in the A degradative process with ϕ value near zero and a 1.01 slope in plots of (log K_ψ against $-Ho$), water would not participate in the rate-determining step, displaying a typical A-1 mechanism according to Zucker and Hammett (9). Therefore, degradative pathway B prevails at low acid concentrations and A prevails at high acid concentrations.

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New Compounds: *N,N*-Dimethyl-[3-(1-alkylpiperidyl)]carbamates, Potential Cholinesterase Inhibitors

IAN W. MATHISON▲, KATHLEEN C. FOWLER, and ELIZABETH R. PETERS

Abstract □ The synthesis of 10 piperidine carbamates was carried out by condensation of various 3-hydroxypiperidines with dimethylcarbamyl chloride or, alternatively, by treatment of the hydroxy compound with phosgene followed by dimethylamine. Changes were made in the length of the alkyl chain substituted on the heterocyclic nitrogen. The compounds were developed as potential cholinesterase inhibitors as a continuation of previous studies.

Keyphrases □ *N,N*-Dimethyl-[3-(1-alkylpiperidyl)]carbamates—synthesized as potential cholinesterase inhibitors □ Cholinesterase inhibitors, potential—synthesis of *N,N*-dimethyl-[3-(1-alkylpiperidyl)]carbamates □ Piperidine carbamates—synthesized as potential cholinesterase inhibitors

The established interest of these laboratories in the synthesis and evaluation of potential cholinesterase inhibitors (1, 2) led recently to the completion of the synthesis of some compounds intimated in earlier work (1). The studies related to the effects on inhibitory potency of a series of compounds showing isosteric replacements of known cholinesterase inhibitors. The compounds possessed the general structural formulas indicated for I and II and were correlated with compounds of general formula III which were synthesized earlier (3) and shown to be active inhibitors. The data suggested (1) that the compounds having the urea moiety (II) provided a better "fit" in the area of the esteratic site than those possessing the acetamide function (I). To complete the series of isosteric modifications of the acetylcholine skeleton, the synthesis of carbamate derivatives of piperidines was considered appropriate. This approach was further substantiated by the presence of the carbamate moiety in physostigmine—a potent cholinesterase inhibitor. The compounds reported in this paper possess the general formula shown for IV and can be readily related to compounds of the general structures I–III.

The synthetic route adopted involved a preliminary quaternization of 3-hydroxypyridine followed by catalytic hydrogenation to the corresponding *N*-alkyl-3-hydroxypiperidine (Scheme I).

Two methods were chosen to introduce the carbamate function: treatment of the 3-hydroxypiperidine with di-

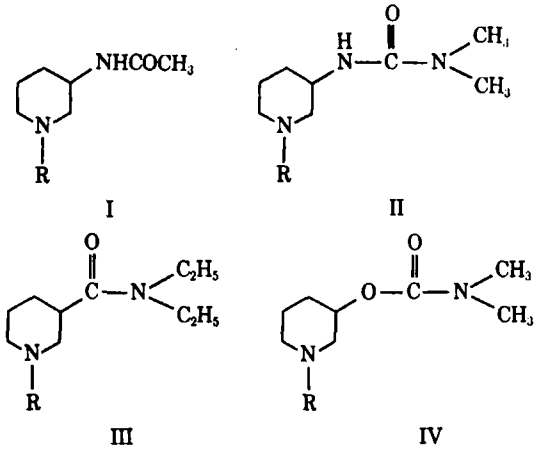
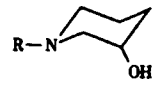


Table I—*N*-Alkyl-3-hydroxypiperidines



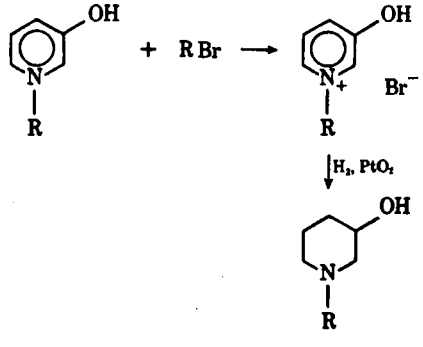
R	Boiling Point (mm. Hg)	Yield, %
CH_3	30–34° (0.1)	35.4
C_2H_5	32–34° (0.05)	30.4
C_3H_7	26–46° (0.05)	40.0
C_4H_9	26–60° (0.15)	43.7
C_5H_{11}	58–68° (0.1)	57.8
C_6H_{13}	60–76° (0.1)	21.0
C_7H_{15}	72–82° (0.05)	47.6
C_8H_{17}	85–96° (0.05)	56.6
C_9H_{19}	66–98° (0.05)	48.9
$C_{10}H_{21}$	110–112° (0.05)	32.0

methylcarbamyl chloride (4) (Scheme II) or treatment of the hydroxy compound with phosgene followed by dimethylamine (5) (Scheme III). Neither procedure showed superiority over the other and the yields varied considerably. Particular difficulty was noted with Compound 2, and only after a prolonged effort was the product obtained and in low yield.

