denser; 0.125 mole of 3-diethylaminopropylamine was added with swirling, and the exit of the condenser was connected to a suitable trap for nitrous fumes. The flask was heated gently with a free flame, until a vigorous reaction began, as indicated by rapid boiling and a sharp evolution of nitrous fumes. The flame was removed at this point and the reaction was allowed to proceed until boiling became gentle (four to five minutes). The flame was replaced and the mixture refluxed briskly until a piece of starch–potassium iodide paper at the exit of the trap showed no more oxidizing fumes (two to three hours).

Heating was discontinued, the flask cooled under running water and the contents transferred to a 1000-ml. separatory funnel. The flask was washed four times with 50-ml. portions of 20% hydrochloric acid and the washings added to the cymene solution in the separatory funnel, followed by 150 ml. of ethyl ether. The mixture was shaken vigorously and separated; the aqueous layer was washed with an additional 150 ml. of ether. The ethereal layers were combined and washed with 100 ml. of saturated sodium chloride solution.[18] The aqueous layers were combined and run carefully into 100 ml. of 60% sodium hydroxide solution with swirling. The mixture was filtered by suction through a bed of dicalite (this procedure avoids serious emulsions during subsequent extractions) and the filtrate extracted six times with 150-ml. portions of chloroform. The combined extracts were washed through the dicalite bed and the filtrate was distilled to dryness from the steam-bath, the last traces of solvent being removed under reduced pressure. The residue was dissolved in anhydrous chloroform, filtered through a dicalite bed to remove traces of inorganic salts, and the filtrate distilled to dryness as above. The dry residue was distilled at 168–70° (2 mm.) to give a rich, red oil which could not be induced to crystallize; yield, 59%. Table I summarizes the properties, yields and analytical data for the various nitranilines prepared during this work.

### Derivatives of the Nitranilines

**Picrates.**—The free base was dissolved in anhydrous ethanol and treated with an excess of picric acid in the same solvent. The picrate came down as an oil which was washed with anhydrous ether and then crystallized from ethanol or methanol to give a bright yellow product.

**Hydrochlorides.**—The free base was dissolved in anhydrous ethyl ether and treated with a solution of dry hydrogen chloride in the same solvent. The product was worked up as above. Several bases were analyzed directly, since neither crystalline picrates nor hydrochlorides could be obtained.

(18) Cymene and unreacted *o*-dinitrobenzene may be recovered from the ethereal layers.

**Acknowledgment.**—The junior author (F. K.) acknowledges gratefully the encouragement and assistance given during the course of this work by Endo Products, Inc. The authors are indebted to Dr. R. T. Major of Merck and Co., for a generous supply of *o*-xylidine. Micro-analyses were performed by Mr. Wm. Saschek, of the College of Physicians and Surgeons of Columbia University.

## Summary

1. Six known *o*-dinitrobenzene derivatives were prepared in approximately 65% yield by oxidizing *o*-nitranilines with Caro acid to the nitroso-nitro compounds, followed by further oxidation of these compounds with hydrogen peroxide and nitric acid. Other difficultly available *o*-dinitrobenzenes were prepared by a Sandmeyer reaction on a nitro-diazonium hydroxide, or by direct nitration.

2. Twelve new *o*-(dialkylaminoalkyl)-nitranilines were then prepared by the direct replacement of one nitro group of an *o*-dinitrobenzene by a diamine.

3. The use of cymene as a reaction medium for the above replacement reaction was found to be highly advantageous in increasing the yield and purity of the final product and shortening the reaction time.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF BRYN MAWR COLLEGE AND COLUMBIA UNIVERSITY]

# Benzoates, *p*-Aminobenzoates and Phenylurethans of 2-Alkylaminoethanols

BY ARTHUR C. COPE AND EVELYN M. HANCOCK[1]

The reduction of ethanolamine with ketones and aldehydes provides an easy synthesis for 2-alkylaminoethanols,[2] which is particularly satisfactory for the secondary alkyl homologs, $RR'CHNHCH_2CH_2OH$. This paper reports a practical method for converting these aminoalcohols into esters (I, as hydrochlorides). The local anesthetic action of the esters has been investigated.

Compared to the very large number of esters of *tertiary* aminoalcohols which have been prepared, relatively few esters of alcohols substituted by *secondary* amino groups have been investigated. Aminoalcohols of the latter class have not been readily available, and their reaction with acid chlorides can lead either to esters (I) or to amides (II). Further reaction can produce ester-amides (III).[3] An additional complication noted by several investigators is the fact that esters containing primary or secondary amino groups (such as I, R′ = hydrogen or alkyl) are stable as salts but the bases rearrange rapidly into the corresponding amides (II).[4] Certain of the substituted

$RCOOCH_2CH_2NHR'$ (I) $\quad RCON(R')CH_2CH_2OH$ (II)

$RCOOCH_2CH_2N(R')COR$ (III)

(1) Sharp and Dohme Research Associate.

(2) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

(3) Mannich and Wieder, *Ber.*, **65**, 389 (1932).

(4) (a) Wolfheim, *Ber.*, **47**, 1447 (1914); (b) Gabriel, *Ann.*, **409**, 326 (1915); (c) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 403 (1915); (d) Kanao, *J. Pharm. Soc. Japan*, **48**, 1070 (1928); (e) Hartung, Munch and Kester, THIS JOURNAL, **54**, 1526 (1932); (f) Immediata and Day, *J. Org. Chem.*, **5**, 512 (1940).

