New Carbamates and Related Compounds

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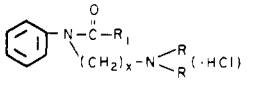
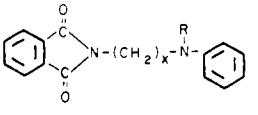
The preparation of 19 *N,N*-dialkylaminoalkylanilinocarbamate hydrochlorides, *N*-phenyl-*N*-(phthalimidoalkyl)carbamoyl halides, and related compounds is reported. Ethyl *N*-(2-chloroethyl)-*N*-phenylcarbamate was distilled (80% yield) without decomposition to oxazolidone as previous investigators had reported with such halocarbamates.

DATA on some new urethanes, *N,N*-dialkylaminoalkylanilinocarbamate hydrochlorides (I, R = H or alkyl, R_1 = alkoxy or aryloxy), *N*-phenyl-*N*-(phthalimidoalkyl)carbamoyl halides (II, R = —COX, x = 2, 3), and related compounds

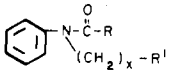


I



II

—i.e., III, IV and V are outlined in this paper.



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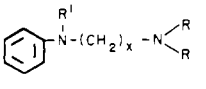

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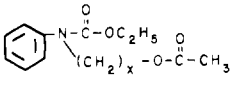


V

The compounds were needed for the continuation of authors' chemical studies (*1, 5, 7, 13, 14*).

Care should be exercised in working with all of the halogen phthalimido compounds; sensitive individuals may experience severe contact dermatitis.

EXPERIMENTAL

Tables I and II give constants of the new compounds.

Anilinoalkylamines. The anilinoethyl halides were prepared according to published directions (*15, 20, 24*) from commercially available anilinoethanol.

The *N*-(dialkylaminoethyl)anilines (IV, R′ = H, R = alkyl, x = 2,3) were prepared from the anilinoethyl halide by reaction with the desired dialkylamine (*4, 8, 17*).

The higher members of the homologous series of IV, x > 2, were not made easily from the intermediate halides because of ring closure, and were prepared, therefore, by reaction of aniline with the haloalkynitrile to yield the anilinoalkyl cyanides (*10, 25*). These cyanides were reduced to the amines by the use of high pressure and a Raney nickel catalyst (*25*). Lithium aluminum hydride reduction also was used according to the directions of Nystrom and Brown (*9, 19*) except that dilute hydrochloric acid instead of sodium potassium tartrate was used to hydrolyze the lithium aluminum complex. Since these diamines are soluble in both ether and water, a minimum of water was employed.

N-Phenyl-N-(alkylphthalimido)-N-carbamoyl Halide (II, R = COX, x = 2,4). These compounds were synthesized via the reaction of phosgene with the anilinoalkylphthalimides, according to the directions of Raiford and Alexander (*21*). The fluoro derivatives were made by reacting the chloro compounds with antimony trifluoride (*18*).

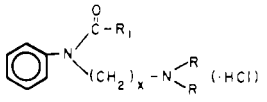
Ethyl *N*-Phenyl-*N*-(2-phthalimidoethyl)carbamate (II, R = —C(=O)—OC_2H_5, x = 2). This carbamate was prepared from the anilinoethylphthalimide (*2, 24*) and ethyl chloroformate according to published directions (*6, 11, 12, 17, 27*). The final product was obtained pure only after many recrystallizations. Other similar carbamates, not reported, were used as intermediates after several recrystallizations if their analytical data were reasonable.

Alkyl or Aryl *N*-Phenyl-*N*-(dialkylaminoalkyl)carbamate, Hydrochloride (I, R = alkyl, R_1 = alkoxy or aryloxy, x = 2,3). The following synthesis of phenyl *N*-phenyl-*N*-(2-diethylaminoethyl)carbamate, hydrochloride is typical for this series.

Approximately 20 grams, (0.1 mole) of *N*-(diethylaminoethyl) aniline (IV, R′ = H, R = ethyl) was placed in a 500-ml., three-necked round-bottomed flask equipped with a mechanical stirrer, drying tube, condenser, and dropping funnel; dry ethyl acetate, 250 ml., was added, and the mixture was cooled to about 20° C. (No appreciable difference in yield was observed when the reactions were run at any temperature between 5° and 25° C.) Phenyl chloroformate (16 grams, 0.1 mole) was added dropwise to the well-stirred mixture; precipitation of the carbamate-hydrochloride occurred immediately. The whole was stirred at 25° C. for 3 hours, filtered, and the recovered crystals were washed with dry ethyl acetate and ether. After drying in vacuo over $CaCl_2$ and recrystallizing three times from ethyl acetate plus a small amount of absolute ethanol, a pure product was obtained.

