showed a strong infrared absorption band, typical of sulfonic acids, at 1033 cm^{-1}; infrared data (cm^{-1}): 695 m, 770 w, 825 w, 1033 s, 1160 s, 1500 m, 1600 m, 1625 s, 1650 m, 2900 w, 3400 s.

Aniline–Formaldehyde Copolymer (II).—A solution containing 8 ml (0.088 mole) of aniline, 400 ml of water, and 3 ml of concentrated HCl was heated to incipient reflux, and 8 ml (0.099 mole) of 37% of CH_2O solution was added. The solution became turbid, and within 60 sec, oily droplets appeared. The mixture was refluxed for 4 hr, and the hot supernatant liquid was decanted. The resin was allowed to solidify, powdered, and washed with warm water. The yield of product melting at 85–120° was 5.5 g; infrared data (cm^{-1}): 690 w, 750 m, 815 m, 940 w, 1260 w, 1310 w, 1520 s, 1620 s, 2850 m, 3000 m, 3330 m.

Sulfonation of the Aniline–Formaldehyde Copolymer (VII).—Two grams of powdered II was added with strong agitation to 12 ml of fuming H_2SO_4. The solution was heated at 70° for 2.5 hr and then added slowly, with caution, to 250 g of crushed ice. The acid solution was made basic with $CaCO_3$ and the precipitated $CaSO_4$ removed by filtration. The filtrate was then carefully treated with sufficient Na_2CO_3 to convert the calcium sulfonate salt of VII to the sodium salt. The precipitated $CaCO_3$ was filtered off, and the filtrate was evaporated almost to dryness. The residue was treated with 10 ml of concentrated HCl, and the brown precipitate was collected by filtration and dried under vacuum. The product did not soften or melt below 300°. A strong infrared absorption band characteristic of the sulfonic acid group appeared at 1032 cm^{-1}. The infrared spectrum of this material was comparable to that of VII prepared by the hydrolysis of IV; infrared data (cm^{-1}): 750 w, 830 w, 900 w, 1032 s, 1200 s, 1300 m, 1490 m, 1595 m, 1660 m, 3000 m, 3400 s.

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Synthesis of Substituted β-Lactams

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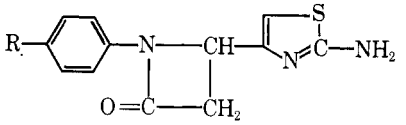
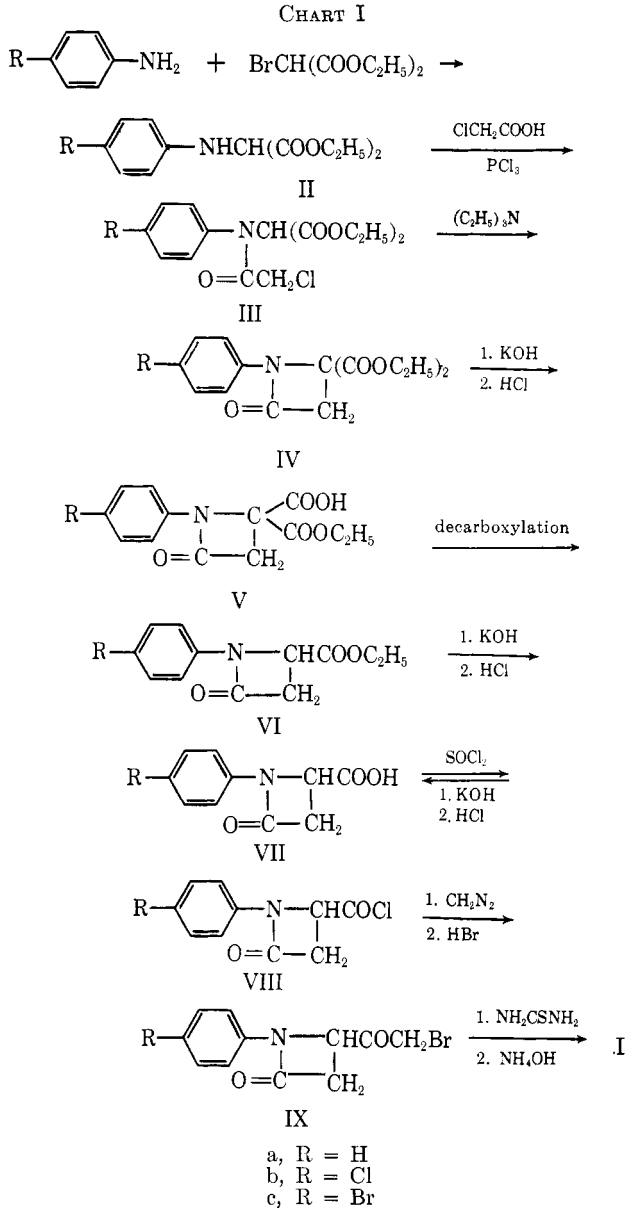
In view of the β-lactam structure in such biologically important compounds as the penicillins and cephalosporins, it was thought of interest to place this ring between *para*-substituted phenyl and thiazolyl functions. The latter two occur in 4-aminophenyl (2-amino-5-thiazolyl) sulfone (Promizole)[1] and its cyclopropane analog.[2] The synthesis of three β-lactams (I) is recorded in this note.



