hydrogenolysis over 2 g. of 10% palladium-on-charcoal in 100 ml. of reagent grade dioxane at 50° and 40 p.s.i.g. for 6 hr. The reaction mixture was heated, filtered to remove the catalyst and diluted with water to incipient turbidity. Upon cooling, there separated a colorless crystalline product, which was collected by filtration; yield 1.35 g. (88.5%), m.p. 227–229° (cor.). Recrystallization from 95% ethanol gave the analytically pure acid, m.p. 229–230° (cor.).

Anal. Calcd. for $C_{15}H_{12}O_7S$: C, 53.57; H, 3.59; S, 9.53. Found: C, 53.77; H, 3.66; S, 9.23.

Benzyl *p*-[*p'*-(*p''*-**Mesyloxybenzoyloxy**)-**benzoyloxy**]-**benzoate** (**V**).—*p*-(*p'*-Mesyloxybenzoyloxy)-benzoic acid (2.2 g., 0.0064 mole) was added to a solution of mesyl chloride (0.74 g., 0.0064 mole) in 15 ml. of pyridine, protected from atmospheric moisture and permitted to stand at 26° for 2 hr. Benzyl *p*-hydroxybenzoate (1.47 g., 0.0064 mole) then was added to the mixture thus prepared and the resulting mixture permitted to stand for 24 hr. The crude product was isolated in the usual manner by pouring the mixture into 200 ml. of 6 *N* hydrochloric acid. Recrystallization from methanol gave glistening white plates of the benzyl ester; yield 1.84 g. (51% based on *p*-(*p'*-mesyloxybenzoyloxy)-benzoic acid), m.p. 136–140° (cor.). Repeated crystallization from methanol and ethyl acetate gave the analytically pure ester, m.p. 139.5–140.5° (cor.).

Anal. Calcd. for $C_{29}H_{22}O_9S$: C, 63.73; H, 4.06; S, 5.87. Found: C, 63.84; H, 4.30; S, 6.02.

p-[*p'*-(*p''*-**Mesyloxybenzoyloxy**)-**benzoyloxy**]-**benzoic Acid** (**VI**).—Benzyl *p*-[*p'*-(*p''*-mesyloxybenzoyloxy)-benzoyloxy]-benzoate (1.5 g.) was subjected to hydrogenolysis over 1.36 g. of 10% palladium-on-charcoal as previously outlined. Isolation in the usual manner gave 1.14 g. (92%) of the acid, m.p. 254–257° (uncor.). Recrystallization from glacial acetic acid gave the colorless, crystalline, analytically pure acid, m.p. 257–259° (uncor.).

Anal. Calcd. for $C_{22}H_{16}O_9S$: C, 57.89; H, 3.53. Found: C, 58.34; H, 3.56.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES INC.]

Benzylphenol Derivatives. VIII.[1] Carbamates

BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, JR., GERALD F. STINER AND LEE C. CHENEY

RECEIVED JULY 23, 1956

A series of quaternary ammonium salts derived from N,N-dialkylcarbamates of phenolic Mannich bases is described; a number of these compounds display either parasympathomimetic or curare-like action. Several N-substituted carbamates of benzylphenols are also described.

Our investigation of the benzylphenols as starting materials for the synthesis of physiologically active compounds has continued and we wish to report the preparation of a number of N-substituted carbamates.

The fact that neostigmine, a parasympathomimetic agent, is a dimethylcarbamate of a phenolic quaternary ammonium compound,[2] and that the benzylphenols readily participate in the Mannich reaction[1] prompted us to prepare a series of quaternary ammonium compounds as follows: benzylphenol → phenolic Mannich base → N,N-dialkylcarbamate → quaternary.

Because of the thermal instability of the phenolic Mannich bases, most of them were not purified but were used in the crude form for the subsequent reaction. Two exceptions were 2-benzyl-4-chloro-6-dimethylaminomethylphenol, which could be crystallized,[1] and 4-benzyl-2-diethylaminomethylphenol, which was isolated as the crystalline hydrochloride. Conversion to the N,N-dialkylcarbamates was accomplished in fair yields by heating the appropriate phenol with an N,N-dialkylcarbamyl chloride or N,N-dialkylthiocarbamyl chloride. These reactions were carried out in pyridine on the steam-bath for some 16 hours; no attempts were made to recover any unreacted phenols. Quaternization (Tables I and II) proceeded with ease by treating the tertiary amino carbamates with an excess of methyl or ethyl iodide in a polar solvent such as isopropyl alcohol.