TABLE I

2-ALKYLAMINOETHYL BENZOATES, $C_6H_5COOCH_2CH_2NHR$

| | Yield, % | Boiling point, °C. | Mm. | $n^{25}D$ | Formula | Nitrogen, % Calcd. | Found | Hydrochlorides M. p., °C. | Formula | Chlorine, % Calcd. | Found | Anesthetic activity Topical, × cocaine | Toxicity, subcutaneous $LD_{50}$, mg./kg. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Isopropyl | 88 | 150–152 | 13 | 1.5020 | $C_{12}H_{17}O_2N$ | 6.76 | 6.70 | 169–170[a] | $C_{12}H_{18}O_2NCl$ | 14.55 | 14.52 | 0 | |
| *s*-Butyl | 77 | 164–165 | 14 | 1.5005 | $C_{13}H_{19}O_2N$ | 6.33 | 6.23 | 141–142.5[b] | $C_{13}H_{20}O_2NCl$ | 13.76 | 13.75 | 0.05 | |
| 2-Pentyl | 85 | 130–132 | 1 | 1.4972 | $C_{14}H_{21}O_2N$ | 5.95 | 6.01 | 150–151[c] | $C_{14}H_{22}O_2NCl$ | 13.05 | 13.07 | 0.03 | >400 |
| 3-Pentyl | 85 | 127–128 | 1 | 1.4984 | $C_{14}H_{21}O_2N$ | 5.95 | 5.97 | 161–162[b] | $C_{14}H_{22}O_2NCl$ | 13.05 | 13.08 | 0 | >400 |
| Cyclohexyl | 80 | 146–147 | 1 | 1.5219 | $C_{15}H_{21}O_2N$ | 5.66 | 5.70 | 190–191[b] | $C_{15}H_{22}O_2NCl$ | 12.49 | 12.48 | 0.05 | >400 |
| 2-(4-Methylpentyl) | 82 | 131–132 | 1 | 1.4935 | $C_{15}H_{23}O_2N$ | 5.62 | 5.60 | 101–102.5[d] | $C_{15}H_{24}O_2NCl$ | 12.40 | 12.37 | 0.1 | >400 |
| 2-Heptyl | 67 | 148–150 | 1.5 | 1.4946 | $C_{16}H_{25}O_2N$ | 5.32 | 5.32 | 138–139[d] | $C_{16}H_{26}O_2NCl$ | 11.83 | 11.79 | 0.2 | >100 |
| 2-Octyl | 80 | 157–158 | 1 | 1.4914 | $C_{17}H_{27}O_2N$ | 5.05 | 5.18 | 130–131.5[d] | $C_{17}H_{28}O_2NCl$ | 11.30 | 11.25 | 0.3 | >100 |

[a] Recrystallized from absolute alcohol. [b] From acetone and alcohol. [c] From alcohol and ether. [d] From acetone.

TABLE II

2-ALKYLAMINOETHYL *p*-NITROBENZOATE HYDROCHLORIDES, $p$-$NO_2C_6H_4COOCH_2CH_2NHR \cdot HCl$

| Alkyl group | Yield, % | M. p., °C. | Formula | Chlorine, % Calcd. | Found |
|---|---|---|---|---|---|
| Isopropyl | 72 | 219 –220[a] | $C_{12}H_{17}O_4N_2Cl$ | 12.28 | 12.26 |
| *s*-Butyl | 65 | 199 –200[a] | $C_{13}H_{19}O_4N_2Cl$ | 11.71 | 11.75 |
| 2-Pentyl | 73 | 201 –202[b] | $C_{14}H_{21}O_4N_2Cl$ | 11.19 | 11.16 |
| 3-Pentyl | 76 | 195 –196[b] | $C_{14}H_{21}O_4N_2Cl$ | 11.19 | 11.17 |
| 2-(4-Methylpentyl) | 85 | 167 –168.5[a] | $C_{15}H_{23}O_4N_2Cl$ | 10.72 | 10.67 |
| 2-Heptyl | 73 | 172 –173[a] | $C_{16}H_{25}O_4N_2Cl$ | 10.28 | 10.24 |
| 4-Heptyl | 84 | 129 –130[d] | $C_{16}H_{25}O_4N_2Cl$ | 10.28 | 10.32 |
| 2-Octyl | 83 | 155.5–156.5[a] | $C_{17}H_{27}O_4N_2Cl$ | 9.88 | 9.85 |
| 2-Nonyl | 77 | 158 –160[a] | $C_{18}H_{29}O_4N_2Cl$ | 9.51 | 9.46 |
| 5-Nonyl | 77 | 127 –128[d] | $C_{18}H_{29}O_4N_2Cl$ | 9.51 | 9.54 |
| 4-(2,6-Dimethylheptyl) | 83 | 164.5–165.5[a] | $C_{18}H_{29}O_4N_2Cl$ | 9.51 | 9.59 |
| 2-Decyl | 76 | 143 –144[a] | $C_{19}H_{31}O_4N_2Cl$ | 9.16 | 9.19 |
| Cyclohexyl | 71 | 231 –232 (dec.)[c] | $C_{15}H_{21}O_4N_2Cl$ | 10.78 | 10.75 |
| 1-Methylcyclohexyl | 70 | 223 –224 (dec.)[c] | $C_{16}H_{23}O_4N_2Cl$ | 10.34 | 10.32 |
| 4-Methylcyclohexyl | 69 | 195 –196[b] | $C_{16}H_{23}O_4N_2Cl$ | 10.34 | 10.34 |
| 3,3,5-Trimethylcyclohexyl | 84 | 202 –203[b] | $C_{18}H_{27}O_4N_2Cl$ | 9.56 | 9.57 |
| *l*-Menthyl | 73 | 179 –180[a] | $C_{19}H_{29}O_4N_2Cl$ | 9.21 | 9.16 |
| Butyl | 71 | 174 –175[a] | $C_{13}H_{19}O_4N_2Cl$ | 11.71 | 11.67 |
| Isobutyl | 74 | 206 –207[b] | $C_{13}H_{19}O_4N_2Cl$ | 11.71 | 11.60 |
| *n*-Amyl | 52 | 158 –159[a] | $C_{14}H_{21}O_4N_2Cl$ | 11.19 | 11.26 |
| *n*-Heptyl | 67 | 139 –141[e] | $C_{16}H_{25}O_4N_2Cl$ | 10.28 | 10.29 |
| 2-Ethylhexyl | 86 | 95 – 97[e] | $C_{17}H_{27}O_4N_2Cl$ | 9.88 | 9.90 |
| 1-Phenylethyl | 76 | 221 –222[c] | $C_{17}H_{19}O_4N_2Cl$ | 10.11 | 10.09 |