I

Several methods[3-6] are available for the synthesis of β-lactams, but some of them are not very general in applicability; furthermore, the yields are very different with the same method for different substituted β-lactams. We have chosen the method developed by Sheehan and Bose[7,8] for the synthesis of the β-lactam moiety of compounds of type I. The sequence of reactions used is shown in Chart I.

CHART I



a, R = H
b, R = Cl
c, R = Br

These β-lactam derivatives proved to be of little biological interest. They were found to be inactive when tested *in vitro* against several species of protozoa and against *Escherichia coli* (at 1 mg/ml). Little CNS activity was exhibited in mice. In preliminary enzyme screens Ia was found to be inactive. Diuretic activity of Ib was determined in rats dosed at 5 and 50 mg/kg intraperitoneally[9]; the compound was found to be inactive although it exhibited some toxicity. Table I summarizes the properties of the compounds prepared during this investigation.

Experimental Section[10]

A typical procedure for the synthesis of compounds of type I is described below in the preparation of 1-*p*-chlorophenyl-4-(2-aminothiazolyl)-2-azetidinone (Ib).

(1) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945).
(2) D. G. Markees and A. Burger, *ibid.*, **70**, 3329 (1948).
(3) H. Staudinger, "Die Ketene," F. Enke, Stuttgart, 1912.
(4) H. Staudinger, H. W. Klever, and P. Kober, *Ann.*, **374**, 1 (1910).
(5) R. Breckpot, *Bull. Soc. Chim. Belges*, **32**, 412 (1923).
(6) H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).
(7) J. C. Sheehan and A. K. Bose, *ibid.*, **72**, 5158 (1950).
(8) J. C. Sheehan and A. K. Bose, *ibid.*, **73**, 1261 (1951).
(9) J. E. Baer and K. H. Beyer, *Am. J. Pharm.*, **132**, 5 (1960).
(10) Infrared spectra were kindly determined by Professor A. K. Bose of Stevens Institute of Technology, and Dr. I. P. Varshney of Aligarh University, India. Melting points and boiling points are uncorrected.

TABLE I
THE PROPERTIES AND ANALYSES OF 1-ARYL-4-(2-AMINOTHIAZOLYL)-2-AZETIDINONES AND THEIR INTERMEDIATES[a]