N,N-Disubstituted carbamates of the non-basic phenols, 2- and 4-benzylphenol and 2-benzyl-4-chlorophenol, were prepared similarly from the phenol and carbamyl chloride (Table III). In all these reactions, the yields reported represent only one experiment, and thus may not indicate the maximum yield possible. The two N-monosubstituted carbamates in Table III (19 and 20) were prepared by heating 4-benzylphenol with an isocyanate in an inert solvent. A few drops of triethylamine was added as a catalyst in the case of ethyl isocyanate. Appreciable amounts of 4-benzylphenol were recovered from these reactions.

Pharmacology.—Pharmacologic tests carried out with these compounds have shown that those in Table I exhibit curare-like properties. Although this activity is slight in most cases [3-benzyl-2-(dimethylcarbamyloxy)-benzyl] trimethylammonium iodide (compound 1) is quite effective in producing curare-like paralysis at low doses.

The compounds in Table II tend to exhibit neostigmine-like activity with [5-benzyl-2-(dimethylcarbamyloxy)-benzyl]-trimethylammonium iodide (compound 6) and [5-benzyl-2-(dimethylcarbamyloxy)-benzyl]-diethylmethylammonium iodide (compound 8) being practically as effective as neostigmine.

Acknowledgment.—The authors are indebted to Dr. H. L. Dickison for the above information on the pharmacologic activity of these compounds. Analyses were performed by Mr. R. M. Downing.

Experimental[3]

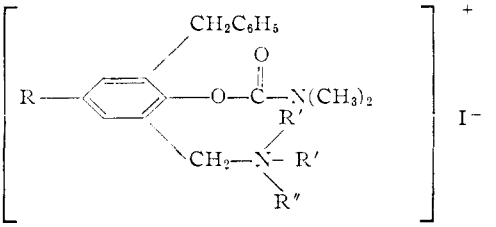
Phenolic Mannich Bases.—The preparation of 2-benzyl-6-dimethylaminomethylphenol and 2-benzyl-4-chloro-6-dimethylaminomethylphenol has been described previously.[1] In the same manner Mannich reactions were carried out to give three more basic phenols.

(1) Paper VII, W. B. Wheatley and L. C. Cheney, THIS JOURNAL, **74**, 2940 (1952).

(2) J. A. Aeschlimann and M. Reinert, *J. Pharm. Exp. Therap.*, **43**, 413 (1931).

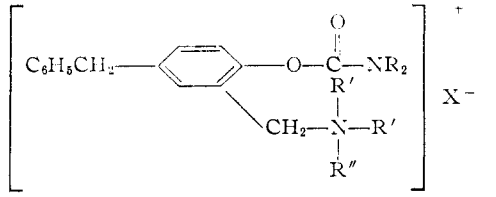
(3) Melting points and boiling points are uncorrected.

TABLE I



Cmpd.	R	R′	R″	Yield, %	M.p., °C.	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	H	CH_3	CH_3	76	206.0–209.0	*i*-PrOH–MeOH	$C_{20}H_{27}IN_2O_2$	52.9	52.8	6.0	6.1
2	H	CH_3	C_2H_5	61	188.0–190.0	*n*-BuOH	$C_{21}H_{29}IN_2O_2$	53.8	54.1	6.2	6.5
3	H	C_2H_5	CH_3	47	162.0–165.0	*n*-BuOH–EtOAc	$C_{22}H_{31}IN_2O_2$	54.8	55.1	6.5	6.6
4	Cl	CH_3	CH_3	51	224 dec.	MeOH–Et_2O	$C_{20}H_{26}ClIN_2O_2$	49.1	49.2	5.4	5.4
5	Cl	CH_3	C_2H_5	34	185.0–188.0	*i*-PrOH–EtOAc	$C_{21}H_{28}ClIN_2O_2$	50.2	49.6	5.6	5.9