[a] Recrystallized from absolute alcohol. [b] From 95% alcohol. [c] From alcohol and water. [d] From alcohol and ether. [e] From acetone.

amides (II) rearrange back into salts of the esters (I) on treatment with acids.[4d,f]

Goldberg and W. F. Whitmore[5] have prepared *p*-aminobenzoates from several 2-alkylaminoethanols and 3-alkylaminopropanols by treating the aminoalcohols with *p*-nitrobenzoyl chloride and aqueous sodium hydroxide, and reducing the nitro compounds formed directly with tin and hydrochloric acid. Formation of esters to the exclusion of amides under the conditions of the Schotten–Baumann reaction would be surprising, but the amides might rearrange to the esters during reduction in the presence of acid. We have confirmed the formation of 2-*n*-butylaminoethyl *p*-aminobenzoate hydrochloride from *n*-butylaminoethanol under these conditions. In our hands the yield of the ester was 10%. When the intermediate nitro compound was isolated, N-*p*-nitrobenzoyl 2-*n*-butylaminoethanol, $p$-$NO_2C_6H_4CON(C_4H_9)CH_2CH_2OH$, was obtained in 70% yield. It was not possible to isolate a crystalline hydrochloride from the product of either chemical or catalytic reduction of this amide. These results indicate that both the ester (I) and the amide (II) are formed when *n*-butylaminoethanol reacts with *p*-nitrobenzoyl chloride and aqueous sodium hydroxide, with the amide in larger amount; after reduction of the mixture the *p*-aminoester hydrochloride is isolated because of its crystalline properties.

By blocking the amino group secondary aminoalcohols can be esterified in good yields. This was accomplished by converting the aminoalcohols into salts. The aminoalcohols were dissolved in chloroform or methylene chloride,

(5) Goldberg and W. F. Whitmore, THIS JOURNAL, **59**, 2280 (1937).

