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2-pyrrolidinoethyl esters of para alkoxybenzoic and para alkox alkoxycinnamic acids

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2-PYRROLIDINOETHYL ESTERS OF PARA ALKOXYBENZOIC AND PARA ALKOXYCINNAMIC ACIDS

BY

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THESIS
SUBMITTED TO THE GRADUATE FACULTY
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APPROVED BY:

J Stanton Pierce

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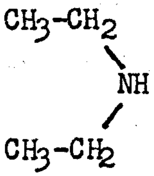
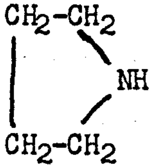
INTRODUCTION

One of the most important groups of local anesthetics is the class of alkyl and dialkylaminoalkyl esters of aromatic acids. Of these compounds, the diethylaminoethyl esters are particularly valuable.

Diethylamine has the formula



; pyrrolidine has the formula



It is obvious that pyrrolidine is merely a modified form of diethylamine. The purpose of this work is to learn the effect of substituting the N-pyrrolidyl nucleus for the diethylamino nucleus in various esters of the local anesthetic type.

HISTORICAL

Since the principal use of this section will be as a reference guide for future workers, a word as to its scope might well be in order.

It was originally intended to list all known compounds of the type formulas XC_6H_4COOalkylene-NHR, XC_6H_4COOalkylene-NR_2, and XC_6H_4COOalkylene-NR_1R_2, where X may be almost any substituent on the benzene ring, alkylene is a saturated carbon chain, either straight or branched, and R, R_1, and R_2 are saturated alkyl groups or the allyl radical. Because of the very limited time available, however, the literature search is only approximately complete, and a great many modifications of the original plan had to be made.

With the sole exception of cinnamic acid, only acids in which the carboxyl group is joined directly to the aromatic nucleus have been included.

Acids in which a heterocyclic group, such as thienyl, pyrridyloxy, etc., is joined to the benzene ring have not been included, with the exception of 3,4-methylenedioxy benzoic acid (piperonylic acid). N-Acyl derivatives of amino-benzoic acids also have been omitted.

Esters of polycarboxylic acids, as well as those of polyhydroxy alcohols, have been omitted.

Compounds containing aryl groups, unsaturation, or functional groups in the alcohol part of the molecule likewise have been omitted.

In the case of patents, only patents in which examples are given in the patent abstract are included. Patents of processes have been omitted. Where a given compound has been patented in other countries and the United States, only the United States patent has been listed.

The references for the methods of preparation of the esters are merely samples, not necessarily the earliest in existence.

Where a compound's earliest appearance in the available literature is in Beilstein, only the Beilstein reference is given. In the case of the German patents referred to in the section on preparation of the esters, only the Chemisches Zentrallblatt reference has been given. Although some of these patents are listed in Chemical Abstracts, no useful information whatever is given there.

GENERAL METHODS OF PREPARATION OF ALKAMINE ESTERS

The majority of alkyl and dialkylaminoalkyl esters are prepared by one of two standard methods;

(a) Condensation of the alkamine alcohol with the corresponding acid chloride, for example:

$$pEtOC_6H_4COCl + HOCH_2CH_2N(C_2H_5)_2 \longrightarrow$$

$$pEtOC_6H_4COOCH_2CH_2N(C_2H_5)_2 \cdot HCl \quad (1)$$

Conditions vary widely. For monoalkyl aminoalkyl benzoates, the solid hydrochloride of the alcohol often is heated on a water bath with the appropriate acid chloride (2). If the amino alcohol is soluble in dilute base, however, the reaction may be effected by warming the acid chloride with a mildly alkaline solution of the amino alcohol (3).

Dialkylaminoalkyl esters may be prepared either by heating the reactants together directly (4) or by refluxing in an inert solvent

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(1) C. A. 41, 155; W. G. Christiansen and S. E. Harris (to E. R. Squibb & Son) U. S. 2,404,691 (1946).

(2) J. S. Pierce, J. M. Salsbury, W. W. Haden and L. H. Willis, J. Am. Chem. Soc. 64, 2884-5 (1942).

(3) S. D. Goldberg and W. F. Whitmore, J. Am. Chem. Soc. 59, 2280-2 (1937).

(4) L. S. Fosdick and A. F. Dodds, J. Am. Chem. Soc. 65, 2305-6 (1943.

such as benzene (6), ether (7) or chloroform (8). This is the principal method used today.

(b) Heating the haloalkyl ester with the corresponding primary or secondary amine under pressure (9) or in a sealed tube at 100-110° (10), for example:

$$pNO_2C_6H_5COOCH_2CH_2Cl + HN(C_2H_5)_2 \longrightarrow$$
$$pNO_2C_6H_5COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

This method is seldom used today, as methods have been worked out whereby it is now much easier to prepare the corresponding alcohols than it was formerly.

The remaining methods have been used much less frequently than the preceding two.

(c) An aromatic acid anhydride may be heated with a water solution or suspension of the alkamine alcohol. For instance, benzoic anhydride, when heated with a water solution of dimethylaminoethanol, yields dimethylaminoethyl benzoate (11)

$$(C_6H_5COO)_2O + HOCH_2CH_2N(CH_3)_2 \longrightarrow$$
$$C_6H_5COOCH_2CH_2N(CH_3)_2 + CH_6COOH$$

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(6) O. Kamm, J. Am. Chem. Soc. 42, 1030-3 (1920).

(7) C. A. 42, 1319; R. P. Parker and A. J. Hill (to American Cyanamide Co.) U. S. 2,429,275 (1947).

(8) C. A. 43, 2640; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,456,556 (1949).

(9) Beilstein, Handbuch der Organischen Chemie, IX 393; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 179,627 (1904) Chem. Zentr. (1907) I, 1363.

(10) Beilstein, Handbuch der Organischen Chemie, IX 424; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 194,748, Chem. Zentr. (1908) I, 1004.

(11) Beilstein, Handbuch der Organischen Chemie, IX 173; Chem. Fabr. Schering, Ger. 175,080, Chem. Zentr. (1906) II, 1226.

(d) An alkyl ester, usually the methyl ester, of an aromatic acid may be heated with the alkamine alcohol, followed by distillation of the methanol formed. For example, methyl benzoate, on being heated with diethylaminoethanol, yields diethylaminoethyl benzoate (12).

$$C_6H_5COOCH_3 + HOCH_2CH_2N(C_2H_5)_2 \longrightarrow$$

$$C_6H_5COOCH_2CH_2N(C_2H_5)_3 + CH_3OH$$

(e) An aromatic acid may be esterified directly with an alkamine alcohol. For example, p-aminobenzoic acid, on being heated with diethylaminoethyl alcohol in the presence of concentrated sulfuric acid, yields diethylaminoethyl-p-aminobenzoate (13).

$$pNH_2C_6H_4COOH + HOCH_2CH_2N(C_2H_5)_2 \xrightarrow{H_2SO_4}$$

$$pNH_2C_6H_4COOCH_2CH_2N(C_2H_5)_2 + H_2O$$

(f) The dry alkali metal salt of an aromatic acid may be heated with an alkyl or a dialkylhaloalkyl amine. For instance, sodium p-aminobenzoate may be heated with diethylchloroethylamine at 110-120° C. to produce diethylaminoethyl-p-aminobenzoate or its hydrochloride (14).

$$pNH_2C_6H_4COONa + ClCH_2CH_2N(C_2H_5)_2$$

$$pNH_2C_6H_4COOCH_2CH_2N(C_2H_5)_2 \cdot HCl +$$

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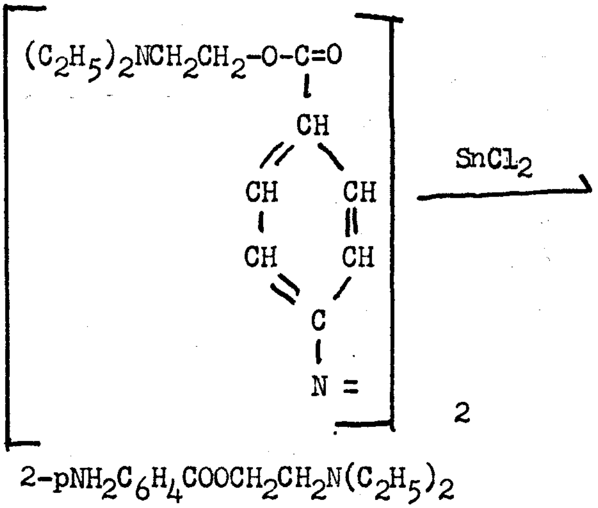
(12) Beilstein, Handbuch der Organischen Chemie, IX 173; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 187,209 Chem. Zentr. (1907) II, 1464.

(13) Beilstein, Handbuch der Organischen Chemie, XIV 424; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 180,291 Chem. Zentr. (1907) I, 1365.

(14) E. Merck, Ger. 189,335, Chem. Zentr. (1907) II, 2003.

(g) Aminobenzoic acid esters may be prepared by reduction of the alkamine esters of azobenzene dicarboxylic acid. For example, 2-diethylaminoethyl-p-aminobenzoate is prepared by the action of stannous chloride on azobenzene-4-4^{1} dicarboxylic acid, bis (diethylaminoethyl ester) (15).



More often, however, the corresponding nitro ester is reduced. As a rule, any of the standard methods of reduction may be used.

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(15) Beilstein, Handbuch der Organischen Chemie, XIV, 424; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 180,292 Chem. Zentr. (1907) I, 1365.

ALKYL AND DIALKYLAMINOALKYL ESTERS OF BENZOIC ACID

A. Alkylaminoalkyl esters

2-Alkylaminoethyl benzoates

$C_6H_5COOCH_2CH_2NHR$

Compounds, obtained originally or used as their hydrochlorides, have been prepared in which R is methyl (16), isopropyl (17), butyl (18) (19), isobutyl (18) (19), sec-butyl (17), amyl (18) (19), 2-amyl (17) (18) (19), cyclopentyl (19) (20), hexyl (18) (19), 4-methyl-2-amyl (17) (19), cyclohexyl (19), 2-methyl cyclohexyl (19), 4-methyl cyclohexyl (19), heptyl (19), 2-heptyl (18) (19), octyl (19), 2-octyl (17) (18) (19) and 2-ethylhexyl (17).

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(16) Beilstein, Handbuch der Organischen Chemie, IX 173.

(17) A. C. Cope and E. M. Hancock, J. Am. Chem. Soc. 66, 1448-53 (1944).

(18) C. A. 41, 5263; J. R. Reasenberg and S. D. Goldberg (to Oradent Chemical Co.) U. S. 2,421,129 (1947).

(19) J. R. Reasenberg and S. D. Goldberg, J. Am. Chem. Soc. 67, 933-9 (1945).

(20) C. A. 44, 5547; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,486,374 (1949).

2-Alkylamino-2-methylethyl benzoates hydrochlorides

$C_6H_5COOCH_2\text{-}CH(CH_3)NHR \cdot HCl$

Compounds of this type have been prepared where R is cyclopentyl (20) (21), cyclohexyl (20) (21), and (diisobutyl) methyl (20) (22).

2-Alkylamino-2-ethylethyl benzoate hydrochloride

$C_6H_5COOCH_2CH(C_2H_5)NHR$

Compounds of this type have been prepared where R is isopropyl (21) (22), cyclopentyl (21), cyclohexyl (20) (21), and (diisobutyl) methyl (21) (22).

2-Alkylamino-2-2-dimethylethyl benzoates

$C_6H_5COOCH_2C(CH_3)_2NHR \cdot$

Compounds of this type have been prepared or used as the hydrochlorides in which R is butyl (17) (18), isobutyl (18), amyl (17) (18), cyclohexyl (18), 2-methylcyclohexyl (18), 4-methylcyclohexyl (18), octyl (17), and 2-octyl (17) (18).

2-Alkylamino-1-methylethyl benzoate hydrochlorides

$C_6H_5COOCH(CH_3)CH_2NHR \cdot HCl$

Compounds of this type have been prepared in which R is cyclopentyl (20) (21) and cyclohexyl (20) (21).

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(21) C. A. 45, 181; Sharp & Dohme, Inc., Brit. 632,561 (1949).

(22) C. A. 44, 7880; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,497,394 (1950).

2-Alkylamino-1,1-dimethylethyl benzoate hydrochlorides

$C_6H_5COOCH(CH_3)_2CH_2NHR \cdot HCl$

Compounds of this type have been made in which R is cyclopentyl (20) (21) and cyclohexyl (20) (21).

2-Methylamino-1,1,2-trimethylethyl benzoate

$C_6H_5\overset{COO}{\wedge}C(CH_3)_2CH(CH)_3NHCH_3$ (23)

3-Methylaminopropyl benzoate

$C_6H_5COOCH_2CH_2CH_2NHCH_3$ (24)

3-Cyclohexylamino-2-methylpropyl benzoate hydrochloride

$C_6H_5COOCH_2CH(CH_3)CH_2NHC_6H_{11} \cdot HCl$ (25)

3-Alkylamino-1,3-trimethylpropyl benzoate

$C_6H_5COOCH(CH_3)CH_2C(CH_3)_2NHR$

Compounds of this type have been prepared in which R is methyl (26), ethyl (26) and propyl (26).

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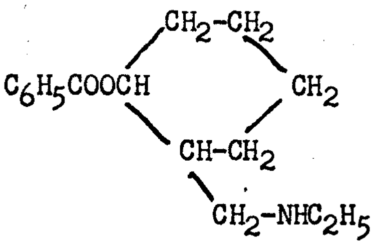
(23) C. A. 26, 2966; C. Mannich and H. Wieder, Ber. 65B, 385-90 (1932).

(24) C. A. 15, 2877; J. vonBraun and O. Braunsdorf, Ber. 54B, 685-703 (1921).

(25) A. C. Cope and E. M. Hancock, J. Am. Chem. Soc. 66, 1738-47 (1944).

(26) Beilstein, Handbuch der Organischen Chemie, IX, 176.

2(Ethylaminomethyl) cyclohexyl benzoate (27)



B. Dialkylaminoalkyl esters

(1) Esters in which the alkyl groups are not mixed

Dialkylaminoethyl benzoate hydrochlorides

$C_6H_5COOCH_2NR_2 \cdot HCl$

Compounds of this type have been prepared in which R is ethyl (29) (30), propyl (30), butyl (30) and isoamyl (30).

Alkyl-dimethylaminomethylmethyl benzoates and hydrochlorides

$C_6H_5COO\overset{H}{C}(R)N(CH_3)_2$ X

Compounds of this type have been prepared in which R is cyclohexylmethyl (28), isoamyl (28) and propyl (28).

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(27) C. A. 22, 590; C. Mannich and W. Hof, Arch. Pharm. 265, 589-98 (1927).

