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.

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-

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(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.