Compd	Bp (mm) or mp, °C	Crystn solvent	% yield	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
IIb	91–92	Petr ether	98.0	54.64	54.52	5.60	5.71	4.90	4.82
IIc	92–93	Petr ether	98.0	47.27	47.32	4.84	4.92	4.24	4.31
IIIb[b]	240–245 (15)	...	82.0	49.72	49.95	4.69	4.91	3.86	4.01
IIIc[c]	240–250 (20)	...	78.0	44.28	44.41	4.18	4.32	3.44	3.57
IVb[d]		...	82.0	55.28	55.49	4.91	5.20	4.30	4.45
IVc[e]	220–230 (25)	...	85.0	48.10	48.75	4.32	4.45	3.77	3.81
Vb	118–120	Ether–petr ether	82.6	52.43	51.87	4.03	4.52	4.71	4.93
Vc	90–91	Ether–petr ether	73.2	45.58	45.61	3.50	4.04	4.09	4.21
VIb	86	Petr ether	77.4	56.81	57.27	4.76	4.96	5.52	5.57
VIc	89–90	Petr ether	73.0	48.34	48.52	4.06	4.18	4.69	4.71
VIIb	143–144	Benzene–ether	74.0	53.23	54.41	3.57	3.88	6.21	6.38
VIIc	147–148	Benzene–ether	80.0	44.44	44.24	2.96	3.20	5.18	5.28
VIIIa	...	...	92.0	...	...	...	...	...	...
VIIIb	102–104	Petr ether	94.0	49.54	48.48	2.86	3.00	5.73	5.81
VIIIc	98	Petr ether	85.0	41.59	41.91	2.42	2.80	4.86	4.61
IXa	131–132	Aq ethanol	50.0	49.25	49.52	3.73	3.66	5.22	5.30
IXb	144	Ethyl alcohol	53.0	43.63	44.52	2.96	3.80	4.62	4.70
IXc	142	Benzene	51.0	38.03	38.44	2.59	3.00	4.03	4.10
Ia	195–196	Ethanol	90.4	58.80	59.30	4.49	5.00	17.14	17.45
Ib	221	Ethanol	77.0	51.49	51.80	3.58	3.60	15.02	15.20
Ic	215	Ethanol	77.0	44.44	44.62	3.08	3.40	12.96	13.21

[a] IIa to VIIa are known compounds. [b] n^{30}D 1.5187. [c] n^{30}D 1.5320. [d] n^{30}D 1.5260. [e] n^{30}D 1.5393.

Diethyl *p*-Chloroanilinomalonate (IIb).—A mixture of 25.5 g of *p*-chloroaniline and 23.9 g of diethyl bromomalonate was placed in a 100-ml flask which was evacuated to a pressure of 40 mm. The reaction mixture was then allowed to stand in an oven maintained at 60–70° for 8 hr. The solid cake was powdered and extracted several times with ether. The crude *p*-chloroanilinomalonate, obtained on the removal of the solvent was recrystallized from petroleum ether (bp 60–80°); it was identical with a sample obtained earlier.[11]

Diethyl Chloro(*p*-chloroacetanilido)malonate (IIIb).—A benzene solution of 5.0 g of diethyl *p*-chloroanilinomalonate was refluxed with 5.0 g of monochloroacetic acid and 2.5 ml of PCl_3 for 4–5 hr. The reaction mixture after cooling was washed with water a number of times. On removing the solvent from the dried benzene solution, 5.5 g of a viscous brown liquid was obtained. Evaporative distillation at 240–245° (15 mm) afforded a golden yellow liquid, λ_{max}^{Nujol} 5.78 (ester) and 6.00 μ (amide).

Anal. Calcd for $C_{15}H_{17}Cl_2NO_5$: C, 49.72; H, 4.69; N, 3.86. Found: C, 49.95; H, 4.91; N, 4.01.

1-(*p*-Chlorophenyl)-4,4-dicarbethoxy-2-azetidinone (IVb).—To a benzene solution of 5.5 g of diethyl chloro(*p*-chloroacetanilido)malonate was added 1.53 g of triethylamine. The reaction mixture was left overnight and the precipitate of triethylamine hydrochloride was removed by filtration. The benzene solution was washed with dilute HCl and then with water. A viscous liquid was obtained (4.0 g) on the removal of the solvent. The crude material, when subjected to evaporative distillation, yielded a golden yellow liquid, λ_{max}^{Nujol} 5.68 (β-lactam) and 5.73 μ (ester).

Anal. Calcd for $C_{15}H_{16}ClNO_5$: C, 55.28; H, 4.91; N, 4.30. Found: C, 55.49; H, 5.20; N, 4.45.