(28) C. A. 26, 2966; C. Mannich, B. Lesser and F. Silten, Ber. 65B, 378-85 (1932).

(29) E. V. Lynn and F. V. Loefgren, J. Am. Pharm. Assoc. 14, 970-2 (1925).

(30) E. V. Lynn and F. V. Loefgren, J. Am. Pharm. Assoc. 21, 541-8 (1932).

Dialkylaminoethyl benzoates

$C_6H_5COOCH_2CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (1), ethyl (1), butyl (31), sec butyl (31), isoamyl (1), piperidino (33) (34) (35) (36), N-ethyl-2-piperidino (37), 3-methylpiperidino (38) (39) (40), 4-methylpiperidino (41), and 4-morpholino (35). The hydrochlorides of these compounds also have been prepared.

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(31) E. S. Cook and C. W. Kreke, J. Am. Chem. Soc. 62, 1591-3 (1940).

(32) C. A. 19, 153; R. Adams, E. H. Volwiler and R. L. Jenkins, U. S. 1,513,730 (1924).

(33) C. A. 32, 8361; H. Horenstein and H. Pahliche, Ber. 71B, 1644-57 (1938).

(34) L. A. Walter and R. J. Fosbinder, J. Am. Chem. Soc. 61, 1713-14 (1939).

(35) M. T. Leffler and H. C. Brill, J. Am. Chem. Soc. 55, 365-70 (1933).

(36) C. A. 24, 208; F. L. Pyman, J. Chem. Soc. 93, 1793-1807 (1906) Proc. Chem. Soc.

(37) W. H. Hunt and R. J. Fosbinder, Anesthesiology 1, 305-11 (1940).

(38) S. M. McElvain, J. Am.Chem. Soc. 49, 2835-40 (1927).

(39) J. R. Thayer and S. M. McElvain, J. Am. Chem. Soc. 50, 3348-55 (1928).

(40) C. A. 25, 1037; S. M. McElvain, U. S. 1,784,903 (1930).

(41) C. F. Bailey and S. M. McElvain, J. Am. Chem. Soc. 52, 1633-40 (1930).

2-Dialkylamino-1-methylethyl benzoates

$C_6H_5COOC(CH_3)-CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (42), ethyl (42), isoamyl (43), and 2-methylpiperidino (44).

2-Dialkylamino-1,1-dimethylethyl benzoates

$C_6H_5COOC(CH_3)_2CH_2-NR_2$

Compounds of this type have been prepared in which R is methyl (43) and ethyl (45).

2-Dialkylamino-1-ethylethyl benzoates

$C_6H_5COOCH(CH_3)(C_2H_5)CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (43) (46) and ethyl (45).

2-Dimethylamino-1-methyl-1-alkylethyl benzoates

$C_6H_5COOC(CH_3)(R)CH_2N(CH_3)_2$

Compounds of this type have been prepared in which R is propyl (47), isobutyl (47) and isoamyl (47).

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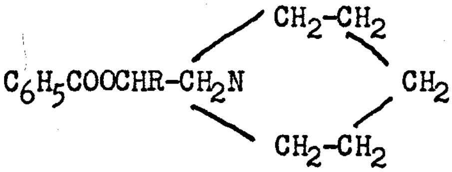
(42) Beilstein, Handbuch der Organischen Chemie, IX, 174.
(43) Beilstein, Handbuch der Organischen Chemie, IX, 175.
(44) S. M. McElvain and T. P. Carney, J. Am. Chem. Soc. 68, 2592-600 (1946).
(45) W. T. Olsen and F. M. Whitacre, J. Am. Chem. Soc. 65, 1019-20 (1943).
(46) C. A. 15, 2672; M. Cano and J. Ranedo, Anales Soc. espanola fis quim. 18, 184-206 (1920).
(47) Beilstein, Handbuch der Organischen Chemie, IX, 176.

2-Piperidino-1-alkylethyl benzoates

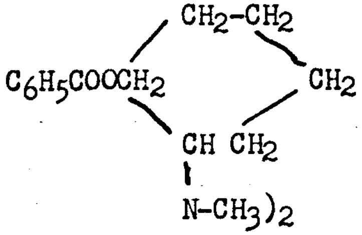


Compounds of this type have been prepared in which R is propyl (28) and isobutyl (28).

2-Dimethylamino-1,1-diethylethyl benzoate

$C_6H_5COOC(C_2H_5)_2CH_2N(CH_3)_2$ (46)

2-Dimethylamino-1-cyclohexyl benzoate



(48)

2-Diethylamino-2-ethylethyl benzoate

$C_6H_5COOCH_2-CH(C_2H_5)N(C_2H_5)_2$ (45)

2-Dialkylamino-1,1,2-trimethylethyl benzoates

$C_6H_5COOC(CH_3)_2CH(CH_3)NR_2$

Compounds of this type have been prepared in which R is ethyl (28) and piperidino (28).

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(48) C. A. 20, 2831; A. Koetz and P. Merkel, J. Prakt. Chem. 113, 49-76 (1926).

3-Dialkylaminopropyl benzoates

$C_6H_5COOCH_2CH_2CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (49), ethyl (42) (50), pyrrolidino (51), piperidino (38), 2-methylpiperidino (38) (39), 4-methylpiperidino (41), 2-propylpiperidino (44), 2-isopropylpiperidino (44), 2-amylpiperidino (44), 2-(3-amyl) piperidino (44), 2-hexylpiperidino (44), 4-isopropylpiperidino (44), 4-amylpiperidino (44), 2,3-dimethylpiperidino (44), 2,4-dimethylpiperidino (44), 2,5-dimethylpiperidino (44), 2,6-dimethylpiperidino (44) and 2,4,6-trimethylpiperidino (44).

3-Dialkylamino-1-alkylpropyl benzoates

$C_6H_5COOCHR_1CH_2CH_2N(R)_2$

Compounds of this type have been prepared in which R is methyl (27), piperidino (27) and 2-methylpiperidino (44) when R_1 is methyl; in which R. is piperidino when R_1 is isobutyl (27); and in which R is ethyl when R_1 is ethyl (45).

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(49) C. A. <u>27</u>, 2761; C. Mannich, Ger. 571,295 (1929).

(50) C. A. <u>30</u>, 4160; C. Rohmann and B. Scheurle, Arch. Pharm. <u>274</u>, 110-26 (1936).

(51) L. H. Andrews and S. M. McElvain, J. Am. Chem. Soc. <u>51</u>, 887-92 (1929).

(52) C. A. <u>22</u>, 590; C. Mannich and W. Hof, Arch Pharm. <u>265</u>, 589-98 (1927).

3-Dialkylamino-2-alkylpropyl benzoates

$C_6H_5COOCH_2CHR_1CH_2NR_2$

Compounds of this type have been prepared in which R_1 is methyl (27) and 2-methylbutyl (53) when R is methyl, and in which R is piperidino when R_1 is methyl (27).

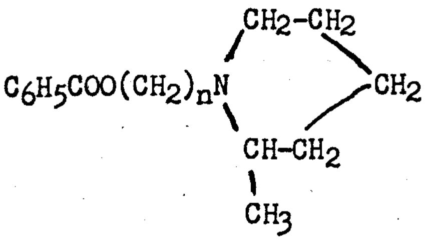
3-Dialkylamino-2,2-dimethylpropyl benzoates

$C_6H_5COOCH_2\text{-}C(CH_3)_2CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (49), ethyl (49) and 4-methylpiperidino (44).

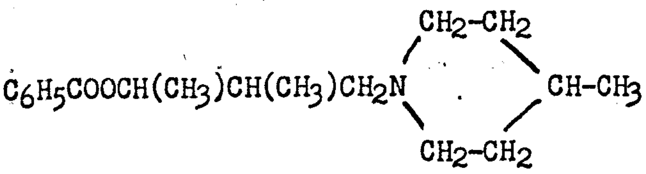
3-(4-Methylpiperidino)-2,3-dimethylpropyl benzoate

-2-Methylpiperidinoalkyl benzoates



Compounds of this type have been prepared in which n is 4, 5 and 6 (44).

3-(4-Methylpiperidino)-1,2-dimethylpropyl benzoate

 (44)

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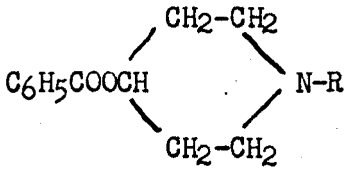
(53) C. A. 22, 591; C. Mannich and Ph. Hoenig, Arch. Pharm. 265, 598-610 (1927).

3-Dialkylamino-1,3,3-trimethylpropyl benzoates

$C_6H_5COOCH(CH_3)CH_2C(CH_3)_2NR_2$

Compounds of this type have been prepared in which R.is methyl and ethyl (47).

1-Alkyl-4-piperidyl benzoates

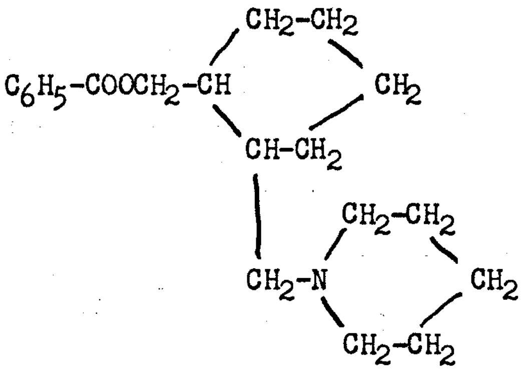


Compounds of this type have been prepared in which R is methyl, ethyl, propyl, butyl and isoamyl (54).

5-Diethylaminoamyl benzoate

$C_6H_5COO(CH_2)_5N(C_2H_5)_2$ (50)

2-(Piperidinomethyl) cyclohexylmethyl benzoate



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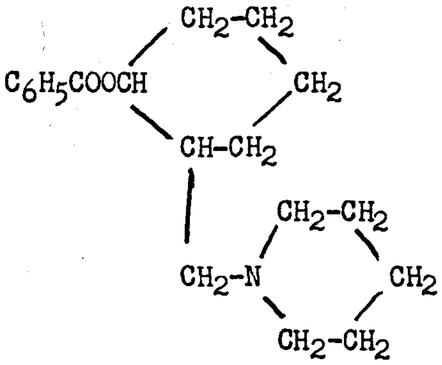
(54) N. W. Bolyard and S. M. McElvain, J. Am. Chem. Soc. <u>51</u>, 922-8 (1929).

2-(Piperidinomethyl)-cyclohexyl benzoate



(53)

(2) Esters in which the alkyl groups are different

2-Ethylisopropylaminoethyl benzoate

$C_6H_5COOCH_2CH_2N(C_2H_5)\quad CH(CH_3)_2$ (55)

3-Methylethylaminopropyl benzoate

$C_6H_5COO(CH_2)_3N(CH_3)(C_2H_5)$ (55)

3-Ethylisopropylaminopropyl benzoate

$C_6H_5COO(CH_2)_3N(C_2H_5)\quad CH(CH_3)_2$ (55)

3-Methylethylamino-1,3,3-trimethylpropyl benzoate

$C_6H_5COOCH(CH_3)CH_2C(CH_3)_2N(CH_3)(C_2H_5)$ (47)

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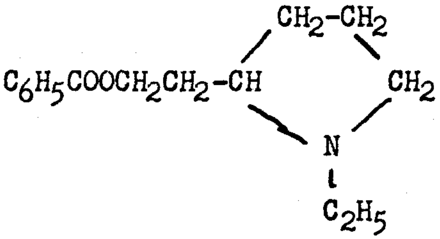
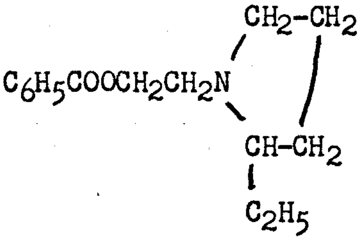
(55) H. C. Brill, J. Am. Chem. Soc. 54, 2484-7 (1932).

2-(1-Ethyl-2-pyrrolidino) ethyl benzoate



(56)

2-(2-Ethyl-1-pyrrolidino) ethyl benzoate



(57)

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(56) R. C. Fuson and C. L. Zirkle, J. Am. Chem. Soc. 70, 2760-2 (1948).
(57) Henri Normant, Compt. rend. 226, 1734-6 (1948).

ALKYL AND DIALKYLAMINO ESTERS OF ALKYLBENZOIC ACIDS

A. Esters of unsubstituted alkylbenzoic acids

(1) p-$CH_3C_6H_4COOH$

The following alkamine esters have been prepared: 2-ethylaminoethyl (19), 2-butylaminoethyl (18) (19), 2-isobutylaminoethyl (18) (19), 3-diethylaminopropyl (58) and 3-piperidinopropyl (44).

(2) p-$C_2H_5C_6H_4COOH$

The following alkamine esters have been prepared: 2-butylaminoethyl (18) (19) and 2-isobutylaminoethyl (18) (19).

(3) p-$(CH_3)_2CHC_6H_4COOH$

The following alkamine esters have been prepared: 2-butylaminoethyl (18) (19), 2-isobutylaminoethyl (18) (19), 2-amylaminoethyl (18) (19), 2-dimethylaminoethyl (59), 2-diethylaminoethyl (59), 2-diethylaminopropyl (59) and 3-piperidinopropyl (44).

(4) 3-(2-Methyl-1-piperidino) propyl-p-cyclopentyl benzoate (60)(61).

(5) 3-(2-Methyl-1-piperidino) propyl-p-cyclohexyl benzoate (60) (61).

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(58) C. A. 10, 2387; E. A. Wildman and L. Thorp, U. S. 1,193,651 (1916).

(59) J. T. Bryan and P. A. Foote, J. Am. Pharm. Assoc. 39, 644 (1950).

(60) C. A. 44, 3523; Eli Lilly & Co., Brit. 616,312 (1949).

(61) C. A. 42, 5470; S. M. McElvain and T. P. Carney, U. S. 2,439,818 (1948).

B. Esters of side chain substituted alkybenzoic acids

(1) -Dialkylaminoalkylene-p-(5-hydroxyamyl) benzoates

$p\text{-}HO(CH_2)_5C_6H_4COO(CH_2)_nNR_2$

Compounds of this type have been prepared in which R is methyl, ethyl, 2-methylpiperidino and 2,6-dimethylpiperidino when n is 2 and in which R is 2-methylpiperidino and 2,6-dimethylpiperidino when n is 3 (62).

(2) 2-Diethylaminoethyl-p-(2-ethoxyethyl) benzoate (1)

(3) o-Alkoxymethyl benzoates

(a) $o\text{-}ROCH_2C_6H_4COOCH_2CH_2N(C_2H_5)_2$

Compounds of this type have been prepared in which R is ethyl, butyl and isoamyl (63).

