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.

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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-

(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.

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TABLE I

ALKYL N-SUBSTITUTED CARBAMATES, RNHCOOR'

R	R'	B.p., °C.	Mm.	M.p. °C.	Yield, %	Nitrogen, % Calcd.	Found	Method
β-Phenylethyl	Methyl	118–124	0.5	29.5–31[a]	93.0	7.81	7.58	A
β-Phenylethyl	Ethyl	.....	...	35–35.5[b]	96.5	7.25	7.33	A
β-Phenylethyl	*n*-Propyl	127–135	2.5	.....	86.0	6.76	6.61	A
β-Phenylethyl	Isopropyl	.....	...	29.5–30[c]	83.7	6.76	6.48	A
β-Phenylethyl	*n*-Butyl	125–135	0.5	6–7	80.5	6.33	6.44	A
β-Phenylethyl	Isobutyl	....	...	31–32[d]	91.5	6.33	6.25	A
α-Methyl-β-phenylethyl-	Methyl	111–120	0.3	.....	77.3	7.25	7.06	A
α-Methyl-β-phenylethyl-	Ethyl	110–120	0.3	23–23.5[e]	92.7	6.76	6.60	A
α-Methyl-β-phenylethyl-	*n*-Propyl	126–134	0.5	.....	87.5	6.33	6.26	A
α-Methyl-β-phenylethyl	Isopropyl	.....	...	50–51[f]	75.0	6.33	6.22	A
α Methyl-β-phenylethyl-	*n*-Butyl	131–138	0.4	.....	96.5	5.95	5.87	A
α-Methyl-β phenylethyl-	Isobutyl	.....	...	35–36[d]	80.0	5.95	5.90	A
2-Pyridyl-	Methyl	.....	...	131–132[g]	30.0	18.40	18.37	B
2-Pyridyl-	Ethyl	.....	...	104–105[i,p]	51.5	13.83	13.53[i]	C
2-Pyridyl-	*n*-Propyl	.....	...	74–75[i]	29.0	15.55	15.58	B
2-Pyridyl-	Isopropyl	.....	...	82–83[i]	30.8	15.55	15.76	B
2-Pyridyl-	*n*-Butyl	.....	...	62–63[k]	26.0	14.43	14.72	B
2-Pyridyl-	Isobutyl	.....	...	74–76[k,m]	22.0	14.43	14.50	B
3-Pyridyl-	Methyl	.....	...	120–122[h]	78.5	18.40	18.38	D
3-Pyridyl	Ethyl	.....	...	91–92[l,r]	73.0	16.95	16.86	D
3 Pyridyl-	*n*-Propyl	.....	...	82–83[h]	69.0	15.55	15.73	D
3-Pyridyl-	Isopropyl	.....	...	137–139[n]	62.7	15.55	15.65	A
3-Pyridyl-	*n*-Butyl	.....	...	71–72[l]	44.5[q]	14.42	14.44	D
3-Pyridyl-	Isobutyl	.....	...	103–105[n,q]	61.0	14.42	14.70	D

[a] Melting point of solidified distillate. [b] Thick white needles from ligroin. Weerwan and Jongkees[9] observed a melting point of 34–35°. [c] Thick white rods from benzene–ligroin. [d] Fine white powder from ligroin. [e] A sample of the distillate when crystallized from ligroin have fine white needles. [f] Fine white needles from ligroin. [g] From ethyl acetate. [h] From methanol–water. [i] Analysis of the hydrochloride. [j] From methanol. [k] The crude product was purified by extracting the material with carbon tetrachloride such that approximately ⅔ was dissolved at room temperature. After filtering, the solvent was evaporated and the residue dissolved in dilute HCl. Precipitation with dilute NaOH, filtering and washing with water gave the pure product. [l] From water. [m] From carbon tetrachloride. [n] Plates from ligroin. [p] Camps[10] observed a melting point of 105°. [q] A 10% molar excess of both sodium and bromine gave the best yield. [r] Camps[10] gave m.p. of 90° and Curtius and Mohr[11] 86–87°.

wise, with vigorous stirring, a solution of 16.7 g. (0.1 mole) of 2-aminopyridine in 250 ml. of benzene. A white precipitate formed and finally the whole mass was a thick paste. Stirring was continued in the cold for one-half hour. The mixture was then heated, and upon reaching the reflux temperature the solid decomposed with evolution of carbon dioxide and formation of a yellow oil. After refluxing for 2 hours, the mixture was cooled to room temperature whereupon the oil crystallized. The clear benzene layer was poured off and set aside. The crystalline cake was converted to a yellow solid by digestion with sodium carbonate solution. After filtering, washing with water, drying and recrystallizing from benzene, 0.1 g. of N,N'-(2,2-dipyridyl)-urea m.p. 166–167° was obtained.

Anal. Calcd. for $C_{11}H_{10}ON_4$: N, 26.15. Found: N, 26.04.

The alkaline mother liquor was acidified with hydrochloric acid and concentrated. Treatment with anhydrous sodium carbonate followed by extraction of the mass with ether, yielded the unreacted 2-aminopyridine.

The benzene layer from the reaction mixture was distilled to remove the solvent. The remainder, a yellow oil which crystallized on cooling, was washed with sodium carbonate solution, then with water and dried giving 13 g., m.p. 90–100°. The crude product was recrystallized twice from methanol–water giving 10 g. (34%) of ethyl N-(2-pyridyl)-carbamate. The methanol–water mother liquor yielded on evaporation 2.1 g. of a mixture of carbamate and dipyridylurea.

Method C.—This procedure was carried out in the same manner as Method B except that 21.7 g. (0.2 mole) of ethyl chlorocarbonate was treated with 37.6 g. (0.4 mole) of 2-aminopyridine. After working up in the same manner, there was obtained 17.1 g. (51.5%) of ethyl N-(2-pyridyl)-carbamate, 3.3 g. of dipyridylurea and 17.1 g. of recovered 2-aminopyridine.

Method D.—An ice-cold suspension of 12.2 g. (0.1 mole) of nicotinamide in solution of 4.6 g. (0.2 mole) of sodium in 235 ml. of ethanol was treated dropwise with 16.0 g. (0.1 mole) of bromine with vigorous stirring. After heating on a steam-bath for 45 minutes, the alcohol was removed by vacuum distillation. The residue was treated with 125 ml. of water whereupon an oil formed which solidified on cooling. The cake was broken up, filtered, washed twice with water and dried giving 12 g. of the carbamate. Saturation of the mother liquor with sodium chloride yielded an additional 2.0 g. of carbamate. The crude product was decolorized with charcoal and recrystallized from water yielding 12.1 g. (73%) of ethyl N-(3-pyridyl)-carbamate, m.p. 91–92°.

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