TABLE III

2-ALKYLAMINOETHYL *p*-AMINOBENZOATE HYDROCHLORIDES, $p$-$NH_2C_6H_4COOCH_2CH_2NHR \cdot HCl$

| Alkyl group[n] | M. p., °C. | Formula | Chlorine, % Calcd. | Found | Anesthetic activity Topical, × cocaine | Infiltration, × procaine | Toxicity subcutaneous $LD_{50}$, mg./kg. |
|---|---|---|---|---|---|---|---|
| Isopropyl[a] | 203–204[d] | $C_{12}H_{19}O_2N_2Cl$ | 13.70 | 13.65 | 0 | | >400 |
| *s*-Butyl[a] | 180–181[d] | $C_{13}H_{21}O_2N_2Cl$ | 13.00 | 12.96 | 0.2 | 0.3 | >400 |
| 2-Pentyl[a] | 159–161[d] | $C_{14}H_{23}O_2N_2Cl$ | 12.36 | 12.36 | 0.5 | 1 | 150 |
| 3-Pentyl[a] | 188.5–189.5[e] | $C_{14}H_{23}O_2N_2Cl$ | 12.36 | 12.34 | 1 | 1 | 425 |
| 2-(4-Methylpentyl)[a] | 165–166.5[d] | $C_{15}H_{25}O_2N_2Cl$ | 11.79 | 11.67 | 1 | 1 | 125 |
| 2-Heptyl[a] | 140–142[f] | $C_{16}H_{27}O_2N_2Cl$ | 11.26 | 11.22 | 2 | 2 | 125 |
| 4-Heptyl[a] | 157–158[e] | $C_{16}H_{27}O_2N_2Cl$ | 11.26 | 11.24 | 0.8 | | 300 |
| 2-Octyl[a] | 159–160[d] | $C_{17}H_{29}O_2N_2Cl$ | 10.78 | 10.77 | 5 | 5 | 250 |
| 2-Nonyl[b] | 161.5–162.5[e] | $C_{18}H_{31}O_2N_2Cl$ | 10.34 | 10.36 | 2 | | 200 |
| 5-Nonyl[a] | 146–147[d] | $C_{18}H_{31}O_2N_2Cl$ | 10.34 | 10.21 | 1 | | 175 |
| 4-(2,6-Dimethylheptyl)[a] | 154–156[g] | $C_{18}H_{31}O_2N_2Cl$ | 10.34 | 10.44 | 1 | | 250 |
| 2-Decyl[b] | 143–144[d] | $C_{19}H_{33}O_2N_2Cl$ | 9.93 | 10.03 | 2 | | 250 |
| Cyclohexyl[a] | 177–178[d] | $C_{15}H_{23}O_2N_2Cl$ | 11.87 | 11.84 | 1 | 2 | 400 |
| 1-Methylcyclohexyl[c] | 198–199[e] | $C_{16}H_{25}O_2N_2Cl$ | 11.33 | 11.29 | 0.7 | | >300 |
| 4-Methylcyclohexyl[c] | 182–183[d] | $C_{16}H_{25}O_2N_2Cl$ | 11.33 | 11.21 | 0.8 | | 175 |
| 3,3,5-Trimethylcyclohexyl[b] | 200–201[e] | $C_{18}H_{29}O_2N_2Cl$ | 10.40 | 10.36 | 1 | | 225 |
| *l*-Menthyl[b] | 218–219 (dec.)[h] | $C_{19}H_{31}O_2N_2Cl$[i] | 9.99 | 9.93 | [o] | | |
| Butyl[k,a] | 143–144[e] | $C_{13}H_{21}O_2N_2Cl$ | | | 0.2 | 1.5 | 250 |
| Isobutyl[k,c] | 189–190[e] | $C_{13}H_{21}O_2N_2Cl$ | | | 0.5 | 2 | 450 |
| *n*-Amyl[k,a] | 150–152[d] | $C_{14}H_{23}O_2N_2Cl$ | | | 1 | | 125 |
| *n*-Heptyl[m] | 157–158[d] | $C_{16}H_{27}O_2N_2Cl$[j] | 11.26 | 11.61 | [p] | | |
| 2-Ethylhexyl[a] | 134–136[i] | $C_{17}H_{29}O_2N_2Cl$ | 10.78 | 10.75 | 0.5 | | 200 |

[a] Reduced in water solution or suspension. [b] Reduced in dilute alcohol. [c] Reduced in dilute acetic acid. [d] Recrystallized from absolute alcohol and ether. [e] From absolute alcohol. [f] From absolute alcohol and acetone. [g] From acetone and ether. [h] From dilute alcohol. [i] From acetone. [j] Also analyzed for nitrogen. Calcd.: N, 8.89. Found: N, 8.83. [k] Described by Goldberg and W. F. Whitmore, ref. 5. [l] Also analyzed for nitrogen. Calcd.: N, 7.90. Found: N, 7.82. [m] Reduced in a mixture of methyl ethyl ketone and absolute alcohol. [n] Yields between 83 and 96% were obtained except as follows: 2-nonyl, 75%; 4-methylcyclohexyl, 71%; *l*-menthyl, 63%; and *n*-heptyl, 60%. [o] Too insoluble for test. [p] Too irritating for test.

TABLE IV

2-ALKYLAMINOETHYL PHENYLURETHAN HYDROCHLORIDES, $C_6H_5NHCOOCH_2CH_2NHR \cdot HCl$

| Alkyl group | M. p., °C. | Formula | Chlorine, % Calcd. | Found | Anesthetic activity Topical, × cocaine | Infiltration, × procaine | Toxicity subcutaneous $LD_{50}$, mg./kg. |
|---|---|---|---|---|---|---|---|
| *s*-Butyl[a] | 124–126 (dec.)[a] | $C_{13}H_{21}O_2N_2Cl$ | 13.00 | 13.04 | 0.5 | .. | 700 |
| 2-Pentyl[f] | 174–176[b] | $C_{14}H_{23}O_2N_2Cl$ | 12.36 | 12.39 | 1 | .. | 500 |
| 2-Octyl[g] | 172–174[c] | $C_{17}H_{29}O_2N_2Cl$ | 10.78 | 10.78 | | .. | 500 |
| Cyclohexyl[h] | 206.5–207 (dec.)[d] | $C_{15}H_{23}O_2N_2Cl$ | 11.87 | 11.84 | 0.5 | .. | 575 |

[a] Recrystallized from acetone. [b] From absolute alcohol. [c] From absolute alcohol and ether. [d] From 95% alcohol. Yield 36%. [f] Yield 82%. [g] Yield 76%. [h] Yield 86%.