(b) $o\text{-}R_1OCH_2C_6H_4COO(CH_2)_nNR_2$

Compounds of this type have been prepared in which R is butyl when n is 3 and R_1 is ethyl, and in which R is butyl when n is 2 and R_1 is isoamyl (63).

(4) Aminoalkylbenzoic acids

(a) $p\text{-}NH_2CH_2C_6H_4COO(CH_2)_nNR_2$

Compounds of this type have been prepared in which R is ethyl, piperidino and 4-morpholino when n is 2 and in which R is piperidino when n is 3 (64).

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(62) R. O. Clinton, U. J. Salvador, S. C. Laskowski and J. S. Buck, J. Am. Chem. Soc. <u>72</u>, 1331-4 (1950).

(63) C. A. <u>40</u>, 96; R. P. Parker and A. J. Hill (to American Cyanamide Co.) U. S. 2,383,074 (1945).

(64) F. F. Blicke and W. M. Lilienfeld, J. Am. Chem. Soc. <u>65</u>, 2281-4 (1943).

(b) $p-NH_2CH_2CH_2C_6H_4COOH$

(1) $p-NH_2CH_2CH_2C_6H_4COO(CH_2)_nNR_2$

Compounds of this type have been prepared in which R is 4-morpholino and piperidino when n is 2 and piperidino when n is 3 (64).

(2) 3-piperidino-2-2-dimethylpropyl-p-(2-aminoethyl) benzoate (64)

(c) $p-NH_2(CH_2)_3C_6H_4COOH$

(1) $p-NH_2(CH_2)_3C_6H_4COO(CH_2)_nNR_2$

Compounds of this type have been prepared in which R is piperidino when n is 2 and butyl when n is 3 (64).

(2) 3-piperidino-2,2-dimethylpropyl-p-(3-aminopropyl) benzoate (64).

(d) $p-NH_2CH(CH_3)-CH_2C_6H_4COOH$

The following alkamine esters have been prepared: 2-piperidinoethyl, 3-piperidinopropyl, 3-morpholinopropyl and 3-piperidino-2,2-dimethylpropyl (65).

(5) $p-(p-NO_2C_6H_4CH_2)C_6H_4COOCH_2CH_2N(C_2H_5)_2$ (1).

(6) $p-(p-NH_2C_6H_4CH_2)C_6H_4COOCH_2CH_2N(C_2H_5)_2$ (1).

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(65) F. F. Blicke and W. M. Lilienfeld, J. Am. Chem. Soc. 65, 2377-8 (1943).

(7) Dialkylaminoalkylbenzoic acid

(a) $(C_2H_5)_2NCH_2C_6H_4COOH$

(1) Ortho isomer

The following alkamine esters have been prepared: 2-diethylaminoethyl, 3-diethylaminopropyl and 2-dibutylaminoethyl (7).

(2) Meta isomer

The 2-diethylaminoethyl ester has been made (66).

(3) Para isomer

The following alkamine esters have been prepared: 2-isobutylaminoethyl (19), 2-diethylaminoethyl (67) and 3-dibutylaminopropyl (67).

(b) $(C_4H_9)_2NCH_2C_6H_4COOH$

(1) Ortho isomer

The following alkamine esters have been prepared: 2-diethylaminoethyl, 3-diethylaminopropyl and 2-dibutylaminoethyl (7).

(2) Meta isomer

The following alkamine esters have been prepared: 2-diethylaminoethyl and 2(4-morpholino) ethyl (66).

(3) Para isomer

The following alkamine esters have been prepared: 2-diethylaminoethyl (19) and 2-(4-morpholino) ethyl (19).

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(66) C. A. 42, 603; R. P. Parker and A. J. Hill (to American Cyanamide Co.) U. S. 2,428,239 (1947).

(67) C. A. 41, 486; R. P. Parker and A. J. Hill (to American Cyanamide Co.) U. S. 2,406,627 (1946).

(8) p-(ω-Dialkylaminoalkyloxy) benzoic acids

$p\text{-}(R)_2N(CH_2)_nOCH_2C_6H_4COOH$

The following alkamine esters have been prepared:

$$p\text{-}(R)_2N(CH_2)_nOCH_2C_6H_4COO(CH_2)_xN(R_1)_2 \qquad (68)$$

R	n	x	R
ethyl	2	2	ethyl
ethyl	2	3	ethyl
ethyl	3	2	ethyl
ethyl	3	3	ethyl
butyl	2	2	butyl
butyl	3	2	butyl

The 2-diethylamino-2-methylethyl ester of p-3-diethylaminopropyloxymethyl benzoic acid also has been prepared (68).

(9) p-(p-Nitrophenoxymethyl) benzoic acid

The 2-diethylaminoethyl ester has been prepared (69).

(10) p-(Phenoxymethyl) benzoic acid

The 2-diethylaminoethyl and 3-diethylaminopropyl esters have been prepared (69).

(11) p-(p-Methylphenoxymethyl) benzoic acid

The 3-diethylaminopropyl and 3-dibutylaminopropyl esters have been prepared (69).

(12) p-Phenylethylbenzoic acid

The following alkamine esters have been prepared: 2-diethylaminoethyl and 1-dimethylaminoethyl-1-methylamyl (70).

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(68) C. A. 40, 176; V. S. Salvin and A. J. Hill (to American Cyanamide Co.) U. S. 2,385,104 (1945).

(69) C. A. 39, 3303; V. S. Salvin and A. J. Hill (to American Cyanamide Co.) U. S. 2,375,138 (1945).

(70) C. A. 41, 2442; W. G. Christiansen and S. E. Harris (to E. R. Squibb & Sons) U. S. 2,412,966 (1946).

C. Esters of ring substituted alkylbenzoic acids

(1) Esters of derivatives of 2-alkylbenzoic acids

The following has been prepared: 2-diethylaminoethyl-2-methyl-4-ethoxybenzoate (1) (71).

(2) Esters of derivatives of 3-alkylbenzoic acids

The following have been prepared: 2-diethylaminoethyl-3-methyl-4-ethoxybenzoate (1), 2-diethylaminoethyl-3-methyl-2-ethoxybenzoate (1), 3-dimethylaminopropyl-3-methyl-4-butoxybenzoate (1) (71), 1-methyl-1-dimethylaminoamyl-3-methyl-4-butoxybenzoate (1) (71), 2-diethylaminoethyl-3-ethyl-4-propoxybenzoate (72), 2-diethylaminoethyl-3-allyl-4-propoxybenzoate (50), 3-diethylaminopropyl-3-methyl-4-phenethylbenzoate (70), and 1-methyl-1-dimethylaminomethylamyl-3-methyl-4-phenethylbenzoate (70).

(3) Esters of derivatives of 4-alkylbenzoic acids

The following has been prepared: 3-piperidinopropyl-2-hydroxy-4-butylbenzoate (44).

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(71) C. A. 41, 995; W. G. Christiansen and S. E. Harris, U. S. 2,409,663 (1946).

(72) C. A. 37, 5708; C. Rohmann and H. D. Wilm, Arch. Pharm. 280, 76-85 (1942).

Esters of alkoxybenzoic acids

A. Methoxybenzoic acid

$CH_3OC_6H_4COOH$

(1) Para isomer

The following alkamine esters have been prepared: 2-butylaminoethyl (73), 2-diethylaminoethyl (50) (74), 2-butylamino-2,2-dimethylethyl (2), 2-piperidinoethyl (75), 3-diethylaminopropyl (76)(77), 3-piperidinopropyl (44) and 5-diethylaminoamyl (50).

(2) Meta isomer

The 2-diethylaminoethyl ester has been prepared (50).

(3) Ortho isomer

The 3-piperidinopropyl ester has been prepared (44).

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(73) H. E. Thompson, C. P. Swanson and A. G. Norman, Botan. Gaz. 107, 476-507 (1946).

(74) W. A. Lott, S. E. Harris, W. G. Christiansen, J. A. Pharm. Assoc. 27, 661-5 (1938).

(75) C. A. 36, 1608; C. Rohmann, W. Haas and H. Bergstermann, Arch. Pharm. 278, 425-37 (1941).

(76) C. A. 4, 2119; A. Einhorn and E. Uhlfelder, Ann. 371, 162-179.

(77) C. A. 33, 173; T. Sabalitschka and E. Bohm, Brit. 487,824 (1938).

B. Ethoxybenzoic acid

$$C_2H_5\overset{O}{}C_6H_4COOH$$

(1) Para isomer

(a) Alkylaminoalkyl esters

The following have been prepared: 2-alkylaminoethyl, where alkyl may be ethyl (1) (74) (78), butyl (79), isobutyl (78) or amyl (78); 2-alkylamino-2,2-dimethylethyl, where alkyl may be amyl or hexyl (2) (73); and 2-alkylamino-2-ethylethyl, where alkyl may be ethyl, butyl or hexyl (2).

(b) Dialkylaminoalkyl esters

Esters of 2-dialkylaminoethanol have been prepared in which alkyl is ethyl (1) (50) (80), butyl (1) (74) and piperidino (34).

Esters of 3-dialkylaminopropanol have been prepared in which alkyl may be ethyl (1) (74) (81), butyl (65) and piperidino (50).

The 5-diethylaminoamyl ester also has been prepared (50).

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(78) C. A. 43, 4430; W. G. Christiansen and G. O. Chase (to E. R. Squibb & Sons) U. S. 2,444,395 (1948).

(79) J. S. Pierce, J. M. Salsbury and J. M. Fredericksen, J. Am. Chem. Soc. 64, 1691-4 (1942).

(80) F. H. Case, J. Am. Chem. Soc. 47, 3003-5 (1925).

(81) J. C. Wagner, R. F. Sievers, A. L. Bennet and A. R. McIntyre, J. Pharmacol. 68, 437-53 (1940).

(c) Miscellaneous esters

The following have been prepared: 2-diethylaminocyclohexyl (1) (74), 2-diethylaminoisohexyl (1), 2-diethylaminoethyl-1-methyl-1-ethylethyl (74) and 2-diethylamino-2-isobutylethyl (74).

(2) Ortho isomer

The following alkamine esters have been prepared: 2-butylamino-2,2-dimethylethyl (2) and diethylaminoethyl (1).

(3) Meta isomer

The following alkamine esters have been prepared: 2-butylamino-2,2-dimethylethyl (2), 2-amylamino-2,2-dimethylethyl (2) and diethylaminoethyl (1).

C. Propoxybenzoic acid

$C_3H_7OC_6H_4COOH$

(1) Para isomer

The following alkamine esters have been prepared: butylaminoethyl (79), 2-alkylamino-2,2-dimethylethyl, where alkyl is butyl (2), amyl (2) (73) or hexyl (2); 2-alkylamino-2-ethylethyl, where alkyl may be butyl or hexyl (2); 2-diethylaminoethyl (1) (44) (50) (74) (81), 2-dipropylaminoethyl (82), 2-piperidinoethyl (75) and 3-piperidinopropyl (82).

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(82) C. A. 32, 4727; C. Rohmann, Ger. 658,359 (1938).

(2) Ortho and meta isomers

The following alkamine esters have been prepared: 2-butylaminoethyl-o-propoxybenzoate (2) and 2-diethylaminoethyl-m-propoxybenzoate (72).

D. Isopropoxybenzoic acid

$p\text{-}(CH_3)_2CHOC_6H_4COOH$

The following alkamine esters have been prepared: 2-butylaminoethyl (79), 2-diethylaminoethyl (50) (74) (83), 2-piperidinoethyl (75) and 2-butylamino-2-ethylethyl (2).

E. Allyloxybenzoic acid

$p\text{-}CH_2{=}CHCH_2OC_6H_4COOH$

The following alkamine esters have been prepared: 2-diethylaminoethyl (1) (35) (50) (74), 2-piperidinoethyl (75), 3-piperidinopropyl (44) and diethylamino-2,2-dimethylpropyl (1).

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(83) C. A. 41, 2442; W. G. Christiansen and S. E. Harris (to E. R. Squibb & Sons) U. S. 2,412,966 (1946).

F. Butoxybenzoic acid

$C_4H_9OC_6H_4COOH$

(1) Para isomer

(a) Alkylaminoalkyl esters

The following have been prepared: 2-alkylaminoethyl, where alkyl may be ethyl (78) (79), propyl (79), isopropyl (73) (79), allyl (79), butyl (73) (79), isobutyl (73) (79) and amyl (73) (79); 2-alkylamino-2,2-dimethylethyl, where alkyl may be ethyl (2) (73), propyl (2), butyl (2) and hexyl (2); and 2-butylamino-2-ethylethyl (2).

(b) -Dialkylaminoalkyl esters

The following have been prepared: 2-dimethylaminoethyl (1) (74) (82) (83), 2-diethylaminoethyl (1) (74) (82) (83), 3-diethylaminopropyl (50), 3-piperidinopropyl (44), 3-(2-methylpiperidino) propyl (84) (85), 3-(3-methylpiperidino)propyl (44), 3-(4-methylpiperidino)propyl (44) and 5-diethylaminoamyl (50).

(c) Miscellaneous esters

The following have been prepared: 2-(2-methylpiperidino)-1-methylethyl (44), 3-(3-methylpiperidino)-1-methylpropyl (44), 3-(4-methylpiperidino)-2,2-dimethylpropyl (44) and 2-diethylamino-1-methyl-1-ethylethyl (83).

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(84) C. A. 43, 694; S. M. McElvain and T. P. Carney, U. S. 2,448,996 (1948).

(85) C. A. 43, 7509; Eli Lilly & Co., Brit. 617,191 (1949).

(2) Ortho isomer

The following alkamine esters have been prepared: 2-isopropylaminoethyl (73) (79), 2-butylaminoethyl (73) (79), 2-isobutylaminoethyl (73), 3-piperidinopropyl (44) and 3-(2,6-dimethylpiperidino)propyl (44).

(3) Meta isomer

The 2-butylaminoethyl ester has been prepared: (79).

G. p-Isobutoxybenzoic acid

$$p(CH_3)_2CHCH_2OC_6H_4COOH$$

The following alkamine esters have been prepared: 2-butylaminoethyl (79), 2-diethylaminoethyl (50), 2-piperidinoethyl (75) and 3-piperidinopropyl (44).

H. p-Secondarybutoxybenzoic acid

$$p\text{-}C_2H_5CH(CH_3)OC_6H_4COOH$$

The piperidinopropyl ester has been prepared (44).

I. p-Amyloxybenzoic acid

$$p\text{-}C_5H_{11}OC_6H_4COOH$$

The following alkamine esters have been prepared: 2-butylaminoethyl (79), 2-alkylamino-2,2-dimethylethyl, where alkyl may be propyl (2), butyl (2) (73) or amyl (2); and 3-piperidinopropyl (44).

