[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME AND OF MERCYHURST COLLEGE]

REACTIONS OF ESTERS WITH TERTIARY AMINES. II. THE REACTION OF SUBSTITUTED BENZYLDIMETHYLAMINES AND OTHER AMINES

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In a previous publication (1) the reaction of benzyldimethylamine with a variety of methyl esters was described. This reaction yields benzyl esters, according to the equation:

$$RCOOCH_3 + C_6H_5CH_2N(CH_3)_2 \rightarrow RCOOCH_2C_6H_5 + N(CH_3)_3 \qquad (A)$$

Evidence was adduced that the reaction proceeds in two stages of which the first is the alkylation of the amine by the ester to give the quaternary ammonium salt $RCOO^-C_6H_5CH_2N(CH_3)_4^+$ and the second benzylation of the acid anion by the quaternary ammonium cation (2, 3).

It seemed of considerable interest to study the mechanism of this reaction, especially of the second step [which involves the little investigated nucleophilic displacement of one of the groups of a quaternary ammonium ion by an anion (4)], by following its rate as a function of substituents in the benzene ring of the amine or ammonium salt (5). In preparation for such a study we have now investigated the reaction of various substituted benzyldimethylamines and some other tertiary amines with two methyl esters. The two esters chosen were the readily available methyl *p*-nitrobenzoate and methyl *o*-chlorobenzoate since the original study (1) had shown that these esters undergo reaction (A) at a comparatively low temperature. Of the two esters, methyl *o*-chlorobenzoate proved the more useful, because the neutral products could be purified readily by fractional distillation.

Of the substituted benzyldimethylamines, the *p*-methyl, *p*-methoxy-, *p*-chloro- and 2,4-dichloro-compounds reacted readily in accordance with reaction (A) to give esters of the corresponding substituted benzyl alcohols in good yield.

3,4-Dimethoxybenzyldimethylamine appeared to yield 3,4-dimethoxybenzyl *o*-chlorobenzoate, for although we were unable to isolate this ester, its hydrolysis products, 3,4-dimethoxybenzyl alcohol and chlorobenzoic acid were identified. *p*-Nitrobenzyldimethylamine gave only a trace of the expected *p*-nitrobenzyl ester with methyl *o*-chlorobenzoate. No substituted benzyl ester could be isolated from the reaction with 2-hydroxy-5-*tert*-butylbenzyldimethylamine (Mannich base derived from *p-tert*-butylphenol), which yielded much tar.

A few other tertiary amines were also investigated. The alkylation reaction failed with gramine (3-dimethylaminomethylindole). Furfuryldimethylamine and 5-methylfurfuryldimethylamine gave furfuryl and 5-methylfurfuryl *p*-nitro-

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benzoate in poor yield only. Attempts to obtain 5-methylfurfuryl *o*-chlorobenzoate from the amine were unsuccessful.

Rather surprisingly, dodecyldimethylamine reacted with methyl *o*-chlorobenzoate to give dodecyl *o*-chlorobenzoate. Up to now it had been thought that alkylations with amines and ammonium salts were limited to alkyl groups such as benzyl and methyl (2). The present work suggests that higher alkyl groups, such as dodecyl, attached to a quaternary ammonium function can also undergo substitution. Aryl groups, on the other hand, do not react: from an attempted reaction of N,N-dimethylaniline with methyl *o*-chlorobenzoate only starting materials were recovered and no volatile amine escaped.

The unexpected reactivity of dodecyldimethylamine becomes plausible when it is recalled that reaction (A) is an equilibrium reaction (3). The possibility of driving an otherwise unfavorable equilibrium forward by removing the volatile product trimethylamine has been stressed elsewhere (22).

EXPERIMENTAL[3]

Synthesis of amines. Furfuryldimethylamine (6), 5-methylfurfuryldimethylamine (7), and gramine (8) were prepared by methods previously described. 2-Hydroxy-5-*tert*-butylbenzyldimethylamine was kindly supplied by the Rohm and Haas Company.

