[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

# Reactions of Esters with Tertiary Amines. I. Benzyl Esters from Methyl Esters and Benzyldimethylamine[1]

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The reaction of the methyl esters of fifteen different carboxylic acids with benzyldimethylamine has been studied at temperatures in the vicinity of 200° in the absence of solvents. In twelve cases, the products were trimethylamine and the benzyl ester of the carboxylic acid, usually isolated in 70–97% yield. With methyl *o*- and *p*-hydroxybenzoate, the ester interchange was accompanied by etherification. With methyl *p*-nitrophenylacetate the reaction failed. A reaction mechanism is proposed and substantiated by evidence.

The recent finding[2] that benzyldimethylamine will alkylate methyl cyanoacetate and tricarbethoxymethane prompted an investigation of the reaction of this amine with the methyl esters of acids which are not readily decarboxylated.

It was found that when a mixture of the methyl ester of such an acid and benzyldimethylamine is heated to a temperature close to 200° in an atmosphere of nitrogen, a gentle but steady evolution of trimethylamine occurs, and at the end of several hours the methyl ester is converted to the corresponding benzyl ester, according to the equation

$$RCOOCH_3 + C_6H_5CH_2N(CH_3)_2 \longrightarrow RCOOCH_2C_6H_5 + N(CH_3)_3$$

Some unchanged methyl ester is usually recovered, and a certain amount of tarry material is formed in some cases. Entrainment losses also appear to interfere with a quantitative recovery of the products. Nevertheless, the yields are almost always over 70% on the basis of the methyl ester employed (taking into account recovered starting material) with conversions ranging from 50 to 97%. The good yield and the ease of manipulation would appear to make this an attractive method for the synthesis of benzyl esters, many of which are not recorded in the literature.

The methyl esters which have been converted to benzyl esters by reaction with benzyldimethylamine are listed in the table. The reaction rate seems to increase with increasing strength of the acid with a corresponding decrease in the optimum reaction time and temperature. The reaction failed in only one case: methyl *p*-nitrophenylacetate produces only tars and a small amount of *p*-nitrotoluene.[3] Methyl anthranilate yields benzyl anthranilate in low yield only, due to the interference of a number of side reactions. Methyl salicylate and methyl *p*-hydroxybenzoate yield benzyl *o*-benzoxybenzoate and *p*-benzoxybenzoate, respectively, accompanied by phenol and phenyl benzyl ether.

The only side product usually obtained, other than unchanged methyl ester and benzyldimethylamine, is a small amount of the free acid, resulting, presumably, from the presence of traces of water in the reaction mixture. When a large excess of benzyldimethylamine is employed in the reaction however, dibenzylmethylamine begins to appear among the reaction products. Since this results in a waste of dimethylbenzylamine, the latter was generally employed in 10 to 25% excess only, despite the slight decrease in conversion of methyl to benzyl esters which this entails. The reaction temperature does not appear to be critical, except in the one case of methyl *p*-nitrobenzoate where excessive heating leads to the formation of benzyl *p*-aminobenzoate, benzaldehyde and tar.

It is almost certain that the ester interchange observed in this work proceeds through a quaternary salt intermediate

$$RCOOCH_3 + C_6H_5CH_2N(CH_3)_2 \rightleftharpoons RCOO^{\ominus}C_6H_5CH_2N(CH_3)_3^{\oplus} \longrightarrow RCOOCH_2C_6H_5 + N(CH_3)_3$$

The driving force in this reaction is the formation of the gaseous trimethylamine. In evidence of the quaternary salt intermediate, the following facts may be cited. (1) Methyl esters are known to react with trimethylamine to yield quaternary ammonium salts[4] at a rate which increases with increasing strength of the acid.[5] The decomposition of these quaternary ammonium salts into trimethylamine and ester has also been reported.[6–10] (2) Carbon alkylation with benzyldimethylamine has been shown to involve quaternary intermediates.[2] It seems probable that oxygen alkylation does likewise, especially since the same by-product dibenzylmethylamine, resulting from self-alkylation of dimethylbenzylamine, is obtained in both cases. (3) The etherification of methyl *o*- and *p*-hydroxybenzoate which accompanies the ester interchange is readily explained on the assumption that quaternary salts are present, since it is known that quaternary ammonium salts will O-alkylate phenols[10–16] The by-products formed in the

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[1] Presented in part before the Organic Division of the American Chemical Society at Chicago, Ill., September 5, 1950.