J. p-Isoamyloxybenzoic acid

$p\text{-}(CH_3)_2CH(CH_2)_2OC_6H_4COOH$

The following alkamine esters have been prepared: 2-diethylaminoethyl (50) (82), 2-piperidinoethyl (75) and 3-piperidinopropyl (44).

K. p-Hexyloxybenzoic acid

$p\text{-}C_6H_{13}OC_6H_4COOH$

The following alkamine esters have been prepared: 2-ethylaminoethyl (79), 2-butylaminoethyl (79), 2-butylamino-2,2-dimethylethyl (73), 3-piperidinopropyl (44) and 3-(2,6-dimethylpiperidino)propyl (44).

L. p-Cyclohexyloxybenzoic acid

$p\text{-}C_6H_{11}OC_6H_4COOH$

The following alkamine esters have been prepared: 3-piperidinopropyl (44) and 3-(methylpiperidino)propyl. The position ofthe methyl group was not given (86).

M. p-Heptyloxybenzoic acid

$p\text{-}C_7H_{15}OC_6H_4COOH$

The following alkamine esters have been prepared: 2-butylaminoethyl (73) (79), 2-alkylamino-2,2-dimethylethyl, where alkyl may be propyl (2) (73), butyl (2) (73), amyl (2) (73) or hexyl (2); and 2-propylamino-2-ethylethyl (2).

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(86) C. A. 43, 8100; D. Cavanna, Minerva Med. 40, I, 615-16 (1949).

N. Dodecyloxybenzoic acid

$C_{12}H_{25}OC_6H_4COOH$

The following alkamine esters have been prepared: 2-butylaminoethyl-p-dodecyloxybenzoate (79) and 2-butylaminoethyl-o-dodecyloxybenzoate (79).

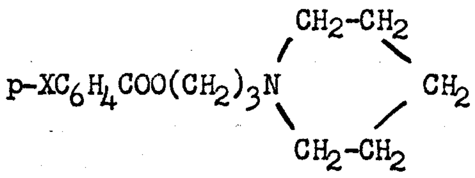
O. Miscellaneous esters

(1) 2-Diethylaminoethyl-p-substituted oxybenzoates

$p\text{-}XC_6H_4COOCH_2CH_2N(C_2H_5)_2$

Compounds of this type have been prepared in which X is 2-diethylaminoethyl (1), 2-bromoallyl (1) (74) (83), p-nitrobenzyl (1) (70), p-aminobenzyl (1) (70), 2-phenylethyl (74), 2-ethoxyethyl (74), 2-(2-diethylaminoethyl)ethyl (74) and phenyl (87).

(2) 3-Piperidinopropyl-p-substituted oxybenzoates



Compounds of this type have been prepared in which X is phenyl, benzyl, 2-phrenylethyl, p-(p-toluidyl), phenyl and secondary hexyl (44).

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(87) R. B. Burtner and G. Lehmann, J. Am. Chem. Soc. 62, 527-32 (1940).

(3) Alkoxybenzoic acids with one or more substituents on the ring

The following have been prepared: 2-diethylaminoethyl-3,4-5-trimethoxybenzoate (88), 2-dimethylamino-1-methyl-1-ethylethyl-3-methoxy-4-acetoxybenzoate (89), 2-diethylaminoethyl-3-methoxy-4-acetoxybenzoate (89), alkamine)-3-methoxy-4-acetoxybenzoates, where alkamine may be 2-diethylamineoethyl, 2-dipropylaminoethyl, 2-dibutylaminoethyl, 3-diethylaminopropyl, 3-dipropylaminopropyl, 3-dibutylaminopropyl (90) and 2-diethylaminoethyl-3-methoxy-4-ethoxybenzoate (1).

(4) Isolated esters

The following have been prepared: 3-diethylaminopropyl-p-2-phenylethoxybenzoate (70), 3-(2,6-dimethylpiperidino)propyl-p-phenoxybenzoate (44) and 2-diethylaminoethyl-3,5-diodo-4-methoxybenzoate (91).

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(88) C. A. 43, 1022; N. Loefgren and B. Lundquist, Swensk. Kem. Tid. 58, 206-17 (1946).

(89) E. Fourneau and J. Matti, J. Pharm. Chim. 18, 247-58 (1933) C. A. 27, 5893.

(90) L. S. Fosdick and A. C. Starke, Jr., J. Am. Chem. Soc. 62, 3352-5 (1940).

(91) C. A. 42, 602; A. A. Goldberg and H. S. Turner (to Ward, Blenkinsop & Co., Ltd.) Brit. 576,035 (1946).

ESTERS OF NITRO AND AMINOBENZOIC ACIDS

These two classes of compounds have been treated together because the nitrobenzoic acid esters are almost invariably intermediates for the preparation of the aminobenzoic acid esters.

Throughout this section X signifies either the nitro or the amino group.

A. Esters of p-nitro and p-aminobenzoic acids

(1) Alkylaminoalkyl esters

2-alkylaminoethyl esters

$p\text{-}XC_6H_4COOCH_2CH_2NHR$

Compounds of this type have been prepared where R is ethyl (19), propyl (3) (92), isopropyl (17), butyl (3) (17) (19) (92), isobutyl (3) (17) (92), 1-methylpropyl (17), amyl (3) (17) (92), isoamyl (3) (92), 2-amyl (17), 3-amyl (17) (93), hexyl (19), isohexyl (17), cyclohexyl (19) (25), 1-methylcyclohexyl (17) (93), 2-methylcyclohexyl (19), 4-methylcyclohexyl (19) (93), 3,3,5-trimethylcyclohexyl (17), 2,2,6-trimethylcyclohexyl (93), 1,3-dimethylbutyl (93), heptyl (17) (19), 2-heptyl (17), 4-heptyl (17) (93), octyl (19), 2-octyl (17) (93) (94), 3-octyl (17) (94), 2-nonyl

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(92) C. A. 35, 7659; S. D. Goldberg and W. F. Ringk, U. S. 2,252,713 (1941).

(93) C. A. 38, 4102; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,339,914 (1944).

(17) (93), 5-nonyl (17) (93), 2,6-dimethylheptyl (93), 2,6-dimethyl-4-heptyl (17), 2-decyl (93) and 1-methyl (17).

2-Alkylamino-1-methylethyl esters

$p\text{-}XC_6H_4COOCH(CH_3)CH_2\text{-}NHR$

Compounds of this type have been prepared in which R is isopropyl, 1-methylpropyl, isoamyl, 3-amyl, isohexyl, cyclohexyl, 4-methylcyclohexyl, 2-heptyl, 4-heptyl, 2-octyl, 5-nonyl, 2,6-dimethyl-4-heptyl, 6-hendecyl, 2,8-dimethyl-5-nonyl, 7-tridecyl, 8-pentadecyl and 10-nonadecyl (95).

2-Alkylamino-1,1-dimethylethyl esters

$p\text{-}XC_6H_5COOC(CH_3)_2CH_2NHR$

Compounds of this type have been prepared in which R is propyl (96a), isopropyl (25) (96), butyl (96a), isobutyl (96a), amyl (96a), isoamyl (25) (96a), 3-amyl (25) (96), hexyl (97), cyclohexyl (25) (98), heptyl (97), 2-heptyl (25) (96) (97), 2-octyl (25) (96) and 3-octyl (97).

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(94) C. A. 42, 5620; Novocol Chemical Manufacturing Co., Inc., Brit. 598,656 (1948).

(95) A. C. Cope and E. M. Hancock, J. Am. Chem. Soc. 66, 1453-6 (1944).

(96a) S. D. Goldberg, W. F. Ringk and P. E. Spoerri, J. Am. Chem. Soc. 61, 3562-4 (1939).

(96) C. A. 43, 3038; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,459,217 (1949).

(97) W. F. Ringk and E. Epstein, J. Am. Chem. Soc. 65, 1222-6 (1943).

(98) C. A. 44, 662; Sharp & Dohme, Inc., Brit. 620,657 (1949).

2-Alkylamino-1,1-diethylethyl esters

$p\text{-}XC_6H_4COOC(C_2H_5)_2CH_2NHR$

Compounds of this type have been prepared in which R is butyl (92), isobutyl (92) and cyclohexyl (99).

2-Alkylamino-2-methylethyl esters

$p\text{-}XC_6H_4COOCH_2\text{-}CH(CH_3)NHR$

Compounds of this type have been prepared in which R is 3-amyl (25), cyclohexyl (25), 4-heptyl (25) (100), 5-nonyl (25) and 2,6-dimethyl-4-heptyl (25) (98).

2-Alkylamino-2-ethylethyl esters

$p\text{-}XC_6H_4COOCH_2CH(C_2H_5)NR$

Compounds of this type have been prepared in which R is isopropyl (96), 3-amyl (96), cyclohexyl (99), 4-heptyl (99), 5-nonyl (99) and 2,6-dimethyl-4-heptyl (98) (99).

2-Alkylamino-2,2-dimethylethyl esters

$p\text{-}XC_6H_4COOCH_2C(CH_3)_2NHR$

Compounds of this type have been prepared in which R is ethyl (97) (101) (102), propyl (19) (97) (101) (102), isopropyl (97) (101)

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(99) C. A. 42, 7794; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,442,797 (1948).

(100) C. A. 42, 5174; A. C. Cope (to Sharp & Dohme, Inc.) U. S. 2,442,721 (1948).

(101) C. A. 39, 3124; W. F. Ringk (to Novocol Chemical Manufacturing Co., Inc.) U. S. 2,363,081-3 (1944).

(102) C. B. Kremer and E. Waldman, J. Am.Chem. Soc. 64, 1089-90 (1942).

(102), butyl (19) (97) (101) (102), isobutyl (19) (97) (101) (102), 1-methylpropyl (25) (96) (97) (101), amyl (19) (97) (101) (102), isoamyl (25) (97) (101) (102), hexyl (97) (101), 2-ethylbutyl (97) (101), cyclohexyl (19) (25), 2-methylcyclohexyl (19), 4-methylcyclohexyl (19), heptyl (97) (101), 2-heptyl (19) (25) (97) (101), octyl (19), 2-ethylhexyl (97) (101) and decyl (97) (101).

2-Alkylamino-2-methyl-2-ethylethyl esters

$p\text{-}XC_6H_4COOCH_2C(CH_3)(C_2H_5)NHR$

Compounds of this type have been prepared in which R is amyl (101) and isoamyl (101).

2-Alkylamino-1,2-dimethylethyl esters

$p\text{-}XC_6H_4COOCH(CH_3)CH(CH_3)NHR$

Compounds of this type have been prepared in which R is ethyl, propyl, butyl, amyl and isoamyl (101).

2-Methylamino-1,1,2-trimethylethyl ester (23)

3-Alkylaminopropyl esters

$p\text{-}XC_6H_4COO(CH_2)_3NHR$

Compounds of this type have been prepared in which R is propyl (3), butyl (3), amyl (3), cyclohexyl (103), 2-heptyl (103), 4-heptyl (103), 2-octyl (103) and 2,6-dimethyl-4-heptyl (103).

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(103) E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright and A. C. Cope, J. Am. Chem. Soc. <u>66</u>, 1747-52 (1944).

3-Alkylamino-3-methylpropyl esters

$p\text{-}XC_6H_4COOCH_2CH_2CH(CH_3)NHR$

Compounds of this type have been prepared in which R is 3-amyl, cyclohexyl, 4-heptyl, 5-nonyl and 2,6-dimethyl-4-heptyl (25).

(2) Dialkylaminoalkyl esters

(a) Esters in which the alkyl groups are the same

Dialkylaminomethyl esters

$p\text{-}XC_6H_4COOCH_2NR_2$

Compounds of this type have been prepared in which R is ethyl, propyl, butyl and isoamyl (30).

2-Dialkylaminoethyl esters

$p\text{-}XC_6H_4COOCH_2CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (104) (105) (106) (107), ethyl (104) (105) (107) (108), propyl (107), isopropyl (105) (106) (107) (109), butyl (106) (110), 1-methylpropyl (32) (107), isobutyl (105) (106) (107) (109),

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(104) Beilstein, Handbuch der Organischen Chemie IX, 393.

(105) Beilstein, Handbuch der Organischen Chemie XIV, 424.

(106) C. A. 4, 2119; A. Einhorn, K. Fiedler, C. Ladisch and E. Uhlfelder, Ann. 371, 142-61.

(107) W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, J. Am. Chem. Soc. 59, 2248-52 (1937).

(108) C. A. 4, 2118; A. Einhorn and E. Uhlfelder, Ann. 371, 131-42.

(109) Beilstein, Handbuch der Organischen Chemie IX, 394.

(110) C. A. 15, 412; O. Kamm, R. Adams and E. H. Volwiler, U. S. 1,358,750 (1920).

pyrrolidino (62) (111) (112), 2-methylpyrrolidino (62), amyl (107), isoamyl (105) (106) (107) (109), piperidino (34) (108) (113), 2-piperidino (114), 1-alkyl-2-piperidino, where alkyl may be methyl, ethyl or propyl (114); 2-methylpiperidino (62), 3-methylpiperidino (62) and 2,6-dimethylpiperidino (62).

2-Dialkylamino-1-alkylethyl esters

$p\text{-}XC_6H_4COOCHalkylCH_2NR_2$

Compounds of this type have been prepared where alkyl is ethyl (28) (115), butyl (28) and cyclohexyl (28) when R is methyl; in which alkyl is methyl (105) (109) when R is ethyl; and in which alkyl is propyl (28) or isobutyl (28) when R is piperidino.

2-Dialkylamino-1,1-dimethylethyl esters

$p\text{-}XC_6H_4COOC(CH_3)_2CH_2NR_2$

Compounds of this type have been prepared where R is methyl (116), ethyl (105) (106) (109) (116) and piperidino (106) (116).

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(111) C. A. 22, 666; J. Supniewski, Roszniki Chem. 7, 163-71 (1927).

(112) F. F. Blicke and E. S. Blake, J. Am. Chem. Soc. 53, 1015-25 (1931).

(113) O. A. Barnes and R. Adams, J. Am. Chem. Soc. 49, 1307-15 (1927).

(114) C. S. Marvel and R. S. Shelton, J. Am. Chem. Soc. 51, 915-17 (1929).

(115) C. A. 16, 2495; E. Fourneau and J. Puyal, Bull. Soc. Chim. 31, 424-35 (1922).

(116) C. A. 24, 3502; J. Trefuel, Mme. J. Trefuel and Ch. Barbelet, Bull. sci. pharmacol. 37, 184-94; 240-54 (1930).