3,4-Dimethoxybenzyldimethylamine. This was prepared by heating veratric aldehyde (56.9 g., 0.34 mole), dimethylformamide (99.3 g., 1.36 moles), and 90% formic acid (6.5 g.) for two hours at 150°. The temperature was then raised to 155–162° for three hours while water was allowed to distil out. The mixture was cooled, 45 g. of dimethylformamide and 3 g. of formic acid were added, and the mixture was boiled under reflux at 150–152° for two hours and then at 155–170° for 3½ hours during which period water was again allowed to distil out. The residue was cooled, acidified with 35 ml. of concentrated hydrochloric acid, extracted twice with ether, made basic by the addition of 150 ml. of 40% aqueous potassium hydroxide, and extracted three times with ether. The combined ether extracts were dried over sodium sulfate, concentrated, and the residue distilled at reduced pressure. 3,4-Dimethoxybenzyldimethylamine boiled at 113–119° (3 mm.) and was obtained in 38% yield (25.1 g.). The *methiodide* melted at 175–176°.

Anal. Calc'd for $C_{12}H_{20}INO_2$: C, 42.74; H, 5.98; N, 4.16.
Found: C, 43.07; H, 6.13; N, 3.92.

The literature (9) reports the b.p. for this amine as 132–137° (12 mm.) and the melting point of the methiodide as 179°.

A considerable amount of a higher-boiling base which solidified in the receiver was also obtained in this reaction, but the material was not identified.

p-Methoxybenzyldimethylamine. The preparation of this amine from anisaldehyde and dimethylformamide by the Leuckart reaction has been described (10). A mixture of 68 g. (0.5 mole) of anisaldehyde, 146 g. (2 moles) of dimethylformamide and 8.6 g. of 85% formic acid was heated at 180–190° for 15 hours. The mixture was worked up as described for the 3,4-dimethoxy compound to yield 46 g. (56%) of *p*-methoxybenzyldimethylamine, b.p. 105–119° (10 mm.); 73–77° (2 mm.). The literature (10) reports b.p. 99–104° (11 mm.). The *methiodide* melted at 155–156°.

Anal. Calc'd for $C_{11}H_{18}INO$: C, 43.00; H, 5.90.
Found: C, 43.49; H, 6.22.

p-Methylbenzyldimethylamine (11). Benzene (200 ml.) was cooled to the freezing point and gaseous dimethylamine was passed through it until 51.4 g. (1.14 moles) had been ab-

[3] Microanalyses by Clark Analytical Laboratories, Urbana, Illinois and Micro-Tech Laboratories, Skokie, Illinois.

sorbed. A solution of 67 g. (0.38 mole) of *p*-xylyl bromide in 100 ml. of benzene was added to the amine solution gradually and with stirring, which resulted in the precipitation of white crystals. The mixture was allowed to stand three days in a well-stoppered flask, then 200 ml. of 6 *N* hydrochloric acid was added and the layers were separated, ether being added to break the emulsion which tended to form. The organic layer was washed with four 50-ml. portions of 3 *N* hydrochloric acid and the acid layers in turn were cleared with 50 ml. of benzene, combined, and made alkaline by the addition of 250 ml. of 40% aqueous potassium hydroxide. The basic oil which separated was extracted with ether, and the extract was dried over potassium hydroxide pellets, concentrated, and distilled. *p*-Methylbenzyldimethylamine boiled at 196–197° at atmospheric pressure, n_D^{25} 1.499, yield 53.6 g. (94%). The literature records a boiling point of 197–198° (11). The *methiodide* melted at 210–211°—literature value (11) 208°. Attempts to prepare *p*-methylbenzyldimethylamine from *p*-tolualdehyde by the Leuckart reaction in analogy with the recently described synthesis of benzyldimethylamine from benzaldehyde (12) were unpromising.

p-Nitrobenzyldimethylamine. This compound was prepared in a manner analogous to that described above for the *p*-methyl compound (13). The *p*-nitrobenzyl chloride (100 g., 0.583 mole) was added slowly to an ice-cold solution of 78.4 g. (1.75 mole) of dimethylamine in 200 g. of benzene. After two days' standing, 100 ml. of 3 *N* hydrochloric acid was added and the mixture was processed as described above, to give 95.5 g. (91%) of *p*-nitrobenzyldimethylamine boiling at 140–146° (13–14 mm.). The literature (13) reports b.p. 146° at 16 mm.

p-Chlorobenzyldimethylamine. This was prepared as the *p*-nitro compound from 80 g. (0.5 mole) of *p*-chlorobenzyl chloride and 67.5 g. (1.5 mole) of dimethylamine in 150 ml. benzene. *p*-Chlorobenzyldimethylamine boiled at 90–95° (9–11 mm.); the yield was 67.7 g. (79%). The *picrate* melted at 127–129°—literature (14) m.p. 125–126°.

