refluxed with 0.2 g of thiourea for 1 hr. After removing the solvent, the product was taken in small amount of water to which dilute NH_4OH was added. A buff-colored precipitate settled (0.15 g). The infrared spectrum of this compound showed λ_{max}^{Nujol} 3.10 (primary amino group), 5.75 (β-lactam carbonyl), 6.58 (N–H deformation), and 6.12 μ (C=N bond of thiazole ring).

Anal. Calcd for $C_{12}H_{10}ClN_3OS$: C, 51.49; H, 3.58; N, 15.02. Found: C, 51.80; H, 3.60; N, 15.20.

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The Role of Analgesic Drug Metabolites in the Formation of Lens Opacities

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The ability of morphinelike analgesic drugs to produce transient lens opacities in mice was reported by Weinstock, Stewart, and Butterworth.[1,2] Weinstock and Stewart[3] showed that the opacity was caused by deposition of an opaque substance on the lens. This substance was inferred by Weinstock[4] to be a metabolite of the drug formed at the lens surface.

The metabolic fate of meperidine has been reported on by Plotnikoff, Elliott, and Way.[5] These authors observed the presence of normeperidine (IV) and hydrolyzed meperidine (II) in significant amounts in both rats and humans. Hydrolyzed normeperidine (V) also appeared to be present.

We have studied some known and hypothetical metabolites of meperidine (I) and are reporting our observations concerning lens opacity in mice with these compounds.

Experimental Section

The compounds which we investigated are listed in Table I along with the dosages used. The compounds were administered subcutaneously to Swiss albino mice (18–25 g of body weight), at a log dose of $^1/_{10}$ less than the LD_{50} value. Aqueous solutions (1%) of the compounds or their hydrochloride salts were used. Ten mice were used in each study and their eyes were examined carefully for signs of lenticular opacity using a microscope.

Results and Discussions

Of the compounds listed above, only meperidine produced significant opacity (8/10 mice were affected). The only other compound that gave any effect (2/10 mice) was meperidine methiodide (VII), but at a rather high dose of 100 mg/kg. If a metabolite of the analgesic drug were responsible for the opacity, it would seem reasonable that the metabolite alone should be more active than the parent drug.

These data, although cursory, indicate that the parent drug or some other less obvious metabolite is responsible for the opacity or that the responsible metabolite is only active when formed in the lens itself.

TABLE I

Compd	Dose, mg/kg
1-Methyl-4-carbethoxy-4-phenylpiperidine hydrochloride (meperidine) (I)	40.0
1-Methyl-4-carboxy-4-phenylpiperidine[a] (II)	100.0
1-Methyl-4-hydroxymethyl-4-phenylpiperidine[b] (III)	100.0
4-Carbethoxy-4-phenylpiperidine (IV)	50.1
4-Carboxy-4-phenylpiperidine[a] (V)	79.4
4-Hydroxymethyl-4-phenylpiperidine (VI)	15.6
Meperidine methiodide[c] (VII)	100.0
1-Methyl-4-carbethoxy-4-*p*-hydroxyphenylpiperidine[d] (VIII)	79.0

[a] Prepared by alkaline hydrolysis of the corresponding ethyl ester. [b] B. Elpern, *J. Am. Chem. Soc.*, **76**, 281 (1954). [c] Prepared by treatment of meperidine with ethanolic methyl iodide; mp 196–197.5°. *Anal.* Found: C, 48.9; H, 6.21; I, 33.0. [d] Prepared from *p*-methoxyphenylacetonitrile by the general method of F. F. Blicke, J. A. Faust, J. Krapcho, and E. Tsao, *J. Am. Chem. Soc.*, **74**, 1844 (1952). The hydrochloride melted at 208–211°. *Anal.* Found: C, 60.4; H, 7.47; N, 4.82.

(1) M. Weinstock, H. C. Stewart, and K. R. Butterworth, *Nature*, **182**, 1519 (1958).

(2) M. Weinstock, H. C. Stewart, and K. R. Butterworth, *Exptl. Eye Res.*, **2**, 28 (1963).

(3) M. Weinstock, and H. C. Stewart, *Brit. J. Ophthalmol.*, **45**, 408 (1961).

(4) M. Weinstock, Ph.D. Thesis, London University, 1961.

(5) N. P. Plotnikoff, H. W. Elliott, and E. L. Way, *J. Pharmacol. Exptl. Therap.*, **104**, 377 (1952).