2-Dialkylamino-1-methyl-1-ethyl esters

$p\text{-}XC_6H_4COOC(CH_3)(C_2H_5)CH_2NR_2$ x

Compounds of this type have been prepared where R is methyl (116), ethyl (105) (109) (116), pyrrolidyl (112) and piperidino (116).

2-Diethylamino-1,1-diethyl esters

$p\text{-}XC_6H_4COOC(C_2H_5)_2CH_2N(C_2H_5)_2$ (105) (106) (109)

2-Dialkylamino-2-alkylethyl esters

$p\text{-}XC_6H_4COOCH_2\text{-}CHRN(alkyl)_2$

<u>Alkyl</u>	<u>R</u>	
methyl	methyl	(115)
ethyl	isobutyl	(117) (118)
	ethyl	(107) (115)
	allyl	(107) (119)
	butyl	(107)
	isobutyl	(117) (118)
	amyl	(107)

2-Diethylamino-2,2-dimethylethyl ester (107)

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(117) C. A. <u>19</u>, 3567; P. Karrer, U. S. 1,555,217 (1925).
(118) C. A. <u>18</u>, 306; Chemische Fabrik Flora, Brit. 200,810 (1923).
(119) C. A. <u>16</u>, 990; O. Kamm and E. H. Volwiler, U. S. 1,388,573 (1921).

2-Dialkylamino-1-alkyl-2-alkylethyl esters

$p\text{-}XC_6H_4COOCHR_3CHR_2N(R_1)_2$

R_1	R_2	R_3	
methyl	methyl	methyl	(120)
ethyl	methyl	methyl	(115)

2-Diethylamino-1,1,2-trimethylethyl ester (28).

2-Piperidino-1,1,2-trimethylethyl ester (28).

3-Dialkylaminopropyl esters

$p\text{-}XC_6H_4COOCH_2CH_2CH_2NR_2$

Compounds of this type have been prepared in which R is methyl (107), ethyl (6), propyl (107), isopropyl (107), allyl (107) (119), butyl (107) (121) (122) (123), isobutyl (123), 1-methylpropyl (107), pyrrolidino (112), 2-methylpyrrolidino (62), amyl (107), isoamyl (107), piperidino (38) (55) (113), 2-methylpiperidino (62) and 3-methylpiperidino (38) (40) (62).

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(120) C. A. 18, 569; W. Schulemann, L. Schuetz and K. Meisenburg, U. S. 1,474,567 (1923).

(121) C. A. 42, 4605; A. W. Weston (to Abbott Laboratories) U. S. 2,437,984 (1948).

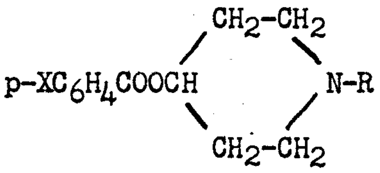
(122) C. A. 22, 3265; R. Adams and E. H. Volwiler (to Abbott Laboratories), U. S. 1,676,470 (1928).

(123) C. A. 15, 412; O. Kamm, R. Adams and E. H. Volwiler, U. S. 358,751 (1920).

Miscellaneous 3-Dialkylaminopropyl esters

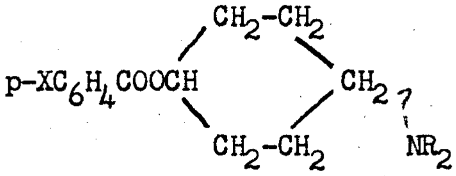
The following have been prepared: 3-dimethylamino-2,2-dimethylpropyl (124), 3-diethylamino-2,2-dimethylpropyl (49) (124), 3-dimethylamino-2-isopropylpropyl (49), 3-diethylamino-1,2-diethylpropyl (120), 3-diethylamino-1-ethyl-2-methylpropyl (120) and 3-diethylamino-1,3,3-trimethylpropyl (125).

1-Alkyl-4-piperidyl esters



Compounds of this type have been prepared in which R is methyl, ethyl, propyl, butyl and isoamyl (54).

y-Dialkylamino-1-cyclohexyl esters



y	R
2	methyl (48)
2	ethyl (126) (127)
3	methyl (127)
3	ethyl (127)
4	methyl (127)

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(124) C. A. 27, 1638; C. Mannich, U. S. 1,889,678 (1932).

(125) C. A. 27, 1452; K. Keimatu, Jap. 93,404 (1931).

(126) A. E. Osterberg and E. C. Kendall, J. Am. Chem. Soc. 43, 1370-1 (1921).

(127) H. Heckel and R. Adams, J. Am. Chem. Soc. 49, 1303-7 (1927).

2-(1-Alkyl-3-piperidyl)ethyl esters

Compounds of this type have been prepared in which alkyl is methyl, ethyl, isopropyl and butyl (128).

4-Diethylaminobutyl ester (107) (129).

5-Diethylaminoamyl ester (107).

(b) Esters in which the alkyl groups are different

2-Dialkylaminoethyl esters

$p\text{-}XC_6H_5COOCH_2CH_2NR_1R_2$

Compounds of this type have been prepared in which R_1, R_2 are butyl, allyl (107) (130); methyl, 2-octyl (103); ethyl, 2-octyl (103); methyl, cyclohexyl (103); and ethyl, cyclohexyl (103).

3-Dialkylaminopropyl esters

$p\text{-}XC_6H_5COO(CH_2)_3NR_1R_2$

Compounds of this type have been prepared in which R_1, R_2 are butyl, allyl (107) (130); propyl, allyl (130); isopropyl, allyl (103) and isoamyl, allyl (130).

2-Dialkylamino-1-methylethyl

$p\text{-}XC_6H_4COOCH(CH_3)\ CH_2NR_1R_2$

Compounds of this type have been prepared in which R_1, R_2 are methyl, cyclohexyl (103) and ethyl, cyclohexyl (103).

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(128) L. T. Sanborn and C. S. Marvel, J. Am. Chem. Soc. 50, 563-7 (1928).

(129) C. A. 35, 4011; L. M. Smorgonskii and Ya. L. Gol'dfarb, J. Gen. Chem. (U. S. S. R.) 10, 1113-19 (1940).

(130) C. A. 18, 568; R. Adams and E. H. Volwiler, U. S. 1,476,934 (1923).

B. Esters of o- and m-nitro and o- and m-aminobenzoic acid

The following alkamine esters have been prepared: 2-diethylaminoethyl (116) (131) (132), 2-piperidinoethyl (34) (133), 2-dialkylamino-1-methyl-1-ethylethyl, where alkyl is methyl, ethyl or piperidino (116); 2-dialkylamino-1,1-dimethylethyl, where alkyl is methyl, ethyl or piperidino (116) and 2-butylamino-2,2-dimethylethyl (101).

Esters of m-nitro and m-aminobenzoic acid

The following alkamine esters have been prepared: 2-alkylaminoethyl, where alkyl is butyl (19), isobutyl (19), amyl (19) and 2-octyl (17) (19); and 2-alkylamino-2,2-dimethylethyl, where alkyl is ethyl (97), propyl (97), isopropyl (97), butyl (19) (97), isobutyl (19) and amyl (19).

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(131) Beilstein, Handbuch der Organischen Chemie, IX, 373.
(132) Beilstein, Handbuch der Organischen Chemie, XIV, 320 and 389.
(133) C. A. 35, 3041; L. A. Walter and R. J. Fosbinder, U. S. 2,229,533 (1941).

C. Esters of ring derivatives of aminobenzoic acids

(1) Para-nitro and para-aminobenzoic acid

(a) One substituent on the ring

Substituent	Position		
F	2	2-diethylaminoethyl	(134) (135)
F	3	2-diethylaminoethyl	(134) (135)
Cl	2	2-diethylaminoethyl	(134) (135)
Cl	2	2-morpholinoethyl	(134) (135)
Cl	2	2-piperidinoethyl	(134) (135)
Cl	2	2-dimethylaminoethyl	(134) (135)
Cl	2	2-butylaminoethyl	(134) (135)
Cl	2	3-diethylaminopropyl	(134) (135)
Cl	2	2-diethylamino-1-methylethyl	(135)
Cl	2	3-dibutylaminopropyl	(135)
Cl	2	2-amylamino-1,1-dimethylethyl	(135)
Cl	2	2-butylamino-2,2-dimethylethyl	(134) (135)
Cl	2	2-amylamino-2,2-	(134)
Cl	2	2-isoamylamino-2,2-	(133) (134)

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(134) M. Rubin, H. C. Marks, H. Wishinsky and A. Lanzilotti, J. Am. Chem. Soc. <u>68</u>, 623-4 (1946).

(135) C. A. <u>44</u>, 5390; H. C. Marks and M. I. Rubin (to Wallace & Tiernan Products, Inc.) U. S. 2,460,139 (1949).

Substituent	Position	Ester	
Br	2	2-diethylaminoethyl	(136) (137)
Br	3	3-dibutylaminopropyl	(138)
Br	5	2-diethylaminoethyl	(137)
I	3	2-diethylaminoethyl	(137)
CH_3	2	2-diethylaminoethyl	(139)
CH_3O	3	ethylaminoethyl	(140) (141)
CH_3O	3	2-diethylaminoethyl	(142)
CH_3O	3	2-piperidinoethyl	(141)
C_2H_5O	3	2-diethylaminoethyl	(142)
C_4H_9O	3	2-diethylaminoethyl	(143)
NH_2	3	2-diethylaminoethyl	(76)
$CH_3)_2N$	3	2-diethylaminoethyl	(76)

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(136) C. A. 19, 2332; J. Frejka and J. Vitka, Spisy Prirodovedeckou Masurykovy University 1925 No. 48, 1-22.

(137) C. A. 24, 2836; Schering Kahlbaum, A. G., Brit. 321,968 (1928).

(138) M. B. Moore and E. H. Volwiler, J. Am. Chem. Soc. 62, 2799-2801 (1940).

(139) C. A. 13, 3282; E. A. Wildman, U. S. 1,317,250 (1919).

(140) C. A. 13, 3283; E. A. Wildman, U. S. 1,317,251 (1919).

(141) C. A. 24, 2141; Schering Kahlbaum, A. G. Brit. 317,296 (1928).

(142) C. A. 25, 3131; W. Schoeller and H. G. Allardt (to Schering Kahlbaum, A. G.) Ger. 522,064 (1928).

(143) C. A. 44, 9480; A. Wander, A. G., Swiss 265,343 (1950).

(b) Two substituents on the ring

Substituent	Position	Ester	
Br,Br	3,5	2-diethylaminoethyl	(137)
Br,Br	3,5	3-dibutylaminopropyl	(138)

(2) o-Nitro and o-aminobenzoic acid

(a) One substituent on the ring

Substituent	Position	Ester	
F	5	2-dimethylaminoethyl	(144)
F	5	2-diethylaminoethyl	(144)
F	5	2-dipropylaminoethyl	(144)
F	5	2-dibutylaminoethyl	(144)
F	5	3-diethylaminopropyl	(144)
F	5	3-dipropylaminopropyl	(144)
F	5	3-dibutylaminopropyl	(144)
Br	4	2-diethylaminoethyl	(137)
CH_3	4	2-diethylaminoethyl	(139)

(b) Two substituents on the ring

Substituent	Position	Ester	
CH_3O, CH_3O	3,5	2-diethylaminoethyl	(145)
CH_3O, CH_3O	3,5	2-piperidinoethyl	(145)

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(144) L. S. Fosdick and R. Blackwell, J. Am. Chem. Soc. 66, 1165-6 (1944).

(145) C. A. 24, 2836; O. Eisleb (to I. G. Farbenind, A. G.) Ger. 494,434 (1927).

(3) m-Nitro and M-aminobenzoic acids

(a) One substituent on the ring

Substituent	Position	Ester	
F	4	2-dimethylaminoethyl	(4)
F	4	2-diethylaminoethyl	(4)
F	4	2-dipropylaminoethyl	(4)
F	4	2-dibutylaminoethyl	(4)
F	4	3-diethylaminopropyl	(4)
F	4	3-dipropylaminopropyl	(4)
F	4	3-dibutylaminopropyl	(4)
Br	2	3-dibutylaminopropyl	(138)
I	4	2-diethylaminoethyl	(137) (146)
C_2H_5	4	2-butylaminoethyl	(19)
C_2H_5	4	2-isobutylaminoethyl	(19)
CH_3O	4	2-diethylaminoethyl	(142)
C_2H_5O	4	2-piperidinoethyl	(34)
CH_3S	4	2-diethylaminoethyl	(147)
CH_3S	4	3-diethylaminopropyl	(147)
C_2H_5S	4	2-diethylaminoethyl	(147)
C_2H_5S	4	3-diethylaminopropyl	(147)
C_3H_7S	4	2-diethylaminoethyl	(147)

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(146) C. A. <u>24</u>, 4120; W. Schoeller and H. G. Allardt (to Schering-Kahlbaum, A. G.) U. S. 1,765,621 (1930).

(147) J. J. Donleavy and P. C. Condit, J. Am. Chem. Soc. <u>69</u>, 1781-4 (1947).

In addition to the foregoing compounds, the following esters of p-methyl-m-nitro and aminobenzoic acids have been prepared: 2-alkylaminoethyl where alkyl may be butyl, isobutyl, amyl, hexyl, 2-octyl or 3-octyl (19) and 2-alkylamino-2,2-dimethylethyl where alkyl may be butyl, isobutyl, amyl or 2-octyl (19).

Esters of aminobenzoic acids and their ring substituted derivatives which may not have been prepared by way of their corresponding nitro compounds for the given reference

The doubt originates in most cases from the fact that the refernces involved are patents of processes for preparation of the given esters. The details are not given in Chemical Abstracts and the original patents were not available.

The list of compounds, some of which have been mentioned previously, is as follows: 3-dialkylaminopropyl-p-aminobenzoates, p-$NH_2C_6H_4COO(CH_2)_3NR_1R_2$, where R_1, R_2 may be butyl, ethyl or butyl, allyl (148), 2-piperidinoethyl-o,m-or p-aminobenzoate (133), 3-dimethylamino-1-methylpropyl-m-aminobenzoate (149), 3-dibutylaminopropyl-m-amino-p-butoxybenzoate (150), 2-diethylaminoethyl and 3-diethylaminopropyl-p-methylmercapto-m-aminobenzoate (151).

In all probability, however, the nitro compounds were obtained as intermediates.

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(148) C. A. 20, 3061; R. Adams, E. E. Dreger and E. H. Volwiler, U. S. 1,590,792 (1926).

(149) C. A. 23, 4300; Etablissments Poulenc Freres, E. Fourneau and J. Trefouel (to Soc. des usines chemiques Rhone-Poulenc) Brit. 301,845 (1927).

(150) C. A. 37, 230; E. B. Vliet and M. B. Moore, U. S. 2,288,334 (1942).