TABLE V

2-(2-OCTYLAMINO)-ETHYL *p*-AMINOBENZOATE SALTS, $p$-$NH_2C_6H_4COOCH_2CH_2NHCH(CH_3)(n\text{-}C_6H_{13}) \cdot HX$

| Salt | M. p., °C. | Formula | Nitrogen, % Calcd. | Found | Anesthetic activity Topical, × cocaine | Infiltration, × procaine | Toxicity subcutaneous $LD_{50}$, mg./kg. |
|---|---|---|---|---|---|---|---|
| Sulfate | 209–210 (dec.)[a] | $C_{34}H_{68}O_8N_4S$ | 8.21 | 8.36 | 2 | | 175 |
| Sulfamate | 120–121[b] | $C_{17}H_{31}O_5N_3S$ | 10.79 | 10.79 | 1 | | 175 |
| *d*-Tartrate | 70–80[b,c] | $C_{38}H_{62}O_{10}N_4$ | 7.63 | 7.56 | 0.7 | | 200 |
| Glycolate | 99–100[d] | $C_{19}H_{32}O_5N_2 \cdot 2H_2O$[g] | 6.92 | 7.04 | 2.5 | 2.5 | 200 |
| Citrate | 73–75[d] | $C_{57}H_{92}O_{14}N_6$ | 5.99 | 6.05 | 2.5 | | 150 |
| Ethyl hydrogen sulfate | 140–141[e] | $C_{19}H_{34}O_6N_2S$ | 6.69 | 6.69 | | | 150 |
| Acetate | 84–85[f] | $C_{19}H_{32}O_4N_2$ | 7.95 | 7.90 | 2.5 | | 200 |

[a] Recrystallized from absolute alcohol. [b] From acetone. [c] Mixture of diastereomers. [d] From alcohol and ether. [e] From alcohol and acetone. [f] From acetone and ether. [g] Under completely anhydrous conditions the glycolate could only be obtained as a glass, which crystallized on the addition of a small amount of water or exposure to the air. The exact amount of water in the hydrate is based on the nitrogen analyses, and is consequently subject to some uncertainty.

saturated with hydrogen chloride, and the hydrochlorides were allowed to react with benzoyl chloride, *p*-nitrobenzoyl chloride or phenyl isocyanate. While the alkylamino group of alkylaminoethanols reacts more rapidly with acylating agents than does the alcoholic hydroxyl, in the

aminoalcohol salts the activity is reversed. The eight benzoates described in Table I were prepared by this general procedure. The esters were liberated from their hydrochlorides, purified by distillation to remove small amounts of the aminoalcohols, and reconverted to hydrochlorides (Table I). The fact that the esters could be distilled in vacuum without rearranging to amides is noteworthy.

The corresponding *p*-nitrobenzoate hydrochlorides (Table II) were prepared in the same manner, and isolated by crystallization. They were reduced with hydrogen and palladinized charcoal to the *p*-aminobenzoate hydrochlorides (Table III). Additional esters which were prepared in a similar manner and are described in the Experimental Part are 2-(2-octylamino)-ethyl *m*-nitro- and *m*-aminobenzoate hydrochlorides and 2-cyclohexylaminoethyl salicylate hydrochloride. Properties of the phenylurethan hydrochlorides prepared from several of the aminoalcohols are recorded in Table IV.

A number of salts were prepared from 2-(2-octylamino)-ethyl *p*-aminobenzoate (Table V).

A study of the isomerization of 2-(2-octylamino)-ethyl *p*-nitrobenzoate was made, to determine the ease of the ester–amide rearrangement in this series. The ester hydrochloride was very stable, being recovered unchanged after heating for seven days at 50–55° in pyridine solution. The free base isomerized slowly; approximately half of a sample was isomerized to N-*p*-nitrobenzoyl 2-(2-octylamino)-ethanol after standing in pentane solution for a month at room temperature.

Ester–amide isomerizations which appear to occur rapidly[4] are those of primary aminoesters (such as I, R′ = hydrogen), and compounds in which the ester group is activated by an adjacent aryl group, such as $ArCH(OCOR)CH_2NHR$. The esters herein described have neither of these structural features, and are relatively stable.

## Experimental Part[6]

**2-Alkylaminoethyl Benzoates.**—Conditions employed in the synthesis of 2-(3-pentylamino)-ethyl benzoate will illustrate the method used for all of the esters in Table I. 2-(3-Pentylamino)-ethanol[2] (26.2 g., 0.2 mole) was dissolved in 32 g. of chloroform. The solution was saturated with dry hydrogen chloride, with cooling. Benzoyl chloride (28 g., 0.2 mole) in 32 g. of chloroform was added to the resulting sirupy solution in a heavy 500-cc. round-bottom flask, which was stoppered, wired shut and allowed to stand at 30 to 35° for sixty hours. The flask was cooled to diminish the pressure of hydrogen chloride, opened and the solution poured into 400 cc. of water containing 75 g. of sodium carbonate monohydrate. The chloroform layer was separated and the water layer extracted four times with ether. The ether and chloroform were removed in vacuum. Distillation of the residue through a vacuum-jacketed Vigreux column gave 40 g. (85%) of the aminoester (Table I). The aminoesters are viscous, high boiling liquids. The two esters of highest molecular weight appeared to decompose very slightly on redistillation; the others were stable at the boiling points listed in Table I.

The above procedure gave somewhat better yields of 2-*s*-butylaminoethyl benzoate hydrochloride than did isolation of the salt directly from the esterification mixture and purification by recrystallization (yield by the latter method 55 to 67%), and was consequently used for all of the benzoates. Preliminary attempts to esterify suspensions of the hydrochloride and sulfate of 2-isopropylaminoethanol in dioxane and in acetone were unsuccessful, while reaction of a suspension of 2-*s*-butylaminoethanol hydrochloride in benzene with benzoyl chloride (at room temperature for a week and 45–50° for seven hours) gave only 12% of the ester.[7] It is important that the reaction mixture be homogeneous, as is the case in chloroform and methylene chloride. Treatment of a water solution of 2-isopropylaminoethanol hydrochloride with benzoyl chloride at room temperature resulted in hydrolysis of the acid chloride rather than esterification. The reaction of 2-*s*-butylaminoethanol (the free base rather than the hydrochloride) with benzoyl chloride in chloroform solution gave a complex mixture.

