tion of the method of Johnstone, *et al.*[13] Friedel-Crafts acylation using *N*-methylaniline and propionyl chloride was unsuccessful in obtaining significant amounts of **6**.

Experimental Section

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, they are within ±0.4% of the theoretical values. Ir spectra in KBr were obtained with a Perkin-Elmer 257 spectrophotometer. Nmr spectra in $CDCl_3$ (Me_4Si) were obtained with a Varian T-60 instrument at ambient temperature in approximately 10% solutions. All spectra were consistent with the proposed structures. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Tlc was carried out using Brinkmann silica gel precoated plastic sheets.

Unless otherwise noted, compounds were purchased from Aldrich Chemical Co. or K & K Laboratories, Inc. *p*-Aminopropiophenone (**1**) and methyl *p*-aminobenzoate (**24**) were purchased from Eastman Kodak Co. 4-Trifluoromethylaniline (**17**) was purchased from Research Organic/Inorganic Chemical Corp. Butyl and isobutyl *p*-aminobenzoates (**26** and **27**) were obtained from Matheson Scientific.

Compounds **9**, **10**, and **11** were prepared from aniline and the corresponding acyl chloride according to Clifford, *et al.*[14] Preparative methods for the hydroxylamine **2** and the nitro derivative **4** have been described.[15]

4-Nitrosopropiophenone (3). The hydroxylamine **2** (330 mg, 2 mmol) was dissolved in CH_2Cl_2 (20 ml) and treated with Ag_2CO_3–Celite reagent (1.7 g, 30 mmol of Ag_2CO_3). The mixture turned black at once, was stirred for 2 min, and filtered. Evaporation of the green filtrate gave a yellow, crystalline residue (301 mg, 92%) which was recrystallized from MeOH: mp 94–95°. *Anal.* ($C_9H_9NO_2$) C, H, N.

4,4′-Dipropionylazoxybenzene (5). A mixture of the hydroxylamine **2** (330 mg, 2 mmol), 0.2 ml of MeOH, and 10 ml of 0.4 *N* NaOH solution was stirred at room temperature for 16 hr at which time it was extracted twice with 20-ml portions of $CHCl_3$. The extracts were washed with 5 ml of H_2O, dried (Na_2SO_4), and evaporated to dryness to give 288 mg (93%) of **5** as an orange solid which was recrystallized from MeOH: mp 135–136°. *Anal.* ($C_{18}H_{18}N_2O_3$) C, H, N.

4-(*N*-Methylamino)propiophenone (6). A mixture of *p*-aminopropiophenone (6 g, 40 mmol), 40 ml of isopropyl alcohol, trifluoroacetic acid (4.56 g, 40 mmol), and 60 ml of CH_2Cl_2 was treated with a solution of dicyclohexylcarbodiimide (9.08 g, 44 mmol) in 20 ml of CH_2Cl_2 and stirred for 1 hr. Dicyclohexylurea was removed by filtration and the filtrate evaporated to give the crude trifluoroacetanilide which was used without further purification. The trifluoroacetanilide was dissolved in 200 ml of acetone to which was added CH_3I (13.64 g, 96 mmol). The mixture was heated almost to reflux for 10 min, evaporated to dryness, treated with 200 ml of H_2O, and refluxed for 15 min. The precipitate was filtered and the filtrate extracted with three 50-ml portions of $CHCl_3$. The precipitate was washed with 20 ml of warm $CHCl_3$ and filtered. This filtrate was combined with $CHCl_3$ extracts, dried (Na_2SO_4), and concentrated. The residue was dissolved in 20 ml of $CHCl_3$ and applied to a column (29 mm diameter) of silica gel (100 g) in $CHCl_3$. The column was eluted with $CHCl_3$ (fractions 1–9), 1% MeOH in $CHCl_3$ (10–12), 2% MeOH in $CHCl_3$ (13–15), and 5% MeOH in $CHCl_3$ (16–18). The first fraction was 200 ml, thereafter 50-ml fractions were taken. Fractions 4–12 were combined, on the basis of tlc, to yield 2.14 g (33%) 4-(*N*-methylamino)propiophenone (**6**). Recrystallization from EtOH–H_2O gave mp 129–131°. *Anal.* ($C_{10}H_{13}NO$) C, H, N. Fractions 14–18 gave 442 mg of **1**.

4-(*N*,*N*-Dimethylamino)propiophenone (7). A mixture of *p*-aminopropiophenone (750 mg, 5 mmol), Na_2CO_3 (1.6 g, 15.1 mmol), CH_3I (5.88 g, 41.4 mmol), and 15 ml of acetone was allowed to stir at room temperature for 24 hr. The solvent was evaporated, H_2O (35 ml) was added, and the mixture was extracted with three 50-ml portions of $CHCl_3$ which were dried (Na_2CO_3) and concentrated to give 770 mg (87%) yellow crystals: mp 90–92°. *Anal.* ($C_{11}H_{15}NO$) C, H, N.