(151) C. A. 37, 6823; J. J. Donleavy (to Allied Laboratories, Inc.) U. S. 2,321,468 (1943).

D. Alkylaminobenzoic acids

p-Methylaminobenzoic acid

The following alkamine esters have been prepared: 2-ethylaminoethyl (19), 2-butylaminoethyl (19), 2-isobutylaminoethyl (19) and diethylaminoethyl (152).

m-Methylaminobenzoic acid

The following alkamine esters have been prepared: 2-butylaminoethyl (19) and 2-isobutylaminoethyl (19).

p-Ethylaminobenzoic acid

The following alkamine esters have been prepared: 2-ethylaminoethyl (19), 2-butylaminoethyl (19), 2-isobutylaminoethyl (19) and 2-diethylaminoethyl (152).

p-Propylaminobenzoic acid

The following alkamine esters have been prepared: 2-diethylaminoethyl (153), 2-piperidinoethyl (153) and 3-diethylaminopropyl (153).

p-Allylaminobenzoic acid

The 2-diethylaminoethyl ester has been prepared (153).

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(152) Beilstein, Handbuch der Organischen Chemie, XIV 426, 429; Hoechste Farbwerke vormals Meister, Lucius und Bruening, Ger. 180,291, Chem. Zentr. (1907) I, 1365.

(153) C. A. 20, 3539; Farbwerke vormals Meister, Lucius und Bruening, Brit. 241,767 (1925).

p-Butylaminobenzoic acid

The following alkamine esters have been prepared: 2-dimethylaminoethyl (154), 2-diethylaminoethyl (155) (156), 2-pyrrolidinoethyl (62), 2-(2-methylpyrrolidino)ethyl (62), 2-(2-methylpiperidino)ethyl (62), 2-(3-methylpiperidino) ethyl (62), 2-(2,6-dimethylpiperidino)ethyl (62), 3-(2-methylpyrrolidino)propyl (62), 3-(2-methylpiperidino)propyl (62) and 3-(3-methylpiperidino)propyl (62).

2-Diethylaminoethyl-p-isoamylaminobenzoate (153)

2-Diethylaminoethyl-p-palmitylaminobenzoate (157)

p-Methoxyethylaminobenzoic acid

The 2-piperidinoethyl and the 2-diethylaminoethyl esters have been prepared (153).

2-Piperidinoethyl-o-methoxyethylamino benzoate (158)

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(154) C. A. 28, 778; O. Eisleb (to I. G. Farbenind, A. G.) Ger. 582,715 (1933).

(155) C. A. 27, 1717; O. Eisleb (to Winthrop Chemical Co.) U. S. 1,889,645 (1932).

(156) C. A. 38, 2345; A. Skita and W. Stuhmer, Ger. 716,668 (1941).

(157) C. A. 28, 3756; R. Knoll (to I. G. Farbenind, A. G.) Ger, 582,390 (1933).

(158) C. A. 23, 1908; O. Eisleb (to Winthrop Chemical Co.) U. S. 1,704,660 (1929).

3-Diethylaminopropyl-p-(2-nitro-2,2-dimethylethylamino)-benzoate (159

3-Diethylaminopropyl-p-(2-amino-2,2-dimethylethylamino)-benzoate (159)

3-Diethylaminopropyl-p-(2-dimethylamino-2,2-dimethylethylamino)benzoate (159)

Esters of ring substituted alkylamino benzoic acid

Alkyl	Substituent	Position	Ester
p-propyl	Br	3	3-dibutylaminopropyl (138)
p-propyl	Br,Br	3,5	3-dibutylaminopropyl (138)
p-butyl	Br	3	3-dibutylaminopropyl (138)
m-butyl	Br	2	3-dibutylaminopropyl (138)

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(159) J. M. Fulmer and H. Burkett, J. Am. Chem. Soc. 71, 1209-10 (1949).

E. Dialkylaminobenzoic acids

p-Dimethylaminobenzoic acid

The following alkamine esters have been prepared: 2-alkylaminoethyl, where alkyl is ethyl (19), butyl (19), isobutyl (19), cyclohexyl (8) (103) or 2-octyl (8); 2-alkylamino-1-methylethyl where alkyl is cyclohexyl (8) (103) and diisobutylmethyl (8) (103); 2-cyclohexylamino-2-ethylethyl (8) (103) and 2-diethylaminoethyl (160).

o- and m-Dimethylaminobenzoic acids

The 2-diethylaminoethyl esters have been prepared (160).

p-Diethylaminobenzoic acid

The following alkamine esters have been prepared: 2-alkylaminoethyl, where alkyl may be ethyl (19), butyl (19), isobutyl (19) and cyclohexyl (8) (103); 2-alkylamino-1-methylethyl, where alkyl is cyclohexyl (8) (103) and diisobutylmethyl (8) (103), 2-cyclohexylamino-2-ethylethyl (8) (103) and 2-diethylaminoethyl (161).

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(160) Beilstein, Handbuch der Organischen Chemie, XIV, 326, 389, 429.

(161) Beilstein, Handbuch der Organischen Chemie, XIV, 429.

ESTERS OF CINNAMIC ACID

A. Alkylaminoalkyl esters

2-Alkylaminoethyl esters

Compounds of this type have been prepared in which alkyl is isobutyl (19) and cyclohexyl (19).

2-Alkylamino-2,2-dimethylethyl esters

Compounds of this type have been prepared in which alkyl is propyl (162), butyl (162) and amyl (19) (162).

3-Cyclohexylamino-2-methylpropyl ester (25)

B. Dialkylaminoalkyl esters

2-Dialkylaminoethyl esters

Compounds of this type have been prepared in which alkyl is ethyl (163), piperidino (34) (35), morpholino (35), pyrrolidino (62), 2-methylpiperidino (164), 3-methylpiperidino (164), 4-methylpiperidino (164) and where dialkyl is butyl, ethyl (55) (165).

3-Diethylaminopropyl ester (33) (76) (163)

3-(a-Methylpiperidino)propyl esters

Compounds of this type have been prepared in which a is 2, 3 and 4 (164).

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(162) J. S. Pierce, R. D. Gano and J. M. Lukeman, J. Am. Chem. Soc. <u>70</u>, 255 (1948).

(163) H. C. Brill and C. F. Cook, J. Am. Chem. Soc. <u>55</u>, 2062-4 (1933).

(164) C. F. Bailey and S. M. McElvain, J. Am. Chem. Soc. <u>52</u>, 2007-10 (1930).

(165) C. A. <u>25</u>, 5512; H. C. Brill, U. S. 1,817,670 (1931).

C. Esters of 3,4 bis methoxycinnamic acid

The following have been prepared: 2-diethylaminoethyl (90), 2-dipropylaminoethyl (90), 2-dibutylaminoethyl (90), 3-diethylaminopropyl (90) (166), 3-dipropylaminopropyl (90) and 3-dibutylaminopropyl (90).

Esters of ring derivatives

Substituent	Position	Ester	
MeO	4	2-diethylaminoethyl	(55) (167)
C_6H_5O	4	2-diethylaminoethyl	(87)
$-O-CH_2-O-$	3,4	2-diethylaminoethyl	(166)
$-O-CH_2-O-$	3,4	2-diethylaminopropyl	(166)
NH_2	2	2-diethylaminoethyl	(167a)
NH_2	3	2-diethylaminoethyl	(167a)
NH_2	4	2-diethylaminoethyl	(167a)

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(166) C. A. 35, 7118; W. A. Lott (to E. R. Squibb & Sons) U. S. 2,251,287 (1941).

(167) C. A. 37, 4206; W. A. Lott (to E. R. Squibb & Sons) U. S. 2,310,973 (1943).

(167a) Beilstein, Handbuch der Organischen Chemie, XIV, 518, 521, 522.

HYDROXYBENZOIC ACID ESTERS

Alkamine esters of o-hydroxybenzoic acid

The following have been prepared: 2-cyclohexylaminoethyl (17), 2-dimethylamino-1-methyl-1-ethylethyl (89), 3-piperidinopropyl (44), 3-(2,6-dimethyl-1-piperidino)propyl (44) (84) (168), 3-(2,3-dimethyl-1-piperidino)propyl (44), 3-(2,4-dimethyl-1-piperidino)propyl (44), and 3-(2,5-dimethyl-1-piperidino)propyl (44).

Alkamine esters of m-hydroxybenzoic acid

The following have been prepared: 2-dimethylamino-1-methyl-1-ethylethyl (89) and 3-piperidinopropyl (44).

Alkamine esters of p-hydroxybenzoic acid

The following have been prepared: 2-diethylaminoethyl (50, 2-dimethylamino-1-methyl-1-ethylethyl (89), 3-diethylaminopropyl (77 and 3-piperidinopropyl (44).

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(168) C. A. 43, 7509; Eli Lilly & Co., Brit. 617,190 (1949).

Alkamine esters of ring substituted hydroxybenzoic acids

A. Orthohydroxybenzoic acid

Substituent	Position	Ester	
CH_3O	3	2-diethylaminoethyl	(89)
CH_3	3	2-diethylaminoethyl	(169)
CH_3	3	3-diethylamino-2,2-dimethylpropyl	(169)
CH_3	4	2-diethylaminoethyl	(169)
CH_3	5	2-diethylaminoethyl	(169)

B. Meta-hydroxybenzoic acid

Substituent	Position	Ester	
CH_3	5	2-diethylaminoethyl	(169)

C. Para-hydroxybenzoic acid

Substituent	Position	Ester	
CH_3	3	2-diethylaminoethyl	(169)
CH_3O	3	2-diethylaminoethyl	(89)

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(169) C. A. 35, 5646; W. G. Christiansen and S. E. Harris (to E. R. Squibb & Sons) U. S. 2,243,694 (1941).

Esters of Diphenylcarboxylic acids and their derivatives

The following alkamine esters have been prepared: -diethylaminoethyl-diphenyl-2-carboxylate (170), -diethylaminoethyl-diphenyl-4-carboxylate (44) (170), -diethylaminoethyl-biphenyl-3-carboxylate (171), -diethylaminoethyl-2-hydroxybiphenyl-3-carboxylate (171), -diethylaminoethyl-4-hydroxylbiphenyl-3-carboxylate (171), -diethylaminoethyl-5-aminodiphenyl-2-carboxylate (172), -dibutylaminopropyl-5-aminodiphenyl-2-carboxylate (172), -diethylaminoethyl-4-ethoxy-4^1aminodiphenyl-3-carboxylate (173), -diethylaminoethyl-2-ethoxydiphenyl-3-carboxylate (174), -diethylaminoethyl-4-ethoxydiphenyl-3-carboxylate (174), -diethylaminoethyl-4-butoxydiphenyl-3-carboxylate (174) and -dibutylaminopropyl-4-ethoxybiphenyl-3-carboxylate (174).

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(170) F. Bell, J. Chem. Soc. 3247-9 (1928).

(171) C. A. 28, 7429; W. G. Christiansen and A. W. Harvey, U. S. 1,976,922 (1934).

(172) C. A. 28, 7430; W. S. Jones and W. Braker (to E. R. Squibb & Sons) U. S. 1,976,940 (1934).

(173) C. A. 28, 7430; W. G. Christiansen and A. W. Harvey, U. S. 1,976,923 (1934).

(174) C. A. 28, 7430; W. G. Christiansen and A. W. Harvey, U. S. 1,976,924 (1934).

ALKAMINE ESTERS OF MISCELLANEOUS AROMATIC ACIDS

Halogenated benzoic acids

p-Fluorobenzoic acid

The following alkylamino esters have been prepared: 2-Dialkylaminoethyl, where alkyl is ethyl (175), propyl (175) and butyl (175), 3-dialkylaminopropyl, where alkyl is ethyl (175), propyl (175) and butyl (175).

p-Chlorobenzoic acid

The following esters have been made: 2-diethylaminoethyl (72) and 3-piperidinopropyl (44).

p-Bromobenzoic acid

The 2-diethylaminoethyl (72) and 3-piperidinopropyl (44) esters have been prepared.

p-Iodobenzoic acid

The 3-piperidinopropyl ester has been prepared (44).

o-Iodobenzoic acid

The 3-piperidinopropyl ester has been prepared (44).

3,4-Diiodobenzoic acid

The 2-diethylaminoethyl ester has been prepared (91).

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(175) E. E. Campaigne, A. C. Starke, Jr., L. S. Fosdick and C. A. Dragstedt, J. Pharmacol. 71, 59-61 (1941).

o-(p-$XC_6H_4NH)C_6H_4COOH$

2-Diethylaminoethyl esters

Esters of this type have been prepared in which X- is H, C_6H_5 and C_6H_5NH. (176)

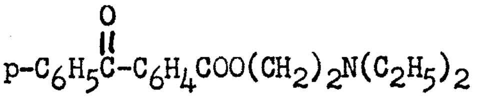
The 2-diethylaminoethyl ester of p-chloro-o-(p-methoxyphenyl) benzoic acid also has been prepared (176).

Hulpien (177) and coworkers have prepared 25 compounds of the type o, m or p-$RSC_6H_4COOR_1$, where R may be methyl, ethyl, propyl or butyl and R may be 2-diethylaminoethyl, 2-dipropylaminoethyl, 3-diethylaminopropyl or 3-piperidinopropyl. The original article was not available to me and Chemical Abstracts did not say which 25 of the possible 48 compounds had been prepared.

The 2-diethylaminoethyl and 2-dibutylaminoethyl esters of p-ethylmercaptobenzoic acid have been made by others (177).

O-$SHC_6H_4COO(CH_2)_3R$ (44)

R is piperidino or 2,6-dimethylpiperidino.



o, m or p-$C_6H_5\overset{\overset{O}{\|}}{C}-C_6H_4COO(CH_2)_2N(C_2H_5)_2$ (178)

p-$(CH_3)_2CH$-m-$NO_2C_6H_3COOH$

The following alkamine esters have been prepared: 2-diethylaminoethyl, 2-diethylaminoethyl and 3-diethylaminopropyl (59).

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(176) C. A. 44, 8373; A. A. Goldberg and H. S. Turner (to Ward, Blenkinsop & Co., Ltd.) U. S. 2,502,451 (1950).

(177) C. A. 38, 4758; S. E. Harris and W. Braker (to E. R. Squibb & Sons) U. S. 2,342,142 (1944).

(178) C. A. 33, 1710; B. Samdahl and T. Christiansen, Bull. Soc. Chim. (5), 1573-80 (1938).

Alkamine esters of acetoxybenzoic acid and its ring substituted derivatives

The following alkamine esters have been prepared: 2,2-dimethylamino-1-methyl-1-ethylethyl o, m or p-acetoxybenzoate (89), 2-dimethylaminomethyl-1-cyclohexyl-o-acetoxybenzoate (89), 2-dimethylamino-1-methyl-1-ethylethyl-4-methyl-2-acetoxybenzoate (89), 2-dimethylamino-1-methyl-1-ethylethyl-3-methyl-2-acetoxybenzoate (89) and 2-diethylaminoethyl-3-methyl-2-acetoxybenzoate (89).