2,4-Dichlorobenzyl bromide. To a refluxing solution of 8.05 g. (0.05 mole) of 2,4-dichlorotoluene in 80 ml. of carbon tetrachloride illuminated with a 500-watt unfrosted tungsten

TABLE I

REACTION OF VARIOUS ALKYLDIMETHYLAMINES WITH METHYL *p*-NITROBENZOATE

Alkyl Group in Alkyldimethylamine	Reaction		Alkyl *p*-Nitrobenzoate Yield, % (crude)	M.P., °C. (Crude)	M.P., °C. (Purified)	Notes
	Time, hrs.	Temp., °C.				
Benzyl	6	170–200	97	77 – 82	83 – 84.5	*a*, *d*
p-Methoxybenzyl	29	130–140	55	87.5– 89.5	92 – 93	*b*
p-Chlorobenzyl	23	170	77	103.5–105.5	110 –111	*c*
Furfuryl	2.75	155–160	43	61 – 67	75.5– 76.5	*d*, *e*
5-Methylfurfuryl	6	*ca.* 150	16	65 – 74	82 – 82.5	*d*, *f*

[a] Ref. (1). All *p*-nitrobenzoates were isolated as described for benzyl *p*-nitrobenzoate in this ref. (p. 540).

[b] The literature (15) reports m.p. 93–94° for *p*-methoxybenzyl *p*-nitrobenzoate. Saponification of our product gave an alcohol, oxidized to an acid, m.p. 182–184° (*p*-anisic acid melts at 184°).

[c] *Anal.* Calc'd for $C_{14}H_{10}ClNO_4$: C, 57.64; H, 3.46. Found: C, 57.58; H, 3.51. Saponification yielded an alcohol of m.p. 70–71°. *p*-Chlorobenzyl alcohol is reported (16) to melt at 71–72.5°.

[d] Amine to ester ratio 2:1 mole.

[e] The literature (17) reports m.p. 75–77° for furfuryl *p*-nitrobenzoate. Our ester did not depress the melting point of an authentic sample.

[f] Undepressed by admixture with an authentic sample of 5-methylfurfuryl *p*-nitrobenzoate, prepared from the alcohol. Lit (23) m.p. 84–85°.

TABLE II

REACTION OF VARIOUS ALKYLDIMETHYLAMINES WITH METHYL *o*-CHLOROBENZOATE

Alkyl Group in Alkyldimethylamine	Reaction		Alkyl *o*-Chlorobenzoate Yield, %	B.P. (Crude), °C.	mm.	n_D^{25}, B.P. or M.P. (Purified)	Notes
	Time, hrs.	Temp., °C.					
Benzyl	8.5	170	72	153–155	1	1.5758	[a]
p-Methylbenzyl	49.5	190–210	91	140–163	0.5	189°/4.5 mm.	[b]
p-Methoxybenzyl	42	150–160	81	149–168	0.2	183.5°/0.1 mm. 1.5772	[c]
3,4-Dimethoxybenzyl	25–38	170–190	—	—		—	[d]
p-Nitrobenzyl	8.5	123–136	0.25	—		m.p. 105–106°	[e]
p-Chlorobenzyl	44	150–180	86	—		m.p. 56.5–57°	[f, g]
2,4-Dichlorobenzyl	34	185–195	74	—		m.p. 70–72°	[f, h]
Dodecyl	33	200	68	189–198	2	187–189/2 mm. 1.4938	[i]

[a] Ref. (1).

[b] *Anal.* Calc'd for $C_{15}H_{13}ClO_2$: C, 69.13; H, 5.03; Sapon. equiv., 260.7. Found: C, 69.71; H, 5.20; Sapon. equiv., 256.4. Saponification gave *o*-chlorobenzoic acid, m.p. 135.5–136°, undepressed by admixture with an authentic sample and *p*-methylbenzyl alcohol, m.p. 59–61°; Lit. (18) m.p. 60–60.5°.

[c] *Anal.* Calc'd for $C_{15}H_{13}ClO_3$: C, 65.10; H, 4.73. Found: C, 65.34; H, 4.97. Saponification gave an acid melting at 138–140° (*o*-chlorobenzoic acid is reported to melt at 142°) and alcohol oxidized to an acid melting at 182–184° (anisic acid is reported to melt at 184°).