Hydrochlorides were prepared from the alkylaminoethyl benzoates in alcohol solution by adding a slight excess of 6 *N* hydrochloric acid. The less soluble salts which crystallized from the alcohol solution were precipitated more completely by the addition of ether, filtered, and dried. The more soluble salts were isolated by evaporating to dryness in vacuum. Yields of the hydrochlorides (Table II) after recrystallization were 82 to 98%. They are white, crystalline salts which are quite stable. After a solution of 1 g. of 2-*s*-butylaminoethyl benzoate hydrochloride in 100 cc. of water had been boiled for two hours, 0.8 g. was recovered in a relatively pure state (m. p. 135–139°).

**2-Alkylaminoethyl *p*-Nitrobenzoate Hydrochlorides (Table II).**—The esterifications with *p*-nitrobenzoyl chloride followed the procedure outlined above for the benzoates except that the reaction time was extended to ninety hours. After this period the chloroform was removed in vacuum, the residues were pulverized and allowed to stand for several hours under dry ether. By filtering the ether suspensions, it was possible to remove some of the unreacted *p*-nitrobenzoyl chloride. The salts were washed with ether, dried, and recrystallized from the solvents listed in Table II.

The reactions carried out in this manner were never quite complete. Preparations of 2-(2-heptylamino)- and 2-(2-octylamino)-ethyl *p*-nitrobenzoate hydrochlorides made with the same proportions of reactants in chloroform solution, but at 50 to 55° at atmospheric pressure for twenty-four hours were more complete, giving 85 and 89% yields of pure products, respectively. This procedure could probably be used to advantage in esterifying all of the aminoalcohols.

**2-Alkylaminoethyl *p*-Aminobenzoate Hydrochlorides.**—The majority of these compounds (Table III) were prepared by dissolving or suspending 10 to 15 g. of the finely powdered *p*-nitrobenzoate hydrochlorides in 300 to 500 cc. of warm water and hydrogenating in the presence of 1 g. of palladinized charcoal.[8] The reductions were usually complete in thirty minutes or less. The less soluble nitro compounds usually went into solution as the reductions proceeded. In a few cases alcohol was added in the beginning to increase their solubility. If the *p*-aminobenzoate hydrochlorides were not in solution at the end of the reduction, enough alcohol was added to dissolve them and the shaking was continued to insure complete reduction. Dilute acetic acid was used as the solvent for a few reductions (see footnotes to Table III). In each preparation the catalyst was filtered and the solvent distilled in vacuum. The residual salts were recrystallized from the solvents indicated in Table III, although in most cases they were

(6) We are indebted to Miss Dorothea Heyl for gravimetric chlorine analyses, and to Mr. C. S. Miller for semimicro Kjeldahl determinations. Melting and boiling points are uncorrected.

(7) After this work was completed, Immediata and Day (ref. 4f) reported the esterification of 1-β-naphthyl-2-alkylaminoethanol hydrochlorides by reaction with benzoyl chloride without a solvent.

(8) Hartung, THIS JOURNAL, **50**, 3372 (1928).

pure as first obtained, and recrystallization usually did not raise their melting points. The *p*-aminobenzoate hydrochlorides are white when perfectly pure. They are fairly readily oxidized and become colored when heated in solutions exposed to the air, particularly in the presence of organic solvents.

**Reaction of 2-*n*-Butylaminoethanol with *p*-Nitrobenzoyl Chloride in Alkaline Solution.**—The directions of Goldberg and W. F. Whitmore,[5] as amplified in the patent literature,[9] were followed as closely as possible. The reaction of 10 g. of 2-*n*-butylaminoethanol[2] with 16 g. of powdered *p*-nitrobenzoyl chloride in the presence of dilute sodium hydroxide gave 18.5 g. of an oil which was reduced with tin and hydrochloric acid. When the reduction mixture was made alkaline with sodium hydroxide, an oil which was only partly soluble in ether separated. The ether soluble portion (6 g.) was dissolved in *n*-propyl alcohol and acidified with concd. hydrochloric acid. The hydrochloride which separated was recrystallized from alcohol and ether; it had m. p. 143–144° and was identical with the product described in Table III; yield 2.2 g. (10%).

A similar preparation from 23.4 g. of 2-*n*-butylaminoethanol and 37.1 g. of *p*-nitrobenzoyl chloride gave an oily nitro compound which was dissolved in benzene and pentane. On standing the product crystallized, and was recrystallized from the same solvent; yield 37 g. (70%), m. p. 73–74°. It was the amide, $p\text{-}NO_2C_6H_4CON(C_4H_9)\text{-}CH_2CH_2OH$, for it was insoluble in dilute acids.

*Anal.* Calcd. for $C_{13}H_{18}O_4N_2$: N, 10.52. Found: N, 10.55.