SUPPLEMENT

Compounds or references to compounds not previously mentioned in this thesis

2-Butylaminoethyl p-NO_2 and p-NH_2 benzoate (179)

2-Morpholinoethyl and 3-morpholinopropyl cinnamates (180)

3-Diethylaminopropyl cinnamate (181)

3-Diethylaminopropyl anisate (182)

p-$(CH_3)_2NCH_2COC_6H_4COO(CH_2)_2N(C_2H_5)_2$ (183)

p-$(C_2H_5)_2N\ CH_2COC_6H_4COO(CH_2)_2N(C_2H_5)_2$ (183)

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(179) C. A. 33, 5999; Novocol Chemical Manufacturing Co., Brit. 501,090 (1939).

(180) J. H. Gardner, C. V. Clarke and J. Semb, J. Am. Chem. Soc. 55, 2999-3000 (1933).

(181) C. A. 10, 2387; E. A. Wildman and L. Thorp, U. S. 1,193,649, (1916).

(182) C. A. 10, 2387; E. A. Wildman and L. Thorp, U. S. 1,193,650, (1916).

(183) C. A. 37, 2726; G. Sanna, Rend. seminar facolta sci. univ. Cagliari 10, 50-3 (1940).

Alkamine esters of alkoxybenzoic and alhoxycinnamic acids (184)

These compounds are covered also by references (2), (79) and (162).

m=$NO_2C_6H_4CH{=}CH\text{-}COOCO_2CH_2N(C_2H_5)_2$ (185)

p-$NO_2C_6H_4CH{=}CH\text{-}COOCO_2CH_2N(C_2H_5)_2$ (186)

$C_6H_5CH{=}CH\text{-}COOCH_2CH_2N(C_2H_5)_2$ (187)

$C_6H_5CH{=}CH\text{-}COOCR(CH_3)CH_2N(CH_3)_2$, where R is methyl, ethyl, butyl or isoamyl (187)

2-Diethylaminoethyl-p-amino-m-nitrobenzoic acid (188)

2-Diethylaminoethyl-p-amino-m-aminobenzoic acid (189)

2-Diethylaminoethyl-3-nitro-4-dimethylaminobenzoic acid (190)

2-Diethylaminoethyl-3-amino-4-dimethylaminobenzoic acid (189)

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(184) C. A. 39, 3630; J. S. Pierce, J. M. Salsbury and J. M. Fredericksen (to J. S. Pierce) U. S. 2,372,116 (1945).

(185) Beilstein, Handbuch der Organischen Chemie, IX, 600.

(186) Beilstein, ibid., IX, 607.

(187) Beilstein, ibid., IX, 586.

(188) Beilstein, ibid., XIV, 441.

(189) Beilstein, ibid., XIV, 451

(190) Beilstein, ibid., XIV, 442.

EXPERIMENTAL

p-Propoxybenzoic acid

$p\text{-}C_3H_7OC_6H_4COOH$

Reactants: $p\text{-}HOC_6H_4COOC_2H_5$, $NaOC_2H_5$ and C_3H_7Br

Procedure: To a solution of 23 gms (1 mole) of sodium in 250 ml absolute alcohol, contained in a 1-liter round-bottomed flask, 166 gms (1 mole) of ethyl-p-hydroxybenzoate and 110 ml (excess Matheson practical propyl bromide (90%) were added. The mixture was refluxed 19 hours, cooled and filtered with suction. The residue in the Buchner funnel was inorganic and was discarded. An organic residue, thought to be unreacted ethyl-p-hydroxy benzoate, remaining in the flask was discarded. The filtrate was evaporated to about half its original volume on a hot plate and approximately 1 liter of water was added to it. The oil which separated was removed by means of a separatory funnel and washed twice with water. Crude yield of ethyl-p-propoxybenzoate: 165 gms (79%). Distilled under reduced pressure: Yield, 105 gms (51%). Range, 191-6° at 41 mm.

The ester was refluxed for 16 hours with 30 gms KOH (app. 2 gms excess) and 100 ml 95% alcohol and allowed to cool. About 500 cc of water were added, the mixture was warmed, the small amount of scum which formed was removed by suction filtration and the unchanged ester was removed by extraction with two 100 ml portions of ether. The ether layers were discarded. The water layer was poured into a beaker and concentrated hydrochloric acid was added until the mixture was strongly acid. The precipitated p-propoxybenzoic acid was filtered with suction, washed twice with water and air dried. Crude yield: 56 gms (31%). M.p. 134.5-135.5°. Recrystallized from a water-alcohol mixture. Yield: 38.6 gms (22%). M.p. 142-5°. The acid was used without further purification.

p-Amyloxybenzoic acid

p-$C_5H_{11}OC_6H_4COOH$

Reactants: p-$HOC_6H_4COOC_2H_5$, $NaOC_2H_5$ and $C_5H_{11}Br$

Procedure: One mole (23 gms) of sodium was dissolved in 250 ml of absolute alcohol in a 1-liter round-bottomed flask fitted with a reflux condenser. To this solution 166 gms (1 mole) of ethyl-p-hydroxybenzoate and 124 ml (151 gms, 1 mole) n-amyl bromide were added. The mixture was refluxed 18 hours, cooled, and filtered with suction. The filtrate was evaporated to about half its original volume, poured into about 10 vols of water and filtered with suction. The precipitate (unchanged ethyl-p-hydroxybenzoate ?)

was transferred to a beaker and washed with water to remove adhering ethyl-p-amyloxybenzoate (procedure much less efficient than extracting with ether from an alkaline solution, adopted to save time). The Buchner funnel also was washed with water, and the water from both washings was added to the filtered ester-water mixture. The oily ester was removed in a separatory funnel and washed twice with water. Crude yield: 175 gms (74%). Distilled under reduced pressure: Yield, 120 gms (51%).

The ester was refluxed 16 hours with 25 gms (app. 1.5 gms excess KOH and 100 m. of 95% alcohol. The mixture was cooled and about six volumes of water were added. The unchanged ester was removed by extraction with two 100 ml portions of ether. The ether layers were discarded. The water layer was made strongly acid with concentrated hydrochloric acid and the crude p-amyloxybenzoic acid was filtered with suction, washed with water and air dried. Crude yield: 70 gms (31%) (overall). M.p. 98-9°. Recrystallized from an alcohol-water mixture: Yield, 54.6 gms (26%). M.p. 104-6°. The acid was used without further purification.

p-Hexyloxybenzoic acid

$p\text{-}C_6H_{13}C_6H_4COOH$

Reactants: $p\text{-}HOC_6H_4COOC_2H_5$, $NaOC_2H_5$ and $C_6H_{13}Br$

Procedure: One mole (23 gms) of sodium was dissolved in 250 ml of absolute alcohol in a 1-liter round-bottomed flask, fitted with a reflux condenser. One mole (166 gms) of ethyl-p-hydroxybenzoate and 92 ml (165 gms, 1 mole) n-hexyl bromide were added. The mixture was refluxed 18 hours, cooled, and filtered with suction. The filtrate was removed, the precipitate was washed with water to remove adhering ester and the washings were saved. The precipitate was discarded. The filtrate was evaporated on a hot plate to about half volume. A solid separated and was removed by suction filtration. The precipitate was washed with water to remove adhering ester and the washings were added to the previous ones. To the filtrate in a beaker, about 8 volumes of water were added. The washings were added to the mixture, the oil was separated in a separatory funnel and washed twice with water. Crude yield: 165 gms (66%). Distilled under reduced pressure: Yield, 107 gms (43).

The ester was refluxed 16 hours with 30 gms (app. 2 gms excess) KOH and allowed to cool. About 200 ml of water were then added. Most of the ester had not saponified, as evidenced by the appearance of an oil. Alcohol (95%) was added until the mixture was homogenous; it was then refluxed 18 hours, cooled and poured into about 2.5 volumes of water. The small amount of scum which formed was filtered off with suction. The mixture was then extracted with 500 ml of ether. So large a volume was necessary because a good deal of the ether dissolved. The ether layer was discarded. The water layer was made strongly acid with concentrated hydrochloric acid. An ether layer separated containing the acid. The ether was evaporated off on a small hot plate, kept on <u>low</u>, in the hood. Crude yield: 96 gms (43) (overall). M.p. 104-6°. Recrystallized from alcohol-water mixture: Yield, 61.3 gms (29%). M.p. 112-15°. The acid was used without further purification.

p-Amyloxybenzaldehyde

$\text{p-}C_5H_{11}OC_6H_4CHO$

Reactants: $\text{p-}HOC_6H_5CHO$, $NaOC_2H_5$ and $C_5H_{11}Br$

Procedure: One mole (23 gms) of sodium was dissolved in 250 ml of absolute alcohol in a 1-liter round-bottomed flask fitted with a reflux condenser. One mole (122 gms) of p-hydroxybenzaldehyde and 124 ml (151 gms, 1 mole) n-amyl bromide were added. The mixture was refluxed 7 hours, cooled and filtered with suction. The precipitate was transferred to a beaker and a relatively large volume of water was added. An oil and a solid separated out. The mixture was filtered with suction. Some of the oil would not come through. The oil in the filtrate was washed with a little sodium hydroxide solution to remove p-hydroxybenzaldehyde. Oil disappeared and a solid precipitated. The mixture was discarded. The filtrate was evaporated to about half its original volume on a hot plate. Bumping was severe; the mixture had to be stirred constantly. About 6 volumes of water were added, the oil was separated in a separatory funnel, washed once with water and distilled under reduced pressure. Yield: 90 gms (47%). Range 203-207° at 43-5 mm.

p-Hexyloxybenzaldehyde

$p\text{-}C_6H_{13}OC_6H_4CHO$

Reactants: $p\text{-}HOC_6H_4CHO$, $NaOC_2H_5$ and $C_6H_{18}Br$

Procedure: One mole (23 gms) of sodium was dissolved in a 1-liter round-bottomed flask fitted with a reflux condenser. One mole (122 gms) of p-hydroxybenzaldehyde and 92 ml (165 gms, 1 mole) of n-hexyl bromide were added. The mixture was refluxed 7 hours, cooled and filtered with suction. The precipitate was transferred to a beaker and washed with water to remove adhering product, but the amount obtained was not worth working up, and was discarded. The filtrate was evaporated to a little over half its original volume on a hot plate. About 5 volumes of water were added and the mixture was poured into a separatory funnel. A partial emulsion was formed, and a good deal of the product adhered to the sides. The mixture was extracted with two 150 ml portions and one 300 ml portion of ether. The 300 ml portion stayed colorless. The first two were combined and washed with 100 ml of 10% (wt/vol) NaOH to remove unreacted p-hydroxybenzaldehyde. Most, but not all, was removed by this treatment. The ether layers were then combined and most of the ether was evaporated off on a small hot plate, kept on low, in the hood. The remaining mixture was vacuum distilled. Yield: 77 gms (38%). Range 213-224° at 41-42.5 mm.

p-n-Amyloxycinnamic acid

$p\text{-}nC_5H_{11}OC_6H_4CH{=}CH\text{-}COOH$

Reactants: $p\text{-}AmOC_6H_5CHO$, $CH_2(COOH)_2$, and pyridine

Procedure: A mixture of 90 gms (.47 mole) of $p\text{-}C_5H_{11}\ OC_6H_5CHO$, 49 gms (.47 mole) of malonic acid and 38 gms (.47 mole) of pyridine were heated in an open flask in a Glass-col at 130-40° for 12 hours. The mixture was cooled and the product was washed into a Buchner funnel with two 50 ml portions and one 100 ml portion of cold 95% alcohol, after which it was air dried. Crude yield: App. 27 gms (24%). Recrystallized from alcohol-water mixture: Yield, 22 gms (20%). M.p. 159-61°.

p-n-Hexyloxycinnamic acid

$p\text{-}C_6H_{13}OC_6H_4CH{=}CHCOOH$

Reactants: $p\text{-}C_6H_{13}OC_6H_5CHO$, $CH_2(COOH)_2$ and pyridine

Procedure: A mixture of 77 gms (.38 mole) of p-hexyloxybenzaldehyde, 40 gms (.38 mole) of malonic acid and 31 gms (.38 mole) of pyridine were heated together in an open flask in a Glass-col at 130-140° for 12 hours. The mixture was cooled and the product was washed into a Buckner funnel with two 50 ml portions of 95% alcohol and was air dried. Yield: 28 gms (30%). M.p. 150-178°. Recrystallized from an alcohol-water mixture: Yield, 22 gms (23%). M.p. 151-178°. Because of limited time, the acid was used without further purification.

p-Ethoxybenzoyl chloride

$p\text{-}C_2H_5OC_6H_5COCl$

Reactants: $p\text{-}C_2H_5OC_6H_5COOH$ and PCl_5

Procedure: One-half mole (83 gms) p-ethoxybenzoic acid was placed in a 500 ml round-bottomed flask fitted with an air condenser. About one-quarter of an 81 gm (.39 mole) sample of PCl_5 was added, the flask was swirled and warmed on steam bath to start the reaction. The rest of the PCl_5 was then added in three portions, with agitation, and the reaction mixture was heated on a steam bath one hour and allowed to cool. The $POCl_3$ formed was removed by distillation under reduced pressure and the residue was vacuum distilled. Redistilled yield: 59.4 gms (82%). Range, 176-8° at 50 mm.

p-Propoxybenzoyl Chloride

$p\text{-}C_3H_7OC_6H_5COCl$

Reactants: $p\text{-}C_3H_7OC_6H_5COOH$ and PCl_5

Procedure: An amount of 39.6 gms (.22 mole) of p-propoxybenzoic acid was placed in a 500 ml round-bottomed flask fitted with an air condenser. About half of a portion of 46 gms (.22 mole) of PCl_5 was added to the acid and the flask was warmed with a free flame to initiate the reaction. When it had subsided the rest of the PCl_5 was added and the mixture was heated on a steam bath for one-half hour. The phosphorus oxychloride formed was removed under vacuum and the acid chloride was vacuum distilled. Yield: 19 gms (44%). Range 187-90° at 48 mm.

p-Amyloxybenzoyl chloride

$p\text{-}C_5H_{11}OC_6H_4COCl$

Reactants: $p\text{-}C_5H_{11}OC_6H_4COOH$ (61 gms, .29 mole) and
PCl_5 (61 gms, .33 mole)

Procedure: The same procedure was used here as was used for p-propoxylbenzoyl chloride. Yield: 30.8 gms (47%). Range 218-222° at 54-56 mm.

p-Hexyloxybenzoyl chloride

$p\text{-}C_6H_{13}OC_6H_4COCl$

Reactants: $p\text{-}C_6H_{13}OC_6H_4COOH$ (54.8 gms, .25 mole) and
PCl_5 (54.8 gms, .25 mole)

Procedure: The same procedure was used here as was used for p-propoxybenzoyl chloride. Yield: 40.8 gms (68%).

p-Amyloxycinnamoyl chloride

$p\text{-}C_5H_{11}OC_6H_4CH{=}CHCOCl$

Reactants: $p\text{-}C_5H_{11}OC_6H_4CH{=}CHCOOH$ and PCl_5

Procedure: A mixture of 22 gms (.094 mole) p-amyloxycinnamic acid and 19.6 gms (.097 mole) was placed in a 500 ml round-bottomed flask with an air condenser attached. The flask was warmed by a free flame until the reaction began. It was then heated on a boiling water bath one-half hour. The phosphorus oxychloride was removed by co-distillation under reduced pressure with each of two 50 ml portions of benzene and two of toluene. The acid chloride was used without further purification.

p-Hexyloxycinnamoyl chloride

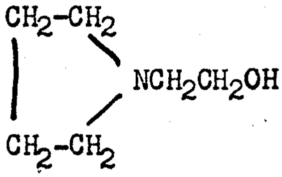
$p\text{-}C_6H_{13}OC_6H_4CH{=}COCl$

Reactants: $p\text{-}C_6H_{13}OC_6H_4CH{=}CHCOOH$ 922 gms, .105 mole) and

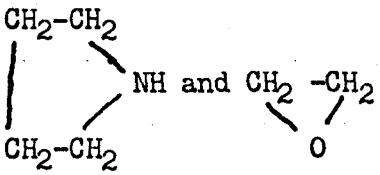
pCl (2.1 gm, .106 mole)

Procedure: The procedure used was identical with that used for p-amyloxycinnamoyl chloride.