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[3] This appears to be connected with the presence of an acidic methylene group; among substituted benzyldimethylamines, *p*-nitrobenzyldimethylamine is the only one with which the ester interchange reaction consistently fails: Th. Ferdinand, B.S. Thesis, University of Notre Dame, 1951.

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TABLE I

| Methyl ester of acid | $pKa$[17] | Reaction Time, hr. | Reaction Temp., °C. | Excess amine, % | Benzyl ester Yield, % | Benzyl ester Conv. % | Crude B.p. °C. | Crude B.p. Mm. | Crude M.p., °C., or $n^{25}D$ | Purified B.p. °C. | Purified B.p. Mm. | Purified M.p., °C., or $n^{25}D$ | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| o-Chlorobenzoic | 2.89 | 8.5 | 170 | 25 | 90 | 72 | 153–155 | 1 | .......... | 129–132 | 0.04 | 1.5758 | a,b |
| Salicylic | 2.00 | 24.5 | 170–210 | $0^c$ | ... | 6 | 225–229 | 1 | 47–50 | $^d$ | | 50–51 | e,t |
| o-Phthalic | 3.00 | 13 | 170–220 | $20^c$ | $92^f$ | 71 | 202–211 | 0.02 | 40–44 | $^d$ | | $44.5–45.5^v$ | a,u |
| Furoic | 3.12[18] | 8 | 130–190 | 0 | 69 | 55 | 173–175 | 13 | 1.5513 | ..... | | ........ | a,g |
| p-Nitrobenzoic | 3.40 | 6 | 170–200 | 100 | 97 | 97 | ..... | ... | 77–82 | $^d$ | | $83–84.5^h$ | h |
| p-Nitrobenzoic | | 12 | 210–225 | 100 | ... | .. | ..... | ... | 88.5–89 | ..... | | ........ | i |
| p-Nitrophenylacetic | 3.4[19] | 4.5 | 150–185 | 0 or 100 | 0 | 0 | ..... | ... | .......... | ..... | | ........ | j |
| Benzoic | 4.17 | 20 | 210–235 | 0 | 91 | 75 | 176–180 | 9 | $18–20^k$ | ..... | | ........ | a |
| Succinic | 4.17 | 20 | 170–205 | $17^c$ | $85^f$ | 70 | 160–180 | 1.5 | 40–46 | $^d$ | | $47–48.5^l$ | a |
| p-Toluic | 4.35 | 23 | 170–210 | 33 | 96 | 82 | 139–140 | 1 | 42–45 | $^d$ | | $46.5^m$ | a |
| Cinnamic | 4.43 | 30 | 210–230 | 17 | 73 | 51 | 154–157 | 0.5 | 28.5–32 | $^d$ | | $34^n$ | a,g |
| Anisic | 4.49 | 20 | 220 | 10 | 73 | 55 | 150–157 | 1 | 20–21 | 156–158 | 0.5 | 26–27 | a,g,o |
| p-Hydroxybenzoic | 4.54 | 14 | 175–190 | $13^c$ | ... | 31 | $^d$ | | $115.5–116.5^p$ | ...... | | ........ | a,p,t |
| Caprylic | 4.85 | 92 | 200–230 | 25 | 77 | 54 | 120–130 | 0.5 | ......... | 112–120 | 0.5 | 1.4919 | a,g,q |
| Capric | ca. 4.85 | 96 | 200–230 | 25 | 74 | 55 | 130–140 | 0.6 | ......... | 112–120 | 0.3 | 1.4866 | a,g,r |
| Anthranilic | 5.00 | 11 | 170–180 | 25 | ... | 28 | 152–170 | 1.6 | 61–71 | $^d$ | | 77–77.5 | a,s,t |