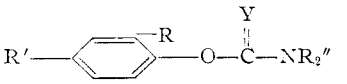
TABLE II



Cmpd.	R	R′	R″	X	Yield, %	M.p., °C.	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
6	CH_3	CH_3	CH_3	I	68	150.0–152.0[a]	Me_2CO–EtOAc	$C_{20}H_{27}IN_2O_2$	52.9	52.8	6.0	5.9
7	CH_3	CH_3	C_2H_5	I	51	148.0–150.0	*n*-BuOH–EtOAc	$C_{21}H_{29}IN_2O_2$	53.8	53.6	6.2	6.3
8	CH_3	C_2H_5	CH_3	I	73	114.0–118.0	*i*-PrOH–EtOAc	$C_{22}H_{31}IN_2O_2$	54.8	55.2	6.5	6.6
9	CH_3	C_2H_5	C_2H_5	I	56	132.0–134.0	*i*-PrOH–EtOAc	$C_{23}H_{33}IN_2O_2$	55.7	55.8	6.7	6.8
10	C_2H_5	C_2H_5	CH_3	I	91	131.5–133.5	*i*-PrOH–EtOAc	$C_{24}H_{35}IN_2O_2$	56.5	56.5	6.9	7.1
11	CH_3	CH_3	CH_2CH_2Br	Br	65	187.0–189.0	*i*-PrOH	$C_{21}H_{28}Br_2N_2O_2$	50.4	50.5	5.6	5.9

[a] A higher melting form, 171.5–173.5°, was obtained from a later experiment.

TABLE III



Cmpd.	R	R′	Y	NR_2''	Method	Yield, %	B.p., °C.	Mm.	$n^{30}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
12	$C_6H_5CH_2$	H	O	$N(CH_3)_2$	A	48	177–179	1.4	1.5655	$C_{16}H_{17}NO_2$	75.3	75.4	6.7	6.8
13	$C_6H_5CH_2$	H	S	$N(C_2H_5)_2$	A	31	189–193	1.4	1.5938	$C_{18}H_{21}NOS$	72.2	71.8	7.1	7.2
14	$C_6H_5CH_2$	Cl	O	$N(CH_3)_2$	A	59			[c]	$C_{16}H_{16}ClNO_2$	66.3	66.4	5.6	5.5
15	$C_6H_5CH_2$	Cl	S	$N(C_2H_5)_2$	A	39	187–204	1	1.5950	$C_{18}H_{20}ClNOS$	64.8	64.8	6.0	6.1
16	H	$C_6H_5CH_2$	O	$N(CH_3)_2$	A	51	180–185	1	1.5712	$C_{16}H_{17}NO_2$	75.3	75.2	6.7	6.6
17	H	$C_6H_5CH_2$	S	$N(C_2H_5)_2$	A	47	205–220	1	1.5912	$C_{18}H_{21}NOS$	72.2	72.2	7.1	7.3
18	H	$C_6H_5CH_2$	O	$N(C_2H_5)_2$	A	60	176–179	1	1.5530	$C_{18}H_{21}NO_2$	76.3	76.6	7.5	7.4
19	H	$C_6H_5CH_2$	O	NHC_2H_5	B	36[a]			[d]	$C_{16}H_{17}NO_2$	75.3	75.2	6.7	6.7
20	H	$C_6H_5CH_2$	O	NHC_6H_5	B	38[b]			[e]	$C_{20}H_{17}NO_2$	79.2	79.2	5.7	5.8

[a] 46% 4-benzylphenol recovered. [b] 53% 4-benzylphenol recovered. [c] M.p. 113.0–115.0°, recrystallized from methanol. [d] M.p. 110.0–111.5°, recrystallized from cyclohexane. [e] M.p. 128.5–130.0°, recrystallized from cyclohexane.

2-Benzyl-6-diethylaminomethylphenol, from 2-benzylphenol, formalin and diethylamine, was obtained in 68% yield as the crude product and used as such without purification.