2-Pyrrolidinoethanol



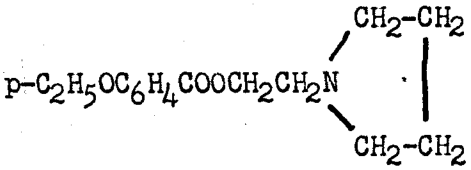
Reactants:



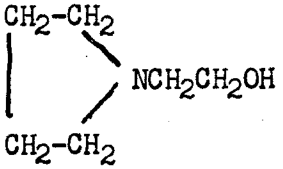
Procedure I: A mixture of 152 ml (131 gms, 1.7 moles) of 95% pyrrolidine and 165 ml (131 gms) of methanol was put into a 1-liter three-necked flask fitted with a condenser, an inlet tube and a thermometer. Ethylene oxide was passed in from a 100 gm bottle through a safety trap at such a rate that the addition took 4 hours. The reaction temperature rose very slowly if the mixture was not cooled externally. The reaction mixture was kept between 45-60° by means of a cold water bath. The flask was shaken from time to time. When the addition of gas was complete, the methanol and unreacted pyrrolidine were distilled off under vacuum. The pressure varied from 38-45 mm. Boiling range taken: 100-110°. Yield: 86 gms (44%).

Procedure II: A mixture of 760 ml (8.6 moles) of 95% pyrrolidine and 960 ml (approximately an equal weight) of methanol was put into a 2-liter three-necked flask equipped with a motor stirrer, a gas inlet tube, a water condenser and a thermometer. The mixture was warmed to about 45° and ethylene oxide was passed in from a cylinder at such a rate that, at 45°, the rate of temperature rise was about 1° every .75 minute if no external cooling was applied. The reaction mixture was kept between 45-60° by a cooling bath. The gas was passed in for 3.5 hours. The mixture was then evaporated on a hot plate until the temperature of the boiling liquid was 100°. Distilled under vacuum (water pump). At first the distillation proceeded very smoothly, but when the volume of distillate was approximately equal to the volume of undistilled material, the stopcock leading to the vacuum line became closed and the stopper of the distillation flask was very violently blown off. The material remaining in the distillation flask yielded no appreciable distillate below 120°. The distillate already collected was redistilled. Yield: 121 gms (12.2%). Range 100-106° at 38 mm. A considerably longer time of passing in ethyleneoxide is recommended.

2-Pyrrolidinoethyl-p-ethoxybenzoate hydrochloride



Reactants:



and $p-C_2H_5OC_6N_4COCl$

Procedure: A solution of 23 gms (.2 mole) of 2-pyrrolidinoethanol in 50 ml of benzene was slowly added to a solution of 33.2 gms (.2 mole) of p-ethoxybenzoyl chloride in 50 ml of benzene contained in a 500 ml round-bottomed flask. A reflux condenser was used during the last part of the addition. The mixture was refluxed one-half hour and allowed to stand overnight. Crystals separated. These were washed into a beaker with 250 ml of water. The benzene was separated in a separatory funnel, washed with 50 ml of water and discarded. The water layers were combined and made basic by addition of moderately strong NaOH solution. An oil precipitated. The mixture was extracted with 125 ml of isopropyl ether. More base was added to the water layer; a little more oil was obtained. The oil-base mixture was extracted with a second 125 ml portion of isopropyl ether. The ether layers were combined and filtered into a beaker. Dry HCl was passed in. Crystals separated. The mixture was filtered with suction, the precipitate washed with benzene and dried in a vacuum desiccator. Yield: 40.5 gms (77%). M.p. 171-172.5.° Recrystallized twice from a benzene-absolute alcohol mixture. M.p. 173.5-174°; 174-174.5°.

2-Pyrrolidinoethyl-p-propoxybenzoate hydrochloride

$p\text{-}C_3H_7OC_6H_4COOCH_2CH_2NC_4H_8 \cdot HCl$

Reactants: $p\text{-}C_3H_7OC_6H_4COCl$ and $C_4H_8NCH_2CH_2OH$

Procedure: A solution of 14.5 gms (.073 mole) of p-propoxybenzoyl chloride in 50 ml of benzene and a solution of 11.5 gms (.1 mole) of 2-pyrrolidinoethanol were mixed and allowed to stand one-half hour. About 5 volumes of water were then added and the benzene was removed in a separatory funnel. The water layer was made basic by the slow addition of concentrated KOH solution until moderately basic to litmus. An oil separated. The mixture was extracted with three 50 ml portions of benzene and the water layer was discarded. Dry HCl was passed into the benzene layer. No precipitate formed. About 300 ml of water and 40 ml concentrated hydrochloric acid were added. The benzene layer was discarded. The water layer was made alkaline by the addition of moderately strong KOH solution and extracted with two 125 ml portions of isopropyl ether. The ether layer was filtered and dry HCl was passed in. An oil separated. The isopropyl ether was removed by decantation. The oil was transferred to a beaker and triturated with dry ether. The hygroscopic crystals which formed were dried in a vacuum desiccator. Yield: 9.9 gms (49%). M.p. 65-82°. Recrystallization of a sort was effected by dissolving in hot methylene chloride, adding just enough isopropyl ether to start precipitation, allowing it to cool somewhat and flooding with isopropyl ether. After two such recrystallizations M.p. was app. 108-11°; however, at about 35° it became brown and amorphous.

2-Pyrrolidylethyl-p-amyloxybenzoate hydrochloride

$p\text{-}C_5H_{11}OC_6H_4COOCH_2CH_2NC_4H_8\cdot HCl$

Reactants: $p\text{-}C_5H_{11}OC_6H_4COCl$ and $C_4H_8NCH_2CH_2OH$

Procedure: A solution of 15 gms (.13 mole) of 2-pyrrolidinoethanol in 30 ml of benzene was slowly added to a solution of 30.8 gms (.137 mole) of p-amyloxybenzoyl chloride in 50 ml of benzene. A reflux condenser was employed during the latter part of the addition. The mixture was refluxed one-half hour, cooled, mixed with 400 ml of .5 NHCl and extracted with 100 ml of ether. The ether-benzene layer was discarded. The water layer was made basic with NaOH and the oil extracted with two 125 ml portions of isopropyl ether. The ether layers were combined and filtered. Dry HCl was passed into the solution. An oil separated, which crystallized when allowed to cool. The compound was dried in a vacuum desiccator. Yield: 40.5 gms (more than 100%). M.p. 112-122°. Evidently some solid product of the acid chloride (which was present in excess) was carried along with the ester. Recrystallized three times from an acetone-ether mixture. M.ps. I, 135-136.5°; II, 135-136°; III, 136-137°.

2-Pyrrolidylethyl-p-hexyloxybenzoate hydrochloride

$p\text{-}C_6H_{13}OC_6H_4COOCH_2CH_2NC_4H_8 \cdot HCl$

Reactants: $C_4H_8NCH_2CH_2OH$ (24 gms, .1 mole) and

$p\text{-}C_6H_{13}OC_6H_4COCl$ (11.5 gms, .1 mole)

Procedure: The procedure was exactly the same as for the preparation of the p-ethoxy ester up to the precipitation of the oily hydrochloride. The oil crystallized in part on being transferred to another beaker and triturated with a very small amount of absolute alcohol. The crystals were removed by suction filtration and dried in a vacuum desiccator. Yield: 11.6 gms (36). M.p. 129-131.5°. Recrystallized from benzene three times . M.ps. I, 130-133°; II, 131-132°; III, 132-133°.

2-Pyrrolidinoethyl-p-amyloxycinnamate hydrochloride

$p\text{-}C_5H_{11}OC_6H_4CH{=}CH\text{-}COOCH_2CH_2NC_4H_8 \cdot HCl$

Reactants: $p\text{-}C_5H_{11}OC_6H_4CH{=}CHCOCl$ and $C_4H_8NCH_2CH_2OH$

Procedure: A solution of 11.5 gms (.1 mole) of 2-pyrrolidylethanol in about 50 ml of benzene was added to the crude p-amyloxycinnamoyl chloride (previously mentioned) in about 50 ml of benzene in a 1-liter round-bottomed flask. The mixture was refluxed one hour and poured into a separatory funnel with 400 ml 1 N HCl and 250 ml of ether. (a) The water layer was made basic with NaOH and extracted with 50 ml of isopropyl ether. The ether was filtered and dry HCl passed into it. An oil separated, which crystallized several days later and was not used. (b) A mixture of 50 ml of concentrated hydrochloric acid and 100 ml of water were added to the ether layer, shaken, and allowed to separate overnight. Twelve hours later three layers were formed. (1) The top layer showed no visible change on being shaken with 50 ml of concentrated hydrochloric acid, and was discarded. (2) The lower layer was made alkaline with NaOH. No precipitate was seen. The lower layer was discarded. (3) Fifty ml of concentrated HCl were added to the middle layer. Over 100 ml came through in the lower layer. The water layer was made basic with NaOH solution and extracted with 100 ml of isopropyl ether. The ether layer was filtered and saturated with dry HCl. An oil settled out. On standing and being stirred it crystallized, was filtered with suction and dried in a vacuum desiccator. Yield: 7 gms (7%) (overall). M.p. 139-45°. Recrystallized twice from a benzene-absolute alcohol mixture. M.p. 159.5-60°, 160-161.5°.

2-pyrrolidinoethyl p-hexyloxycinnamate hydrochloride

$p\text{-}C_6H_{13}OC_6H_4COOCH_2CH_2NC_4H_8 \cdot HCl$

Reactants: $p\text{-}C_6H_{13}OC_6H_4CH{=}CHCOCl$ and $C_4H_8NCH_2CH_2OH$

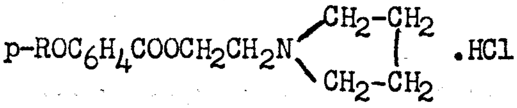
Procedure: A solution of 11.5 gms (.1 mole) of 2-pyrrolidinoethanol in 50 ml of benzene was added to the crude p-hexyloxycinnamoyl chloride previously described, dissolved in 50 ml of benzene. The mixture was refluxed one-half hour and was alloed to cool. It separated into two layers. The volume of the top layer was 115 ml; that of the bottom, 75 ml. (a) The bottom layer was made alkaline with

NaOH and extracted with 50 ml of isopropyl ether. The ether layer was filtered and dry HCl was passed into it. An oil separated.

(b) The top layer was treated in a separatory funnel first with 50 ml of concentrated HCl, then with 50 ml strong NaOH. Emulsion formed, and was allowed to stand. Drew off the lower layer, which was still acidic. Added H_2O. A heavy white precipitate was formed (free acid?). Added excess base. An oil separated. The oil was removed and dissolved in 125 ml of isopropyl ether. The water layer was extracted with a second 125 ml portion and the ether layers were combined and filtered. Dry HCl was passed in. An oil separated, which would not crystallize on trituration with dry ethyl ether. This oil, the oil from (a) and the mother liquor from the trituration were combined and extracted with excess strong sodium bicarbonate solution. The ether layer was filtered and dry HCl was passed in. The oil which separated was thicker than before this treatment. All attempts to crystallize it failed.

TABULATED RESULTS

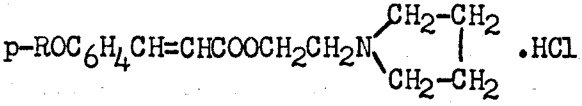
2-Pyrrolidinoethyl p-alkoxybenzoate hydrochlorides



$p\text{-}ROC_6H_4COOCH_2CH_2N\langle(CH_2\text{-}CH_2)_2\rangle \cdot HCl$

R	M.p. °C (uncor.)	Yield %	Cl[a] Calcd.	Analysis Found
Ethyl	174-174.5	77	11.83	11.36
Propyl	108-111	49		
Amyl	136-137	-	10.35	10.32
Hexyl	132.5-133	36	9.97	9.65

2-Pyrrolidinoethyl p-alkoxycinnamate hydrochlorides



$p\text{-}ROC_6H_4CH{=}CHCOOCH_2CH_2N\langle(CH_2\text{-}CH_2)_2\rangle \cdot HCl$

R	M.p. °C (uncor.)	Yield %	Cl[a] Calcd.	Analysis Found
Amyl	160-160.5	7[b]	9.65	9.63
Hexyl				

a) Analyses were done by the Volkard method.
b) Calculated from the acid.

SUMMARY

The preparation of 2-pyrrolidinoethyl esters of p-alkoxybenzoic acid and p-alkoxycinnamic acid is described. The following compounds are reported:

2-Pyrrolidino p-ethoxybenzoate, 2-pyrrolidino p-propoxybenzoate, 2-pyrrolidino p-amyloxybenzoate, 2-pyrrolidino p-hexyloxybenzoate, 2-pyrrolidino p-amyloxycinnamate and 2-pyrrolidino p-hexyloxycinnamate.

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