4-Propylaniline (14) and 2-Propylaniline (16). Propylbenzene was nitrated according to Hurd and Jenkins.[11] The ortho and para isomers were separated on a silica gel column packed in hexane and eluted with 5% $CHCl_3$ in hexane. That the ortho isomer was eluted before the para isomer was shown by oxidation of a sample of the slower eluting material to *p*-nitrobenzoic acid. Both isomers were reduced in EtOH with 10% Pd/C and treated with HCl to give the salts.

Pharmacology. Adult male Sutter mice were used in all experiments. Radiation studies were carried out as before[15] except that a dose of 600 R was used. MetHb levels were obtained as previously described, as were LD_{50} values.[15]

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Synthesis of Seleno-Toluidine Blue

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Toluidine blue has been shown to have high specificity for the parathyroid, pancreas, and heart and has been useful in identifying parathyroid tissue at operation.[1] ^{35}S-Toluidine blue shows a similar distributional pattern[2] but since ^{35}S is an α-emitting isotope this compound is not efficient for scintiscanning. We report here an efficient synthesis of seleno-toluidine blue (**1**) by a procedure suitable for the incorporation of ^{75}Se, a γ-emitting isotope with a convenient half-life (121 days). This compound has physical and biological properties similar to those of toluidine blue and is thus an attractive candidate for diagnostic scintiscanning techniques.[3]

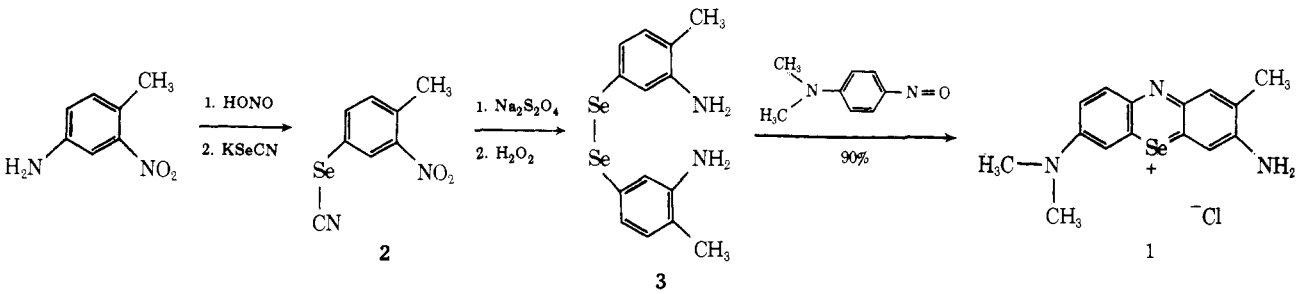
In an initial approach, *N*,*N*-dimethyl-*p*-nitrosoaniline was condensed with *o*-toluidine to give an unstable adduct

Table I. Tissue Distribution of Toluidine Blue and Seleno-Toluidine Blue[a]

	Para-thyroid	Thyroid	Blood	Liver	Pancreas	Heart	Lung	Kidney	Spleen
Toluidine blue	23.2	0.7	0.7	1.0	6.9	7.6	1.6	6.6	1.8
Seleno-toluidine blue	22.5	3.3	1.0	0.7	1.5	2.0	2.4	0.5	1.0

[a]Average of four observations in each category in dogs following intravenous infusion of 10 mg of dye/kg of body weight over a 40-min period. Samples obtained 1 hr after completion of infusion. Values in mg of dye/g of tissue, determined colorimetrically.

Scheme I



which was treated immediately with selenous chloride.[4] This reaction afforded a complex and largely polymeric mixture which was shown by tlc to contain only small amounts (less than 2%) of the desired **1**.

1 was prepared more efficiently *via* Scheme I. Thus, 4-methyl-3-nitrophenyl selenocyanate (**2**) was prepared according to the procedure of Keimatsu and Satoda[5] and converted to diselenide **3** by a modification of the procedure of Bauer.[6] Condensation of **4** with *N,N*-dimethylnitrosoaniline hydrochloride was effected by refluxing equimolar amounts of the reagents with ethanol. The crude product was purified by precipitation from water with sodium chloride and subsequent column chromatography. Seleno-toluidine blue (**1**) separated as a fine blue-black powder with a green-gold luster which was dried *in vacuo* (90% yield).