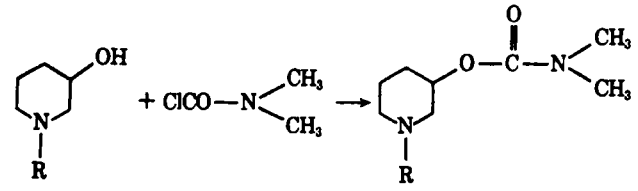
EXPERIMENTAL[1]

***N*-Alkyl-3-hydroxypiperidines**—3-Hydroxypyridine (1.0 mole) and the appropriate *N*-alkyl bromide (1.1 moles) were refluxed in absolute ethanol for 4 days. The ethanol was removed *in vacuo*, leaving the crude *N*-alkyl-3-hydroxypyridinium bromide as a yellow, viscous oil which, in some of the higher molecular weight compounds, solidified on standing at room temperature. The crude product was dissolved in absolute ethanol and hydrogenated at 45 p.s.i. over platinum oxide catalyst (2–5% ratio of catalyst to compound by weight). After 20 hr., the hydrogenation was stopped, the catalyst was removed by filtration, and the solvent was removed *in vacuo*, leaving an oily or a semisolid residue. The residue was dissolved in water, made strongly alkaline with sodium hydroxide pellets, and extracted with ether. The dried ether extract was concentrated to yield a brown oil, which was purified by vacuum distillation to yield the desired compound; in all cases, the compound was a colorless oil. The physical constants for the compounds prepared are shown in Table I. This method was used in the synthesis of Compounds 2–10.

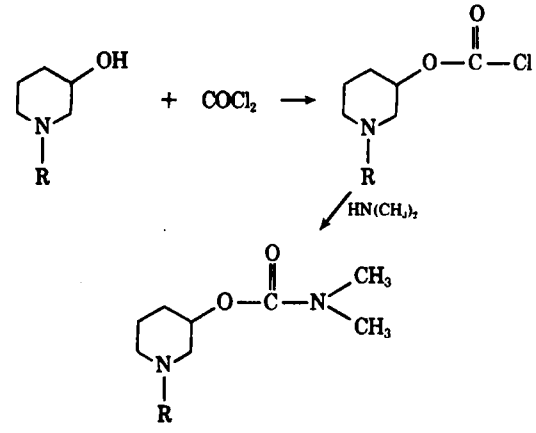
***N*-Alkyl-3-piperidyl Dimethylcarbamate Hydrohalide**—*Method I*—*N*-Alkyl-3-hydroxypiperidine (1.0 mole) was dissolved in benzene, and the solution was cooled in an ice bath. Then a solution of



Scheme I



Scheme II



Scheme III

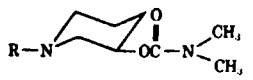
12.5% phosgene in benzene (1.1 moles) was added dropwise with stirring. At the end of the phosgene addition, the resulting bright-yellow solution was left stirring in an ice bath for 0.5 hr. and was then allowed to stand at room temperature with stirring for a further 2 hr. The mixture turned into an opaque, yellow, jelly-like mass. The benzene was removed *in vacuo*, maintaining the temperature below 60°, leaving a yellow tacky residue which was the crude *N*-alkyl-3-piperidyl chlorocarbonate hydrochloride. The crude product was dissolved in chloroform and the solution cooled in an ice bath. A large excess of dimethylamine (5 moles excess) in chloroform was added slowly through an addition funnel, and the reaction mixture (fitted with a condenser) was left stirring in the ice bath and allowed to warm gradually to room temperature as the mixture stirred overnight. The chloroform was then removed *in vacuo*, leaving a pale-yellow granular precipitate suspended in an amber-colored viscous oil. The oil was dissolved in anhydrous ether and the ether was decanted, separating it from the solid precipitate of dimethylamine hydrochloride. The decanted ether solution was reduced in volume, and the resulting reddish-brown oil was purified by vacuum distillation to yield *N*-alkyl-3-piperidyl dimethylcarbamate as a colorless oil. The oil was converted to the appropriate hydrohalide salt which was, in all cases, a white powder. The physical constants for the compounds synthesized together with the recrystallization solvent can be found in Table II. This method was used for the syntheses of Compounds 3, 4, 6, 7, 9, and 10.

***N*-Alkyl-3-piperidyl Dimethylcarbamate Hydrohalide**—*Method II*—*N*-Alkyl-3-hydroxypiperidine (1.0 mole) was dissolved in anhydrous ether, and the solution was cooled in an ice bath. Dimethylcarbamyl chloride (3 moles) was added slowly to the solution fitted with a reflux condenser, The mixture was allowed to warm slowly to room temperature and was left stirring overnight. The ether was then removed *in vacuo*, leaving a brown oil which solidified on standing at room temperature. The residue was suspended in 10% sodium carbonate solution and the mixture was extracted with ether. The ether was dried over anhydrous sodium sulfate and distilled off to leave a brown oil, which was purified by vacuum distillation to yield the *N*-alkyl-3-piperidyl dimethylcarbamate as a colorless oil. The oil was converted to the appropriate hydrohalide salt which was, in all cases, a white powder. The physical constants for the compounds prepared are shown in Table II. This method was used in the syntheses of Compounds 2, 5, and 8.