The Synthesis of Tritium-Labeled Phenoxybenzamine Hydrochloride[1]

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The synthesis of labeled phenoxybenzamine was undertaken in order to quantitate and otherwise analyze the nature of the adrenergic α receptor. With the availability of the labeled compound it might be possible, with a suitable experimental design, to measure the small quantities of phenoxybenzamine which are attached to receptors.

A number of synthetic approaches exist for the preparation of the β-haloalkylamine class of compounds. In general, the methods have relied on the preparation first of the N,N-disubstituted amino alcohol and subsequent replacement of the hydroxyl group with a halogen. Recent reviews of this subject have been written by Ullyot and Kerwin[2] and Graham.[3]

Since the reaction had to be performed on a semimicro scale, it was desirable to employ the most direct method possible with the fewest chances for manipulative loss or separation problems. The method of synthesis chosen[4] was that which had proved success-

(1) A portion of these results was presented during the April 1965 meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J.

(2) G. E. Ullyot and J. F. Kerwin in "Medicinal Chemistry," Vol. 2, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 234–307.

(3) J. D. P. Graham in "Progress in Medicinal Chemistry," Vol. 2, G. P. Ellis and G. B. West, Ed., Butterworth and Co., London, 1962, pp 132–175.

ful for the small-scale synthesis of phenoxybenzamine-C^{14}. The key to the success of this synthetic method lies in the separation of N-(phenoxyisopropyl)ethanolamine (I) from the product, N-benzyl-N-(phenoxyisopropyl)ethanolamine (II). Nikawitz and coworkers[4] achieved separation of I and II by fractional distillation *in vacuo*. This mode of separation proved unsuccessful in our hands because of the small quantities that were involved. It was found that I and II could be separated by utilization of Hinsberg's method[5] since the reaction product of benzenesulfonyl chloride with I can be separated from II by solvent extraction.

Experimental Section[6]

H^3-Labeled N-Benzyl-N-(phenoxyisopropyl)ethanolamine (II).—A mixture of 1.114 g (5.71 mmoles) of I, 360 mg (2.86 mmoles) of benzyl-H^3 chloride,[7] 333 mg (3.14 mmoles) of powdered anhydrous Na_2CO_3, and 8.6 ml of absolute ethanol was heated under reflux for 21 hr. The ethanol was then distilled at reduced pressure and 0.73 ml (5.71 mmoles) of benzenesulfonyl chloride and 8.0 ml of 2.5 *N* aqueous NaOH were added. The mixture was mechanically shaken for 30 min and then extracted three times with 6-ml portions of anhydrous ether. The basic aqueous layer was discarded and the combined ethereal extracts were shaken with three 6-ml portions of 1 *N* HCl. The pooled acid layers were extracted with 2 ml of ether, which were discarded. The pooled acid solutions were made basic with 1.72 ml of 10 *N* NaOH and extracted with three 6-ml portions of ether. After pooling of the combined phases and drying (Na_2SO_4), distillation of the ether solution yielded II as a yellow oil.

H^3-Labeled Phenoxybenzamine Hydrochloride (III).—The conversion of II to III was accomplished by converting it to the salt form with 2 ml of $CHCl_3$ previously made acid by saturation with anhydrous HCl. A mixture of $SOCl_2$ (0.417 ml, 5.74 mmoles) in 2 ml of $CHCl_3$ was then added and heated under reflux for 2 hr. Distillation of the chloroform under reduced pressure left a yellow oil which was induced to crystallize by trituration with ether. Three recrystallizations from ethanol and ether gave 376 mg of pure white crystals of III. The overall yield was 39% based on benzyl-H^3 chloride. The melting point was 137–138°, identical with nonradioactive material, and the melting point of a mixture of the two was not depressed. Comparison of the infrared spectra of III and the nonradiomer showed them to be essentially identical. Chromatography on silica gel G (Stahl) with a solvent system composed of heptane–chloroform–methanol (140:15:25) showed III to be homogeneous and have an identical R_f with nonlabeled material (average R_f of II, 0.47; average R_f of III, 0.90). III was found to have a specific activity of 36.5 mcuries/mmole and reverse isotope dilution analysis showed it to be radiochemically pure.