[a] Identity established by hydrolysis. Solid acids were identified by melting point and, in some cases, mixture melting points, liquid acids by their p-bromophenacyl esters, benzyl alcohol by its p-nitrobenzoate or 3,5-dinitrobenzoate.[20] [b] Calcd. for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.50. Found: C, 68.37; H, 4.71. [c] Excess over two moles per mole of ester. [d] Purified by crystallization. [e] The product was benzyl o-benzoxybenzoate. *Anal.* Calcd. for $C_{21}H_{18}O_3$: C, 79.21; H, 5.70. Found: C, 79.63; H, 5.90. Hydrolysis products: Benzyl alcohol and salicylic acid benzyl ether, m.p. 75–75.5° (lit.[21] 76–77°), undepressed by admixture of an authentic specimen.[21] Also obtained in this reaction were phenol (36%) and benzyl phenyl ether (31%), both identified by mixture melting points.[22] [f] This figure is not very exact, since the low-boiling material appeared to contain both the dimethyl ester and the methyl benzyl ester. [g] There was a tarry distillation residue. [h] Identified by melting point and mixture melting point, lit.[23] 85°. [i] The product was benzyl p-aminobenzoate, identified by melting point and mixture melting point with an authentic sample,[24] lit.[24] 88.5–89.5°. Benzaldehyde, identified by its phenylhydrazone was also obtained. [j] The product was largely tarry. Some p-nitrotoluene, m.p. 51–52°, undepressed by admixture with an authentic sample was isolated by steam distillation followed by crystallization. [k] Lit.[25] 19.4°. [l] Undepressed by admixture of an authentic sample; lit.[26] 47–48°. [m] Lit.[27] 45–47°. [n] Lit.[24] 33–34°. [o] Saponification equivalent, calcd.: 242; found: 243. [p] The product was benzyl p-benzoxybenzoate since it did not depress the melting point (lit.[28] 115°) of an authentic specimen of this ester.[28] *Anal.* Calcd. for $C_{21}H_{18}O_3$: C, 79.24; H, 5.69. Found: C, 79.00; H, 5.82. Benzyl phenyl ether, identified by melting point and mixture melting point[22] was also obtained in this reaction in 28% yield. [q] Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.04; H, 9.01. [r] Calcd. for $C_{17}H_{26}O_2$: C, 77.80; H, 9.99. Found: C, 77.92; H, 9.87. [s] Calcd. for $C_{14}H_{13}O_2N$: C, 73.92; H, 5.89. Found: C, 74.27; H, 6.14. [t] Carbon dioxide was evolved. [u] Benzaldehyde, identified by its phenylhydrazone, and an unidentified solid, b.p. ca. 170° (0.05 mm.), m.p. 133–134°, different from phthalic anhydride (mixture melting point 97–113°) were also isolated. [v] Sample did not depress melting point of authentic specimen; lit.[29] 42–44°. This ester shows a marked tendency to supercool.

reaction with the hydroxybenzoates can also be accounted for without difficulty

$$HO{-}C_6H_4COOCH_3 + C_6H_5CH_2N(CH_3)_2 \longrightarrow HO{-}C_6H_4COO^{\ominus}C_6H_5CH_2N(CH_3)_3^{\oplus}$$

followed by either

$$HO{-}C_6H_4COO^{\ominus} \longrightarrow CO_2 + HO{-}C_6H_4^{\ominus} \longrightarrow C_6H_5O^{\ominus}$$

$$C_6H_5O^{\ominus} + C_6H_5CH_2N(CH_3)_3^{\oplus} \longrightarrow \mathbf{C_6H_5OCH_2C_6H_5} + N(CH_3)_3$$

$$\text{or: } HO{-}C_6H_4COO^{\ominus}C_6H_5CH_2N(CH_3)_3^{\oplus} \longrightarrow N(CH_3)_3 + HO{-}C_6H_4COOCH_2C_6H_5$$

