the original volume. Addition of ether produced a white gelatinous solid; yield 54 g. (88%); m.p. 105–106°. This product is a hydrate of a sodium bromide addition compound of *dimethyloctylbetaine* similar to the known addition compounds of betaine (16).

Anal. Calc'd for $C_{12}H_{25}NO_2 \cdot NaBr \cdot H_2O$: N, 4.17. Found: N, 4.08.

Crystallization from methanol-ether removed the water. From 20 g. there was obtained 16.3 g. after one crystallization; m.p. 108.5–109.5°. Two further crystallizations did not change the melting point; yield 8.5 g. of amorphous solid.

Anal. Calc'd for $C_{12}H_{25}NO_2 \cdot NaBr$: N, 4.40. Found: N, 4.44.

To an aqueous solution of 20 g. of the crude reaction product (hydrate) 24% hydrobromic acid was added until *p*H 2 was obtained. *Carboxymethyldimethyloctylammonium bromide* was precipitated; yield 14.6 g. (83%). After two crystallizations from acetone containing a little methanol the shiny platelets melted at 150.5–151.5°.

Anal. Calc'd for $C_{12}H_{26}BrNO_2$: N, 4.73. Found: N, 4.62.

The other betaine hydrobromides were prepared similarly but without purification of the sodium bromide addition compounds. *N-Hexadecylbetaine* resulted from treatment of a solution of its hydrobromide with silver carbonate. The reaction of hexadecyl bromide with β-dimethylaminopropionitrile was carried out at room temperature in the absence of sodium carbonate and solvent.

SUMMARY

The synthesis of a series of ω-alkyldimethylammonium derivatives of acetic, caproic, caprylic, and hendecanoic acids is described. Several related compounds containing both an alkyldimethylammonium group and an ester, amide, or nitrile group, as well as some ω-alkylaminocaproic and caprylic acids and lactams are also reported.

PHILADELPHIA 32, PA.

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