Pharmacology.—Tritium-labeled phenoxybenzamine hydrochloride (III) was found to possess the expected adrenergic blocking activity. Incubation of III (concentration 0.1 μg/ml) for 5 min produced an almost complete blockade of the response to norepinephrine in preparations of the seminal vesicle of the rat according to Leitch.[8] Preliminary results of the use of III for labeling receptors based on the concept of receptor protection[9] have been presented.[10]

Acknowledgments.—The authors wish to thank Smith Kline and French Laboratories for a generous supply of the necessary precursor, I. This work was supported by Grant No. HD 00443 from the U. S. Public Health Service.

(4) E. J. Nikawitz, W. S. Gump, J. F. Kerwin, and G. E. Ulyot, *J. Am. Chem. Soc.*, **74**, 2438 (1952).

(5) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 103.

(6) Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained between NaCl plates (for II) or as KBr pellets (for III) using the Perkin-Elmer Model 137B Infracord. Radioactive measurements were done using a Packard Tri-Carb liquid scintillation system.

(7) Obtained from New England Nuclear Corp., Boston, Mass., with a specific activity of 35 mcuries/mmole.

(8) J. L. Leitch, C. S. Liebig, and T. J. Haley, *Brit. J. Pharmacol.*, **9**, 236 (1954).

(9) R. F. Furchgott, *J. Pharmacol. Exptl. Therap.*, **111**, 265 (1954).

(10) J. E. Lewis and J. W. Miller, *Federation Proc.*, **24**, 388 (1965).

New Compounds

Silicon-Substituted Medicinal Agents. Phenyl-Substituted Silacarbamates[1]

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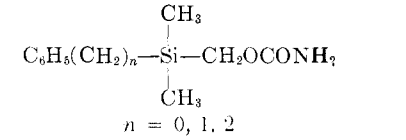
In the course of our work on silacarbamates related to meprobamate,[3] it was convenient to prepare some phenyl-substituted silacarbamates. The synthetic reaction and the biological screening procedures were similar to those described in our previous publication[3] and will not be repeated in detail in this report. In general, these new carbamates showed muscle relaxant activity of short duration.



$n = 0, 1, 2$

(1) This research was supported by Public Health Service Research Grant GM 10122 from the National Institute of General Medical Sciences.

(2) Alfred P. Sloan Fellow, 1965–1967.

(3) R. J. Fessenden and M. D. Coon, *J. Med. Chem.*, **8**, 604 (1965).

Experimental Section[4]

(Hydroxymethyl)dimethylphenylsilane Carbamate.—The reaction of 21.1 g (0.093 mole) of (bromomethyl)dimethylphenylsilane with 19.7 g (0.20 mole) of KOAc and 65 ml of acetic acid, after a 24-hr reflux, work up, and distillation, gave (hydroxymethyl)dimethylphenylsilane acetate, bp 91–105° (3.0 mm), $n^{24}D$ 1.5087, in 69% yield. The product was not purified further, but was carried directly into the next step. (Hydroxymethyl)-dimethylphenylsilane, bp 123–124° (5.0 mm), $n^{22}D$ 1.5241 [lit.[5] bp 130–135° (30 mm), $n^{20}D$ 1.5220], was obtained in 75% yield by the $LiAlH_4$ reduction of the acetate. Treatment of 25.9 g (0.143 mole) of the hydroxymethyl compound with 25.0 g (0.16 mole) of phenyl chloroformate and 60 ml of pyridine, followed by reaction of the carbonate intermediate (not isolated) with liquid NH_3,[3] yielded 17.2 g (53%) of the carbamate, bp 147–150° (2.2 mm), $n^{24}D$ 1.5265.

Anal. Calcd for $C_{10}H_{15}NO_2Si$: C, 57.37; H, 7.24; N, 6.69; Si, 13.41. Found: C, 57.25; H, 7.19; N, 6.84; Si, 13.27.

The infrared spectrum (thin film) was consistent with the structure assignment and showed bands at 2.9 (doublet, NH_2), 5.85 (CO), 7.0 and 9.0 (SiC_6H_5), 8.0 ($SiCH_3$), and 9.4 (COC) μ.

The LD_{50} was assayed to be 400 mg/kg, and the ED_{50} in the rotating rod test was determined to be 111 (103–120) mg/kg.

(4) All melting points (Fisher-Johns melting point apparatus) are corrected. The carbon, hydrogen, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory. Silicon analyses were performed in this laboratory using the wet ash method.

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