$$HO{-}C_6H_4COOCH_2C_6H_5 + C_6H_5O^{\ominus} \longrightarrow \mathbf{C_6H_5OH} + {}^{\ominus}O{-}C_6H_4COOCH_2C_6H_5$$

$${}^{\ominus}O{-}C_6H_4COOCH_2C_6H_5 + C_6H_5CH_2N(CH_3)_3^{\oplus} \longrightarrow N(CH_3)_3 + \mathbf{C_6H_5CH_2O{-}C_6H_4COOCH_2C_6H_5}$$

## Experimental

**General Procedure.**—Most of the reactions indicated in the table were carried out on a 0.1–0.2 molar scale, in a flask equipped with a reflux condenser and nitrogen inlet tube, inside a hood. The methyl esters were commercially available materials or prepared by standard procedures. Benzyldimethylamine was obtained from Rohm and Haas Co., dried over potassium hydroxide and distilled before use. A mixture of the methyl ester and excess benzyldimethylamine (as stated in the table) was heated under a slow stream of nitrogen in a carbowax-bath until gas evolution became fairly vigorous. Usually this was the case when the bath temperature approached 200°. The bath was maintained at the appropriate temperature until the evolution of trimethylamine (identified in some cases by the picrate) ceased. Sometimes it was found convenient to raise the bath temperature by about ten or fifteen degrees when trimethylamine evolution diminished, so as to ensure complete reaction. The reaction mixture was then allowed to cool under nitrogen, taken up in ether, and extracted successively with 1 $N$ hydrochloric acid, water, 10% aqueous sodium carbonate solution and water. In some cases the acid extract was made basic by the addition of sodium hydroxide and the amine liberated was taken up in ether, dried over potassium hydroxide and distilled at reduced pressure after removal of the ether. In all cases, benzyldimethylamine (characterized, in some cases, by the picrate and methiodide) was recovered. When a large excess of benzyldimethylamine was used in the reaction, varying amounts of dibenzylmethylamine, identified[2] by the picrate, m.p. 106.5–107°, and the hydrochloride, m.p. 199–201°, were also obtained. The carbonate extracts were acidified in some cases and small amounts of the acid corresponding to the methyl ester employed were usually recovered.

The ether solution of the neutral reaction products was dried over sodium sulfate, concentrated, and the residue fractionated at reduced pressure with the aid of a short Vigreux column. Since the only neutral products are the desired benzyl ester and recovered methyl ester whose boil-

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ing points differ by about 100°, separation of the product presents no problem. The benzyl esters were characterized by their physical constants (see table) and identified through their hydrolysis products and, in the case of compounds previously unknown, by elementary analysis.

The above isolation procedure was varied in a few cases. Benzyl *p*-nitrobenzoate crystallized when the reaction mixture was cooled and was purified by slurrying it with dilute hydrochloric acid followed by suction filtration. It was washed with sodium carbonate solution and water, dried and recrystallized from ethanol. In the case of benzyl anthranilate, the acid wash was omitted. In the case of the hydroxybenzoates, the ether solution was washed with aqueous sodium hydroxide for the recovery of phenolic products. The only product isolated by acidification of the caustic extracts was phenol. No esters of the phenolic acids were obtained.

**Acknowledgment.**—We are much indebted to the Rohm and Haas Company for a generous supply of benzyldimethylamine.

NOTRE DAME, INDIANA RECEIVED AUGUST 13, 1951

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE STATE UNIVERSITY OF IOWA]

# The Synthesis of N-Substituted Carbamates[1]

BY R. L. SHRINER AND RALPH G. CHILD[2]

Twenty-four carbamates which are derivatives of β-phenylethylamine, α-methyl-β-phenylethylamine, 2-aminopyridine and 3-aminopyridine have been prepared by two methods: (a) action of alkyl chlorocarbonates on the selected amine and (b) by the use of the Hofmann bromamide reaction. The use of the Hofmann bromamide reaction as a means of preparing carbamates has been extended to include *n*-propyl, *n*-butyl and isobutyl carbamates but shown to give only 5% yields in the case of an easily oxidized alcohol such as isopropyl alcohol.