4-Benzyl-2-dimethylaminomethylphenol, obtained in 88% yield from 4-benzylphenol, formalin and dimethylamine, likewise was not purified.

4-Benzyl-2-diethylaminomethylphenol, from 4-benzylphenol, formalin and diethylamine, was isolated as the slightly soluble hydrochloride, which crystallized on attempted extraction with dilute hydrochloric acid while working up the reaction mixture. After recrystallization from isopropyl alcohol, the hydrochloride melted at 147.5–149.0° (64% yield).

Anal. Calcd. for $C_{15}H_{23}NO\cdot HCl$: C, 70.6; H, 7.9. Found: C, 70.7; H, 7.9.

N,N-Dialkylcarbamates of the Phenolic Mannich Bases.—In a typical example, a solution of 22.0 g. (0.09 mole) of 2-dimethylaminomethyl-6-benzylphenol and 12.9 g. (0.12 mole) of N,N-dimethylcarbamyl chloride in 40 ml. of pyridine was heated on the steam-bath for 24 hours. The cooled solution was poured into water and made strongly basic with sodium hydroxide. Extraction with ether, followed by distillation of the combined and dried extracts, gave 20.8 g. (73% yield) of 2-dimethylaminomethyl-6-benzylphenyl N,N-dimethylcarbamate as a light yellow oil, b.p. 154-163° (1 mm.), $n^{20}D$ 1.5540.

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.0; H, 7.7. Found: C, 73.4; H, 7.8.

In a similar manner were prepared the following carbamates.

2-Diethylaminomethyl-6-benzylphenyl N,N-dimethylcarbamate, b.p. 196–201° (1 mm.), 84% yield, $n^{20}D$ 1.5494. *Anal.* Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.1; H, 8.3. Found: C, 74.5; H, 8.2.

4-Chloro-2-dimethylaminoethyl-6-benzylphenyl N,N-dimethylcarbamate, b.p. 197–201° (2 mm.), 38% yield, $n^{20}D$ 1.5704. *Anal.* Calcd. for $C_{19}H_{23}ClN_2O_2$: C, 65.8; H, 6.7. Found: C, 66.4; H, 6.7.

2-Dimethylaminomethyl-4-benzylphenyl N,N-dimethylcarbamate, b.p. 196–197° (1 mm.), 57% yield, $n^{20}D$ 1.5548. *Anal.* Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.0; H, 7.7. Found: C, 73.3; H, 7.9.

2-Diethylaminomethyl-4-benzylphenyl N,N-dimethylcarbamate, b.p. 200–205° (0.5 mm.), 93% yield, $n^{20}D$ 1.5456. *Anal.* Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.1; H, 8.3. Found: C, 74.2; H, 8.2; hydrochloride, m.p. 148.5–150.0° (recrystallized from isopropyl alcohol–Skellysolve B). *Anal.* Calcd. for $C_{21}H_{28}N_2O_2 \cdot HCl$: C, 66.9; H, 7.8. Found: C, 67.2; H, 8.0.

2-Diethylaminomethyl-4-benzylphenyl N,N-diethylcarbamate, b.p. 202–206° (1 mm.), 56% yield, $n^{20}D$ 1.5358. *Anal.* Calcd. for $C_{23}H_{32}N_2O_2$: C, 75.0; H, 8.8. Found: C, 75.0; H, 8.8.

Quaternary Ammonium Compounds.—The compounds listed in Tables I and II were prepared by addition of an excess of alkyl halide to an isopropyl alcohol solution of the carbamate. With methyl iodide, the reaction proceeded rapidly at room temperature so that the product could be collected by filtration after a few hours. With ethyl iodide, the reaction mixture was refluxed for a few hours, then cooled and diluted with ether or ethyl acetate if necessary to cause crystallization. Compound 11 of Table II was obtained instead of the desired bisquaternary when ethylene bromide was used as the alkyl halide.

Carbamates of Benzylphenols.—Typical examples are given for the preparation of disubstituted carbamates (method A) and monosubstituted carbamates (method B). The properties of these compounds are summarized in Table III.