Hydrolysis Rate of Carbamates. The above phenyl- or *p*-nitrophenyl *N*-phenyl-*N*-(2-diethylaminoethyl)carbamate was placed in buffered 0.066*M* sodium phosphate at pH 8.30. The half-life of the phenyl carbamate was 15 minutes which gives a first-order hydrolysis constant of 4.9×10^{-2} per minute. The hydrolysis of

Table I. New Carbamates and Halocarbamides



No.	Empirical Formula	R	R_1	X	M.P., ° C.	Yield, %
1	$C_{17}H_{13}FN_2O_3$	OCC_6H_4CO	F	2	118–122 (Alcohol)	56
2	$C_{19}H_{17}ClN_2O_3$	OCC_6H_4CO	Cl	4	98–100 (Heptane-benzene)	79
3	$C_{19}H_{18}N_2O_4$	OCC_6H_4CO	OC_2H_5	2	82–84 (Isopropanol)	69
4	$C_{18}H_{20}N_2O_2$	$C_6H_5CH=$	OC_2H_5	2	118–119 (Ethanol-water)	36
5	$C_{11}H_{16}N_2O_2 \cdot HCl$	H	OC_2H_5	2	139–142 dec. (Ethanol-ether)	28
6	$C_{19}H_{24}N_2O_2 \cdot HCl$	C_2H_5	OC_6H_5	2	158–160 dec. (Ethyl acetate–ether)	91
7	$C_{19}H_{23}N_3O_4 \cdot HCl$	C_2H_5	$OC_6H_4NO_2$-*p*	2	135–137 dec. (Ether-ethanol)	Quant.
8	$C_{14}H_{22}N_2O_2 \cdot HCl$	CH_3	OC_2H_5	3	140–141 dec. (Ethyl acetate–ethanol)	93
9	$C_{18}H_{22}N_2O_2 \cdot HCl$	CH_3	OC_6H_5	3	220–223 dec. (Ethyl acetate–ethanol)	89

	Analyses %							
	C		H		N		Halogen	
No.	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	65.38	65.20	4.19	4.43	8.97	8.94	6.08	6.23
2	63.95	63.69	4.80	4.78	7.85	7.77	9.95	10.12
3	67.44	67.42	5.36	5.09	8.28	8.12		
4	72.95	72.93	6.80	7.30	9.45	9.41		
5	53.98	53.55	7.00	7.16	11.45	11.28	14.49	14.47
6	65.41	65.89	7.22	7.16	8.03	8.29	10.16	10.27
7	57.94	58.09	6.14	5.89	10.67	10.56	9.00	9.21
8	58.63	58.61	8.08	7.89	9.77	9.86	12.36	12.51
9	64.56	64.55	6.92	6.57	10.59	10.96	8.36	8.53

the *p*-nitrophenyl compound was so rapid that an accurate hydrolysis constant could not be obtained; its half life was probably less than a minute at 37° C.

The *p*-nitrophenoxy group, then, may be useful as another amino group blocking agent (*3*).

Ethyl *N*-(2-Chloroethyl)-*N*-phenylcarbamate(III, R = ethoxy, R′ = Cl, x = 2). Approximately 1.5 moles of anilinoethyl chloride, in stirred excess pyridine (160 ml.), and dry benzene at 10° C., was treated dropwise with 1.5 moles of ethyl chloroformate. After stirring at 25° C. for several hours, cold water was added slowly, and the benzene layer was washed with dilute hydrochloric acid, aqueous saturated sodium bicarbonate, and saturated sodium chloride.

The benzene layer was dried over anhydrous sodium sulfate, then filtered and the solvent removed in vacuo. The residue was rapidly distilled in vacuo and the fraction that came over between 108° to 140° C. at 0.3 to 1.5 mm., was redistilled, and that portion boiling at 115° C. at 0.7 mm. was the desired compound.

From the residue left in the flask usually 10 to 30% of quite pure 3-phenyl-2-oxazolidone (*2*, *16*, *23*) was recovered.

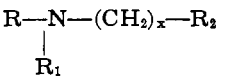
5-Anilinopentyl Acetate. Approximately 300 grams (1.83 mole) of 5-chloropentyl acetate was added to 341 grams (3.66 mole) of aniline and 600 ml. of water, and the whole was refluxed gently for 18 hours. After cooling, the mixture was extracted several times with ether; the ether layer was then washed twice with cold water. The ether was removed and the residue distilled.

Ethyl *N*-(5-Acetoxypentyl)-*N*-phenylcarbamate (V, x = 5). This urethan was prepared from equivalent amounts of the above anilinopentyl acetate, triethyl amine, and ethyl chloroformate in dry benzene, similar to the preparation of the nitriles (*10*, *25*).

***N*-Acetyl-*N*′-(carboethoxy)hexane.** There was added to a 500-ml. three-necked round-bottomed flask, equipped with a condenser, stirrer, dropping funnel and drying tube, 50 grams (0.3 mole) of monoacetyl hexamethylenediamine, 25.4 grams (0.32 mole) of dry pyridine, and 60 ml. of toluene. The whole was cooled to 5° C. and 35 grams (0.32 mole) of ethyl chloroformate was added dropwise over a period of 2 hours with constant stirring. Then, during an additional 2-hour period, 150 ml. of toluene was added, and the mixture stood overnight at room temperature.