The work of Skipper and Bryan[3] indicates that certain variations in the structure of ethyl carbamate (urethan), such as mono or di-substitution on the nitrogen atom, variations in the ester moiety, or substitution of sulfur for oxygen, appear to destroy or lessen the antileukemic action. Nevertheless, it was deemed worthy to explore this field further by synthesizing carbamates which were derivatives of amines known to be physiologically active and particularly carbamates containing a basic nitrogen; a class not previously studied for this purpose.

The carbamates prepared, their yields, physical constants, analytical data and methods of preparation, are given in Table I. Except where noted, these are new compounds.

Twelve carbamates, (RNHCOOR′), where R was β-phenylethyl or α-methyl-β-phenylethyl and R′ was methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl, were prepared in good yield by treating ether solutions of the amines with the corresponding alkyl chlorocarbonates in the presence of sodium carbonate solution.[4]

Six carbamates, where R was 2-pyridyl and R′ was as above, were prepared by treating a cold benzene solution of two moles of the corresponding alkyl chlorocarbonate with a benzene solution of one mole of 2-aminopyridine. A white solid of unknown composition formed which on heating decomposed to the carbamate, 2-aminopyridine hydrochloride, carbon dioxide and small quantities of N,N′-(2,2-dipyridyl)-urea. In general, 20% yields were obtained. However, subsequent work showed that in the case of ethyl N-(2-pyridyl)-carbamate a yield of 51.5% was obtained by treating one mole of ethyl chlorocarbonate with two moles of 2-aminopyridine in the presence of benzene. Since the extra mole of 2-aminopyridine is readily recovered, this procedure is preferred.

Six carbamates, where R was 3-pyridyl and R′ as above, were prepared by a Hofmann bromamide reaction on nicotinamide in the presence of the corresponding alcohol. Yields ranging from 44.3 to 78.5% were obtained except in the case where R′ was isopropyl, which gave only 5%. The low yield in this case is presumed to be due to the oxidation of the isopropyl alcohol by either hypobromite or N-bromoamide. However, conversion of nicotinamide to 3-aminopyridine by a Hofmann bromamide reaction in 68.5% yield followed by condensation of the amine with isopropyl chlorocarbonate in the presence of sodium carbonate solution gave a 62.7% yield of isopropyl N-(3-pyridyl)-carbamate.

## Experimental

**Alkyl Chlorocarbonates.**—The six alkyl chlorocarbonates were prepared from phosgene and the anhydrous alcohols according to the method of Adams, Kamm and Marvel.[5]

**β-Phenylethylamine.**—Benzyl cyanide, purified by distillation over Raney nickel, was catalytically reduced over Raney nickel in ammoniacal methanol according to the procedure of Icke and Redemann to give a 79% yield of the amine.[6]

**α-Methyl-β-phenylethylamine.**—A Leuckart reaction on phenylacetone gave the amine in 45.5% yield. The procedure described by Ingersoll for the preparation of α-phenylethylamine from acetophenone was used.[7]

**3-Aminopyridine.**—A Hofmann bromamide reaction on nicotinamide using a slight excess of bromine and four moles of sodium hydroxide according to the procedure of Allen and Wolf have a 68.5% yield of the amine.[8]

**Alkyl N-Substituted Carbamates. Method A.**—The amines were condensed with alkyl chlorocarbonates according to the procedure of Damschroeder and Shriner.[4]

**Method B.**—To a solution of 38.7 g. (0.257 mole) of ethyl chlorocarbonate in 150 ml. of cold benzene was added drop-

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[1] From a thesis submitted by Ralph G. Child in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate College of the State University of Iowa.

[2] Predoctorate Fellow, National Cancer Institute, U. S. Public Health Service, 1948–1950.

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