The above amide dissolved in alcohol containing a molar equivalent of hydrochloric acid rapidly absorbed the theoretical quantity of hydrogen on shaking in the presence of palladinized charcoal but all efforts to obtain a crystalline hydrochloride of the reduction product failed. Reduction with tin and hydrochloric acid also failed to give a crystalline product.

**2-(2-Octylamino)-ethyl *m*-Nitrobenzoate Hydrochloride.**—This ester was prepared from the aminoalcohol hydrochloride and *m*-nitrobenzoyl chloride, which were heated in chloroform solution at 50° for twenty-four hours; yield 75% after recrystallization from absolute alcohol, m. p. 158.5–159.5°.

*Anal.* Calcd. for $C_{17}H_{27}O_4N_2Cl$: Cl, 9.88. Found: Cl, 9.92.

Catalytic reduction of the above ester in water gave 2-(2-octylamino)-ethyl *m*-aminobenzoate hydrochloride, which was obtained by removing the water in a vacuum, m. p. 127–128°.

*Anal.* Calcd. for $C_{17}H_{29}O_2N_2Cl$: Cl, 10.78. Found: Cl, 10.84.

*Pharmacological data:* Topical anesthetic activity, 3 × cocaine; $LD_{50}$, 150 mg./kg.

**2-Cyclohexylaminoethyl Salicylate Hydrochloride.**—This compound was obtained by treating 2-cyclohexylaminoethanol hydrochloride with the acid chloride of salicylic acid[10] in chloroform at 0° for six hours followed by heating at 50° for twenty-four hours. After recrystallization from alcohol the yield was 83%; m. p. 200–201.5°.

*Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: Cl, 11.83. Found: Cl, 11.85.

*Pharmacological data:* Topical anesthetic activity, 0.5 × cocaine; $LD_{50}$, 700 mg./kg.

**2-Alkylaminoethyl Phenylurethan Hydrochlorides.**—These compounds (Table IV) were prepared by saturating a solution of 0.1 mole of each aminoalcohol in 30 g. of chloroform with hydrogen chloride and adding a solution of 0.1 mole of phenyl isocyanate in 30 g. of chloroform. The mixture was cooled in ice for three-quarters of an hour, warmed slowly to 50°, and kept at that temperature for forty hours. The products were purified in the same manner as the *p*-nitrobenzoate hydrochlorides.

**2-(2-Octylamino)-ethyl *p*-Aminobenzoate Salts (Table V).**—The hydrochloride (3.3 g., 0.01 mole) was dissolved in 15 cc. of alcohol and 250 cc. of water. The free base was liberated by adding an excess of sodium carbonate in the presence of benzene, and the water layer was extracted several times with benzene. An atmosphere of carbon dioxide was maintained during these operations. The benzene solution was added at once to a water or alcohol solution containing an equivalent or molar quantity of the acid in question, and the salts were isolated by concentration in vacuum and recrystallization. In a control experiment the ester was reconverted into the hydrochloride, indicating that no rearrangement (to an amide) occurred in the process.

**Ester–Amide Rearrangement of 2-(2-Octylamino)-ethyl *p*-Nitrobenzoate.**—A sample of the amide, N-*p*-nitrobenzoyl 2-(2-octylamino)-ethanol was prepared by treating 2-octylaminoethanol with *p*-nitrobenzoyl chloride and aqueous sodium hydroxide. After recrystallization from alcohol it melted at 104–105°.

*Anal.* Calcd. for $C_{17}H_{26}O_4N_2$: N, 8.69. Found: N, 8.64.

The free base was liberated from 3 g. of 2-(2-octylamino)-ethyl *p*-nitrobenzoate hydrochloride and allowed to stand for four days under 100 cc. of 0.06 *N* sodium hydroxide, with occasional shaking to disperse the oily ester. After this time, 0.4 g. of N-*p*-nitrobenzoyl 2-(2-octylamino)-ethanol was isolated, while 1.1 g. of the original ester was recovered as the hydrochloride. A sample of the ester which was dissolved in approximately half-normal sodium hydroxide in 50% alcohol and allowed to stand for seven days was completely saponified.

The free base from 2.5 g. of the ester hydrochloride was allowed to stand in pentane solution at room temperature. The amide, which is insoluble in pentane, crystallized slowly; a total of 1.4 g. separated in a month.

In order to determine whether the conditions employed in esterifying would reverse the rearrangement of the amide to the ester hydrochloride, a chloroform solution of 1 g. of N-*p*-nitrobenzoyl 2-(2-octylamino)-ethanol was saturated with hydrogen chloride and allowed to stand at 30 to 35° for five days. The amide (0.8 g.) was recovered.

## Pharmacological

The pharmacological data included in Tables I III, IV and V were obtained at the Merck Institute for Therapeutic Research, and will be published elsewhere by Albert O. Seeler and Samuel Kuna. The number of animals used for testing each substance was small in most cases, since the object was to screen a large series of compounds. The results consequently are to be regarded as only roughly quantitative.

The potencies of the new compounds as topical anesthetics were determined by direct comparison with cocaine as a standard. A 0.05 to 3.0% solution of each compound was instilled into the eye of a rabbit, and the duration of anesthesia was noted. A solution of cocaine hydrochloride, usually of the same concentration, was instilled into the other eye at the same time. The tabulation of "anesthetic activity, topical, × cocaine" is the ratio of the duration of anesthesia produced by the new compounds to the duration with cocaine hydrochloride at the same concentration.[11]

(9) Goldberg, U. S. Patent 2,139,818.