1-(*p*-Chlorophenyl)-4-carboxy-4-carbethoxy-2-azetidinone (Vb).—An alcoholic solution of 1.6 g of KOH was added slowly to an alcoholic solution of 8.0 g of 1-*p*-chlorophenyl-4,4-dicarbethoxy-2-azetidinone. The potassium salt (6.7 g, 78%) separated in 2 hr. On the addition of ice-cold HCl to a solution of the potassium salt in a minimum quantity of water, an oily layer separated. The oil was taken up in ether and the ethereal solution was washed free of mineral acid. The viscous liquid (5.55 g) obtained after the removal of the solvent solidified on scratching. The crude material was crystallized from an ether–petroleum ether mixture.

Anal. Calcd for $C_{13}H_{12}ClNO_5$: C, 52.4; H, 4.03; N, 4.71. Found: C, 51.87; H, 4.52; N, 4.93.

(11) B. G. Chatterjee, P. N. Moza, and S. K. Roy, *J. Org. Chem.*, **28**, 1418 (1963).

1-(*p*-Chlorophenyl)-4-carbethoxy-2-azetidinone (VIb).—1-*p*-Chlorophenyl-4-carboxy-4-carbethoxy-2-azetidinone (5.0 g) was decarboxylated in the presence of 2 drops of pyridine. Decarboxylation started at 120° and was complete at 150° within 1 hr. The material was taken up in benzene and washed successively with dilute Na_2CO_3 solution, dilute HCl, and with water. On the removal of the solvent 3.25 g (77.4%) of a solid was obtained which crystallized from petroleum ether; the infrared spectrum showed the presence of a β-lactam ring.

Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.76; N, 5.52. Found: C, 57.27; H, 4.96, N, 5.57.

1-(*p*-Chlorophenyl)-4-carboxy-2-acetidinone (VIIb).—To a solution containing 0.67 g of KOH in 30 ml of alcohol was gradually added with stirring 3.0 g of monoester VIb. The mixture was left overnight. Potassium salt (2.40 g, 78%) was obtained on removing the solvent. Cold concentrated HCl was added to 2.0 g of this salt in a minimum of water. This solution was then extracted with ether. The ethereal layer was washed with water. On removing the solvent a viscous liquid was obtained which solidified on scratching (1.45 g). The crude solid was crystallized from benzene–ether mixture.

Anal. Calcd for $C_{10}H_8ClNO_3$: C, 53.23; H, 3.57; N, 6.21. Found: C, 53.41; H, 3.88; N, 6.38.

1-(*p*-Chlorophenyl)-4-chlorocarbonyl-2-azetidinone (VIIIb).—A benzene solution of 2.0 g of the monoacid VIIb was refluxed with 1.4 ml of $SOCl_2$ for 4 hr. Excess $SOCl_2$ was removed by repeated addition and distillation of benzene. On removal of the solvent, 2.0 g of the acid chloride was obtained. The compound could not be obtained analytically pure; however, the acid chloride on back hydrolysis gave the parent acid; λ_{max}^{Nujol} 5.65 (β-lactam), 5.75 μ (acyl carbonyl).

Anal. Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.54; H, 2.86; N, 5.73. Found: C, 48.48; H, 3.00; N, 5.81.

1-(*p*-Chlorophenyl)-4-bromoacetyl-2-azetidinone (IXb).—One gram of the crude acid chloride (VIIIb) was added slowly with shaking to 1.5 g of diazomethane in ether. The reaction mixture was left overnight. To this reaction mixture was added slowly an aqueous solution of 42% HBr with stirring until evolution of nitrogen ceased. The ethereal solution was washed free of acid. Removal of the solvent gave a yellow solid (0.7 g). The crude product was recrystallized from ethyl alcohol. The presence of a β-lactam ring was indicated by the infrared spectrum.

Anal. Calcd for $C_{11}H_9BrClNO_2$: C, 43.63; H, 2.96; N, 4.62. Found: C, 44.52, H, 3.80, N, 4.70.

1-(*p*-Chlorophenyl)-4-(2-aminothiazolyl)-2-azetidinone (Ib).—An alcoholic solution of 0.2 g of the bromo ketone IXb was

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-

(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).

(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.