The structure of **1** was apparent from its spectral data and chromatographic behavior *vis-à-vis* those of an authentic sample of toluidine blue (obtained from Eastman Organic Chemicals and further purified as **1**). Thus, the mass spectrum indicated a compound of the correct molecular weight containing *one* selenium atom per molecule. The visible spectrum [λ max (ethanol) 628 nm (4.29×10^4)] was nearly identical with that of toluidine blue [λ max (ethanol) 632 nm (3.65×10^4)],[7] as expected for substitution of an elemental family member. The nmr spectrum of **1** was in accord with the assigned structure [δ (trifluoroacetic acid) 2.08 (3 H, s), 3.15 (6 H, s), 7.38 (3 H, m), 7.90 (2 H, m)]. In addition, samples of **1** were homogeneous to tlc with the same R_f as authentic toluidine blue (see Experimental Section).

Biological Results. Initial distribution studies have shown that **1** retains the specificity of toluidine blue toward the parathyroid although lower levels are observed in pancreas and heart tissue (Table I). Also of interest is the fact that the toxicity of the selenium compound **1** in mice is comparable to that of toluidine blue (LD_{50} = 33 ± 1.3 and 27.56 ± 2.4 mg/kg,[8] respectively).

Experimental Section

Bis(4-methyl-3-aminophenyl) Diselenide (4). 4-Methyl-3-nitrophenyl selenocyanate, 5.0 g (0.02 mol), was dissolved in 150 ml of 95% ethanol and heated to 60°. *The temperature must not be allowed to exceed 60° at any point during the reaction.* Sodium dithionite (94% pure, 21.2 g, 0.12 mol) was added with vigorous stirring. Sodium hydroxide (2 *N*, 150 ml) was added dropwise over a period of 1 hr maintaining the temperature between 55 and 60°. The reaction mixture is maintained at 60° with contiued stirring for 24 hr. Care must be taken to avoid coagulation of the mixture. A distillation head was attached to the reaction flask and the ethanol removed under vacuum with the mixture maintained at 60°. Ice (150 g) was added and as soon as the mixture had cooled to 20° hydrogen peroxide (3%, 11.7 ml, 0.02 mol) was added and the mixture stirred for 15 min.

The crude reaction mixture was extracted with ether, dried over K_2CO_3, concentrated, and dry-bag column chromatographed with chloroform on alumina. The diselenide **4** was isolated from the fastest moving band and recrystallized from chloroform: mp 80–84°; 60%; mass spectrum (70 eV) *m/e* (rel intensity) 374 (1.39), 373 (0.66), 372 (4.86), 371 (0.76), 370 (4.51), 369 (1.74), 368 (2.26), 367 (0.69), 366 (1.04), 215 (16.0), 211 (16.0), 187 (36.0), 107 (100, base); nmr ($CDCl_3$) δ 2.12 (s, 3 H), 3.6 (br s, 2 H), 6.88 (s, 3 H); ir (CCl_4) 3500 (m), 3420 (m), 1620 (s), 1587 (s), 1487 (s), 1408 (s), 1301 (m), 1268 (m), 987 (m), 887 cm^{-1} (m). *Anal.* ($C_{14}H_{16}N_2Se_2$) C, H, N, Se.

Seleno-Toluidine Blue (1). **4** (0.95 g, 0.0026 mol) was dissolved in 60 ml of 95% ethanol and heated to reflux. *p*-Nitroso-*N,N*-dimethylaniline hydrochloride (0.96 g, 0.0051 mol) was added to the reaction mixture in three portions at 15-min intervals. The mixture was continued at reflux for 10 hr. The solvent was evaporated and the residue dissolved in 250 ml of warm water. The pH was adjusted to neutrality with sodium hydroxide and the product precipitated with sodium chloride. The crude product was further purified by column chromatography on Woelm silica with chloroform–ethanol. The resulting material was homogeneous to tlc ($CHCl_3$–CH_3OH–NH_4OH, 80:20:1) with the same R_f (0.17) as authentic toluidine blue. The product was dried *in vacuo* to afford blue-black crystals with a green-gold luster (yield 1.7 g, 90%): λ max (ethanol) 628 nm (4.29×10^4); mass spectrum (70 eV) *m/e* (rel intensity) 320 (20), 319 (20.0), 318 (100, base), 317 (25.6), 316 (52), 315 (28.0), 314 (25.6). *Anal.* ($C_{15}H_{16}N_3SeCl$) C, H, N, Se.