Method A.—A solution of 46.0 g. (0.25 mole) of 2-benzylphenol and 28.0 g. (0.26 mole) of N,N-dimethylcarbamyl chloride in 80 ml. of pyridine was heated overnight on the steam-bath. The cooled solution was poured into 500 ml. of water and extracted three times with benzene. The combined benzene extracts were washed in turn with Claisen alkali, dilute sodium hydroxide and water, then dried and distilled. 2-Benzylphenyl N,N-dimethylcarbamate was obtained as an oil, b.p. 177–179° (1.4 mm.).

Method B.—One mole each of 4-benzylphenol (184 g.) and phenyl isocyanate (119 g.) were stirred together in one liter of cyclohexane and 100 ml. of benzene for one hour at reflux. The solid which formed on cooling amounted to 220 g. and melted from 75–194°. Since this was obviously a mixture, the mother liquor was concentrated to an oil which was taken up in ether and combined with the crude solid. This ether solution was extracted three times with 10% potassium hydroxide (on acidification of these extracts 93 g. (53%) of unreacted 4-benzylphenol were recovered). Two successive concentrations of the ether solution gave a total of 115 g. of 4-benzylphenyl N-phenylcarbamate.

SYRACUSE 1, N.Y.

COMMUNICATIONS TO THE EDITOR

POLYPEPTIDES. XII. THE OPTICAL ROTATION AND CONFIGURATIONAL STABILITY OF α-HELICES[1]

Sir:

In view of the interest in the configuration of synthetic polypeptides and proteins, it is pertinent to record now some work that has been done in our laboratories on the configurational stability of such molecules. Rotatory dispersion studies of poly-γ-benzyl-L-glutamate[2] and poly-L-glutamic acid[3] have shown that in solvents where the α-helical configuration is known to exist, the specific rotation, $[\alpha]D$, has small, positive values and the dispersion is abnormal. In contrast when the configuration is that of a random coil $[\alpha]D$ is negative and the dispersion is normal. These results suggested that the helix is of a single screw-sense. Recent theories of the optical properties of helices[4,5,6,7] have confirmed this view and appear to have established the absolute configuration as being right-handed. Similar conclusions have been reached tentatively by Elliott and Malcolm[8] from X-ray diffraction data.

The specific rotation which the helical configuration confers on the polypeptide chain cannot, however, be rigorously determined by subtracting the rotation in the randomly coiled form from that in the helical form because the environmental effects on the peptide bonds in the two configurations are sufficiently different as to alter substantially the intrinsic residue rotations on going from one form to the other. An alternative approach is possible, however, upon recognizing that copolymers of D and L-residues should exhibit an increase in $[\alpha]D$ as a result of the cancellation of the intrinsic residue rotations of matched D and L residues, thereby revealing the positive contribution made to the rotation by the helix itself.[9,10] The specific rotations of a number of copolymers of γ-benzyl-D and L-glutamate[11] in chloroform, a solvent in which the helical form is known to be the stable one, are

(1) For the last paper in this series see ref. 13.

(2) P. Doty and J. T. Yang, THIS JOURNAL, **78**, 498 (1956).

(3) P. Doty, A. Wada, J. T. Yang and E. R. Blout, paper presented at International Symposium on Macromolecules, Rehovot, Israel, April 4, 1956. To be published January 1957 in *Journal of Polymer Science*.

(4) W. Moffitt, *J. Chem. Phys.*, **25**, 467 (1956).

(5) W. Moffitt and J. T. Yang, *Proc. Nat. Acad. Sci., U. S.*, **42**, 596 (1956).

(6) W. Moffitt, *ibid.*, **42**, 736 (1956).

(7) D. D. Fitts and J. G. Kirkwood, THIS JOURNAL, **78**, 2650 (1956).

(8) A. Elliott and B. R. Malcolm, *Nature*, **178**, 912 (1956).

(9) This effect already has been reported and a preliminary value given in footnote 8 of P. Doty and R. D. Lundberg, THIS JOURNAL, **78**, 4810 (1956).

(10) A. Elliott, W. E. Hanby and B. R. Malcolm, *Nature*, **178**, 1170 (1956).

(11) Prepared by Mr. R. H. Karlson.