[d] No 3,4-dimethoxybenzyl *o*-chlorobenzoate could be isolated by distillation, apparently because of decomposition. However, hydrolysis of the crude reaction product yielded *o*-chlorobenzoic acid and a viscous neutral material, identified as 3,4-dimethoxybenzyl alcohol by its *p*-nitrobenzoate, m.p. and mixture m.p. with an authentic sample 106–107°. Lit. (15) m.p. 108–109°.

[e] The crude reaction product was an oil. Steam-distillation removed unchanged methyl ester; the product then was isolated from the distillation residue by recrystallization from ethanol. After three further recrystallizations the substance had the melting point indicated and did not depress the melting point of an authentic specimen prepared from sodium *o*-chlorobenzoate and *p*-nitrobenzyl chloride (19). The literature (20) reports m.p. 106° for *p*-nitrobenzyl *o*-chlorobenzoate.

[f] Since these products were solids, the reaction mixture was processed as described for the *p*-nitrobenzoates; cf. ref. (1) p. 549.

[g] *Anal.* Calc'd for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 60.07; H, 3.78. Saponification gave an acid melting at 138–140° (reported for *o*-chlorobenzoic acid 142°) and an alcohol melting at 69–71° (reported for *p*-chlorobenzyl alcohol (16) 71–72.5°).

[h] *Anal.* Calc'd for $C_{14}H_9Cl_3O_2$: C, 53.27; H, 2.87. Found: C, 53.60; H, 2.87. Saponification gave *o*-chlorobenzoic acid and an alcohol melting at 60–61°. Since 2,4-dichlorobenzyl alcohol is not a known compound it was analyzed: Calc'd for $C_7H_6Cl_2O$: C, 47.50; H, 3.42. Found: C, 47.88; H, 3.76.

[i] *Anal.* Calc'd for $C_{19}H_{29}ClO_2$: C, 70.25; H, 8.99. Found: C, 70.88; H, 8.88. Saponification gave *o*-chlorobenzoic acid, m.p. 138–139° and dodecyl alcohol, characterized by its 3,5-dinitrobenzoate, m.p. 60°, Lit. (21) 60°.

lamp was added 7.99 g. (0.05 mole) of bromine dissolved in 80 ml. of carbon tetrachloride at such a rate that the red bromine color persisted until after all the halogen had been added (*ca.* 20 minutes). When the bromine color was completely discharged, the solution was fractionally distilled under reduced pressure. The product was collected at 126–133° (8 mm.) and weighed 10.2 g. (85%). Because of its strongly lachrymatory properties it was not analyzed but was used immediately in the next step.

2,4-Dichlorobenzyldimethylamine. This was prepared in the same manner as the *p*-chloro compound from 49 g. (0.2 mole) of 2,4-dichlorobenzyl bromide and 27.6 g. (0.6 mole) of dimethylamine in 100 ml. benzene. The product boiled at 82–88° (1 mm.) and weighed 25.7 g. (62%). The *picrate* melted at 140.5–142°:

Anal. Calc'd for $C_{15}H_{14}Cl_2N_4O_7$: C, 41.59; H, 3.26; N, 12.93.
Found: C, 41.54; H, 3.42; N, 12.64.

Reaction of amines with esters. The general procedure previously described (1) was followed, the mixture of the amine (generally 0.125 mole) and ester (0.1 mole) being heated under nitrogen at the temperatures and for the times indicated in Tables I and II. Basic materials were extracted from the products with acid and the neutral products were fractionated by distillation or crystallization. Yields and physical constants and manner of identification of the neutral products are indicated in Tables I (*p*-nitrobenzoates) and II (*o*-chlorobenzoates).

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SUMMARY

The reaction of methyl *p*-nitrobenzoate and methyl *o*-chlorobenzoate with a number of substituted benzyldimethylamines and related compounds has been investigated. In most cases, the reaction follows the pattern previously established for benzyldimethylamine itself; *i.e.* trimethylamine and substituted benzyl *p*-nitrobenzoates (or *o*-chlorobenzoates) are obtained. The non-benzylic N,N-dimethyldodecylamine reacts analogously with methyl *o*-chlorobenzoate to yield dodecyl *o*-chlorobenzoate.

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