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Centrally Acting Muscle Relaxants. Isomeric 9,10-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes and Their Carbamate Esters†

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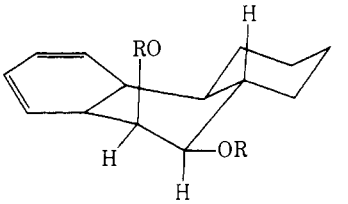
Mephenesin was the first modern psychopharmacological agent developed for its central muscle relaxant effects. In contrast to curare type skeletal muscle relaxants which act upon the myoneural junction, mephenesin was shown to act primarily by selective retardation or blockade of nerve impulses in internuncial pathways of the spinal cord.[2] As such, this drug has little or no effect upon the normal knee jerk but promptly reduces the exaggerated knee jerk, has little effect upon respiration, antagonizes the effects of strychnine, and relieves tetanic spasms. The short duration of action of mephenesin has limited its clinical usefulness. Attempts to prolong the action of this drug resulted in the preparation of various esters and carbamates, eventually leading to meprobamate, which possesses actions similar to mephenesin but is more potent, particularly in its ability to block the convulsive effects of pentylenetetrazole.

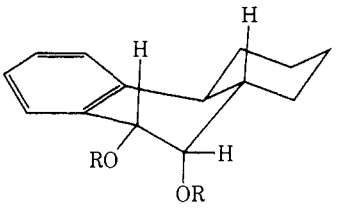
Although a vast amount of work has been accumulated and reviewed concerning structure-activity relationships of muscle relaxant diols and carbamate esters,[2,3] to date no conformational aspects of their varied activities have been examined. To approach a possible stereochemical evaluation of these drugs, the isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes **1**-**4**[4],‡ and their carbamate esters **9**-**12** were prepared and screened for anticonvulsant activity.

Use of the *trans*-octahydrophenanthrene nucleus as a conformationally semirigid carrier for the pharmacophoric groups of medicinal agents such as norephedrine analogs has been reported.[5] Recently, the isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10)-octahydrophenanthrenes **1**-**4** were prepared by a variety of stereoselective methods utilizing electrophilic reagents.[4] These isomeric diols, **1**-**4**, were converted to intermediate bis(phenylcarbonate) esters, **5**-**8**, and subsequently to the dicarbamates **9**-**12**.

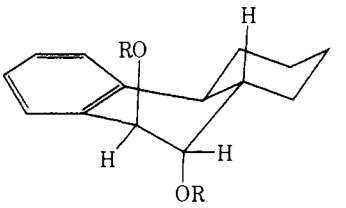
Although several methods are available for the conversion of alcohols to carbamates, some have serious limitations when applied to vicinal diols. For example, a very facile single-step method for preparing monocarbamates by reaction of the alcohol with sodium isocyanate and trifluoracetic acid is reported to give a significant amount of cyclic carbonate with the related vicinal diol phenaglycodol and its *p*-trifluoromethyl analog.[6] Following completion of our work, a similar method was used for conversion of a series of 4-phenyl-1-alkynylcyclohexanols to their respective carbamates.[7] Our studies demonstrate the applicability of the use of phenyl chloroformate followed by liquid ammonia for the high-yield production of dicarbamates from vicinal diols, even in cases where cyclic carbonates would be expected to present difficulties.



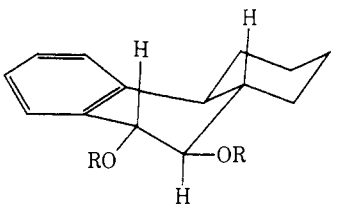
1, R = H
5, R = CO_2Ph
9, R = $CONH_2$



2, R = H
6, R = CO_2Ph
10, R = $CONH_2$

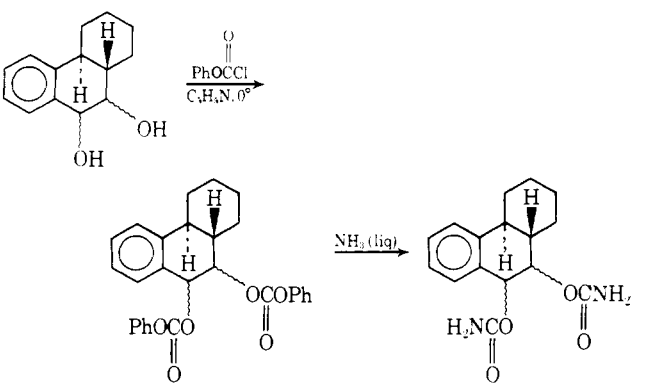


3, R = H
7, R = CO_2Ph
11, R = $CONH_2$



4, R = H
8, R = CO_2Ph
12, R = $CONH_2$

To support the structural assignments, high-resolution mass spectral data were gathered for each of the isomeric



†Taken in part from the Ph.D. Thesis of B. E. Sherwood, submitted to the Graduate School, University of Washington, Feb 1973. A preliminary account of this work was presented.[1]

‡All compounds are racemic although only a single isomer is drawn. The central ring is arbitrarily assigned the half-chair conformation where equatorial (e) and axial (a) substituents at C-9 are in fact pseudoequatorial and pseudoaxial, respectively.