(10) Kopetschni and Karczag, *Ber.*, **47**, 235 (1914).

(11) In most cases, the figures are average values of concordant results obtained with two rabbits. In a few cases, the new compounds were compared to cocaine at a different concentration. In these instances the ratios were calculated on the assumption that the duration of anesthesia is directly proportional to the concentration of anesthetic. A compound which produced thirty minute anesthesia at 0.5% concentration, compared to twenty minute anesthesia for cocaine hydrochloride at 1.0%, would be recorded as three times as effective as cocaine.

Effectiveness compared to procaine hydrochloride in producing infiltration anesthesia was estimated by determining the duration of anesthesia following subcutaneous injection of solutions of the new compounds and procaine hydrochloride at different sites on the abdomen of the same guinea pig. Toxicities were determined by subcutaneous injection in white mice. The $LD_{50}$ values found for the standards were: cocaine hydrochloride, 150 mg./kg.; procaine hydrochloride, 600 mg./kg.


## Summary

The reaction of acid chlorides with the hydrochlorides of 2-alkylaminoethanols ($RNHCH_2CH_2OH \cdot HCl$), dissolved in a solvent such as chloroform or methylene chloride, has been found to be a satisfactory method for esterifying the aminoalcohols. The formation of amides through reaction with the secondary amino group is effectively blocked by converting the aminoalcohols to salts.

The local anesthetic activity of a number of benzoates, *p*-aminobenzoates and phenylurethans of 2-alkylaminoethanols has been examined.


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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF BRYN MAWR COLLEGE AND COLUMBIA UNIVERSITY]

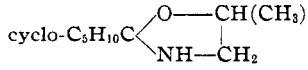
# 1-Alkylamino-2-propanols and their *p*-Nitro- and *p*-Aminobenzoates

BY ARTHUR C. COPE AND EVELYN M. HANCOCK[1]

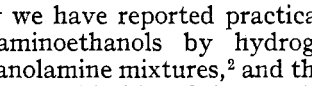
Recently we have reported practical syntheses of 2-alkylaminoethanols by hydrogenation of ketone-ethanolamine mixtures,[2] and the esterification of the hydrochlorides of these aminoalcohols.[3] Similar methods have proved to be equally satisfactory for preparing and esterifying 1-alkylamino-2-propanols, which are described in this paper.

The properties of seventeen 1-alkylamino-2-propanols and picrates derived from most of them are described in Table I. All but three of the aminoalcohols were prepared by hydrogenating ketone–isopropanolamine mixtures in alcohol solution with Adams platinum catalyst. 1-Isoamylamino-2-propanol was prepared similarly from isovaleraldehyde. The aminoalcohols derived from diisobutyl ketone and diisoamyl ketone were obtained by condensing isopropanolamine with these ketones and hydrogenating the anhydro compounds.

Anhydro compounds were prepared from the above ketones as well as cyclohexanone and isopropanolamine by refluxing benzene solutions of the reactants and removing the water formed with a continuous separator. Molecular refractions of the pure anhydro compounds indicate that the product from diisobutyl ketone is the Schiff base, $(i\text{-}C_4H_9)_2C{=}NCH_2CHOHCH_3$, while the cyclohexanone product is an oxazolidine



Anhydro compounds which were formed from these two ketones and ethanolamine were likewise open chain and cyclic, respectively. The molecular refraction of the product from diisoamyl ketone and isopropanolamine indicates that it is an oxazolidine,[4]



The fact that the anhydro compound from isopropanolamine and diisobutyl ketone is a Schiff base, while the diisoamyl ketone product is an oxazolidine, may be due to the factor of steric hindrance cited as a possible explanation of similar differences in the ethanolamine series. There would be less mechanical interference with the formation of a five-membered ring about the carbonyl group in diisoamyl ketone than in diisobutyl ketone, where the point of branching is one carbon atom nearer the carbonyl.

*p*-Nitrobenzoate hydrochlorides were prepared from the 1-alkylamino-2-propanols by reaction of *p*-nitrobenzoyl chloride with the aminoalcohol hydrochlorides in chloroform solution. As in the ethanolamine series, amide formation was blocked by employing the aminoalcohol salts rather than the free bases. Reaction periods of four to five days and temperatures of 50–60° gave relatively complete esterification of the secondary alcohol group present in the 1-alkylamino-2-propanols. The pure hydrochlorides were isolated in 36 to 75% yield (Table II). A similar procedure was used to convert 1-cyclohexylamino-2-propanol hydrochloride into its phenylurethan.

1-Alkylamino-2-propanols derived from unsymmetrical ketones contain two asymmetric carbon atoms and, therefore, yield mixtures of two diastereomeric *p*-nitrobenzoate hydrochlorides. It was possible to isolate the high melting diastereomer in a fairly pure state in two such

(1) Sharp and Dohme Research Associate.

(2) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

(3) Cope and Hancock, *ibid.*, **66**, 1448 (1944).

(4) The observed molecular refractions are in reasonable agreement with the structures indicated for the three anhydro compounds, but such data do not preclude the presence of smaller amounts of the isomeric structures. An oxazolidine and a Schiff base have been shown to form a mobile system in equilibrium by ring-chain tautomerism in one similar case (ref. 2).