About 100 ml. of cold water was added, and the mixture was filtered. The residue was washed with cold water, dried, and recrystallized several times.

Table II. Reaction Intermediates



No.	Empirical Formula	R	R_1	R_2	X	M.P. or B.P. (Mm.) n_d, 25° C.	Yield, %
1	$C_{11}H_{18}N_2$ (*27*)	C_6H_5	H	$N(CH_3)_2$	3	89–95(0.3) 1.5343	60
2	$C_{12}H_{20}N_2$ (*26*)	C_6H_5	H	$N(C_2H_5)_2$	2	77–82(0.3) 1.5283	43
3	$C_{12}H_{20}N_2$	C_6H_5	H	NH_2	6	122–130(0.08) 1.5469	41
4	$C_{12}H_{20}N_2 \cdot 2HCl$	C_6H_5	H	NH_2	6	211–215 dec. (ether-ethanol)	Quant.
5	$C_{20}H_{22}N_2O_2$	C_6H_5	H	$C_6H_4(CO)_2N-$	6	67–68 (aqueous ethanol)	46
6	$C_{11}H_{14}N_2$ (*22*)	C_6H_5	H	CN	4	39–41 (ethanol)	39
7	$C_{11}H_{14}ClNO_2$	C_6H_5	$-C(=O)-OC_2H_5$	Cl	2	115(0.7) 1.5209	76
8	$C_{13}H_{19}NO_2$	C_6H_5	H	$OC(=O)-CH_3$	5	155–169(0.8) 1.5289	47
9	$C_{16}H_{23}NO_4$	C_6H_5	$-C(=O)-OC_2H_5$	$OC(=O)-CH_3$	5	148–160(0.3) 1.4936	64
10	$C_{11}H_{22}N_2O_3$	$CH_3C(=O)-$	H	$N(H)-C(=O)-OC_2H_5$	6	82–83 (ethyl acetate)	40

	Analyses %							
	C		H		N		Cl	
No.	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	74.10	74.45	10.17	9.81	15.71	15.57		
2	74.94	74.22	10.48	9.97	14.57	14.11		
3	74.94	74.98	10.48	10.44	14.57	14.16		
4	54.34	54.28	8.36	8.10	10.56	10.47	26.73	27.49
5	74.50	74.27	6.88	6.87	8.69	8.79		
6					16.08	15.27		
7	58.02	58.02	6.20	6.27	6.15	6.41	15.57	15.39
8	70.55	70.39	8.65	8.45	6.33	6.43		
9	65.51	65.76	7.90	8.34	4.78	5.17		
10	57.36	57.52	9.63	10.26	12.17	12.22		

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5-(1,1-Dinitroethyl)-2-picoline from the Reaction of 5-Ethyl-2-picoline with Nitric Acid

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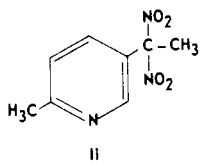
Investigation of the nitric acid oxidation of 5-ethyl-2-picoline revealed the presence of a new substance, 5-(1,1-dinitroethyl)-2-picoline. The latter may be an intermediate in the preparation of nicotinic acid. The substantial yield at moderate temperatures makes this a useful preparative method.

DURING the course of an investigation of the oxidation of 5-ethyl-2-picoline, I, with nitric acid, the authors discovered that a new compound, 5(1,-dinitroethyl)-2-picoline, II, was formed also in respectable yields. This reaction product was obtained



II

from the reaction of 5-ethyl-2-picoline and nitric acid in an autoclave, a tubular reactor, and in simple laboratory glassware. Although these three modes of preparation give different yields of II along with the expected pyridine carboxylic acids, they are similar in that the *gem* dinitro compound is the only significant nitration product. This is shown by an almost quantitative product accountability as described in the experimental section.

There are several methods in the literature for the preparation of *gem* dinitro compounds (*4, 13, 17*). The most useful of these employ the nitro halogen moiety as the starting material as in the Ter Meer reaction (*5, 14*) or the oxidative nitration (*6, 8*) and electrolytic coupling (*1*). Other methods involving the nitration of esters (*3, 9*), conversion of α-oximino esters (*18*), aldoximes (*10*), and olefins (*7, 13*) are reported also for the preparation of *gem* dinitro compounds.

The work of Titov (*15, 16*) and McIntyre (*12*) illustrate two of the few cases reported where the direct nitration of alkyl groups gives *gem* dinitro compounds. The yields for this reaction vary widely and a mixture of nitration products are isolated. Pertinent results from the reaction of 5-ethyl-2-picoline with nitric acid are recorded in Table I.

The authors' data indicate that prolonged residence times at elevated temperatures in the tubular reactor—compare 4, 5, 6 and 8, 9, Table I—in the autoclave—

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