***N*-Methyl-3-piperidyl Dimethylcarbamate Hydrochloride (Compound 1)**—3-Hydroxypyridine (25.0 g.) was dissolved in methanol (250 ml.), and the solution was cooled in an acetone–dry ice bath. Methyl bromide was bubbled through the cooled solution for 0.5 hr. The mixture was allowed to warm to room temperature, methyl

[1] All melting points were determined using a Swissco melting-point apparatus and are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were recorded on a Perkin-Elmer model 137B Infracord spectrophotometer, and examination of the IR spectra of all compounds showed them to be consistent with the proposed structures [OH absorption 3350 cm.$^{-1}$ (thin film); C=O of carbamate 1725 cm.$^{-1}$ (thin film)].

Table II—Physical Data



Number	R	Boiling Point (mm. Hg)[a]	Melting Point[b]	Yield, %[c]	Solvent of Recrystallization[d]	Analysis, % Calc.	Found
1	CH_3	—	201–202°	50.0	Ethanol	C 48.54	48.38
						H 8.60	8.48
						Cl 15.92	16.05
						N 12.58	12.37
2	C_2H_5	62–64° (0.04)	160–162° (sealed tube)	26.0	Ethyl acetate–ethanol	C 50.73	50.93
						H 8.94	9.20
						Cl 14.98	—[e]
						N 11.83	11.57
3	C_3H_7	66–76° (0.1)	161–162.5°	41.5	Ethyl acetate–ethanol	C 44.75	44.89
						H 7.85	7.79
						Br 27.07	27.21
						N 9.49	9.36
4	C_4H_9	50–68° (0.05)	141–146°	41.5	Ethyl acetate–ethanol	C 46.60	46.34
						H 8.15	8.05
						Br 25.84	25.54
						N 9.06	8.77
5	C_5H_{11}	82–88° (0.05)	132.5–134°	40.5	Ethyl acetate–ether	C 56.00	55.92
						H 9.76	9.64
						Cl 12.72	12.89
						N 10.05	9.95
6	C_6H_{13}	90–100° (0.1)	123–125°	90.0	Ethyl acetate	C 49.85	49.71
						H 8.67	8.70
						Br 23.69	23.75
						N 8.30	—[f]
7	C_7H_{15}	98–114° (0.11)	133–134.5°	50.0	Ethyl acetate	C 51.28	51.10
						H 8.89	8.97
						Br 22.74	22.94
						N 7.97	7.91
8	C_8H_{17}	100–118° (0.05)	128.5–130°	48.3	Ethyl acetate	C 52.60	52.45
						H 9.10	9.23
						Br 21.87	22.07
						N 7.67	7.46
9	C_9H_{19}	100–118° (0.05)	111–113°	59.5	Ethyl acetate	C 53.82	53.78
						H 9.30	9.08
						Br 21.06	20.93
						N 7.38	7.16
10	$C_{10}H_{21}$	140–144° (0.15)	117–119°	55.7	Ethyl acetate	C 54.95	55.11
						H 7.12	6.91
						Br 20.31	20.32
						N 9.48	9.26

[a] For the free bases. [b] For the corresponding hydrohalide salts. [c] Calculated for the free base from *N*-alkyl-3-hydroxypiperidine. [d] For hydrohalide salt. [e] No satisfactory analysis for chlorine could be obtained. [f] No satisfactory analysis for nitrogen could be obtained.

bromide was bubbled through for an additional 0.5 hr., and the mixture was allowed to stir at room temperature for 3 days. The methanol was removed *in vacuo*, leaving *N*-methyl-3-hydroxypyridinium bromide (41.0 g.) as a light-tan solid which was recrystallized from ethanol–water. This compound was dissolved in water and hydrogenated over platinum oxide catalyst (2% ratio of catalyst to compound) at 50 p.s.i. The resulting solution was filtered to remove the catalyst, made alkaline with sodium hydroxide pellets, and extracted with chloroform. This extract was dried over sodium sulfate, and the solvent was distilled off to leave a dark oil, which was purified by vacuum distillation to yield *N*-methyl-3-hydroxypiperidine as a clear colorless oil (10.7 g.), b.p. 34–36° (100 μ). The *N*-methyl-3-hydroxypiperidine (10.7 g., 0.093 mole) thus obtained was dissolved in dry ether and the solution was cooled in an ice bath. Dimethylcarbamyl chloride (21.6 g., 0.2 mole) was added to the hydroxy compound solution and allowed to warm slowly to room temperature; it was left stirring overnight during which time a precipitate formed. The ether was evaporated, leaving a yellow powdery precipitate which was recrystallized from ethanol–ether to yield the hydrochloride salt of *N*-methyl-3-piperidyl dimethylcarbamate as off-white granular crystals (10.3 g. crude weight). The physical data for this compound are shown in Table II.

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