Sulfur and Selenium Compounds Related to Acetylcholine and Choline. 11. Selenocarbonyl Ester and Selenocarboxamide Analogs of Local Anesthetics†

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The synthesis of selenocarbonyl esters and of selenocarboxamides related to local anesthetics is described; several of these had considerable activity in blocking axonal conduction. Structure-activity relationships of local anesthetics are discussed.

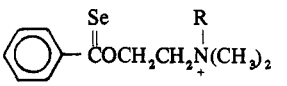
In view of the crucial role postulated to be played by acetylcholine (AcCh) in the transmission of the nerve impulse,[1] a large number of compounds related to this ester have been synthesized. It has been proposed by Nachmansohn and his coworkers[2-4] that local anesthetics block transmission of the nerve impulse through attachment to axonal AcCh receptors, a theory that has been subject to considerable controversy. Although the theory that nerve conduction involves reversible, conformational changes in axonal membranes[1,5] during electrical activity is beginning to find direct experimental confirmation,[6-8] it has proved difficult to determine whether local anesthetics are indeed competitive antagonists of AcCh.

In an investigation of the hypothesis that AcCh plays a crucial triggering role in the conduction of the axonal impulse, we have undertaken a systematic investigation of sulfur and selenium isologs both of cholinergic activators and of local anesthetics. Comparative studies of the biological activities of AcCh, acetylthiolcholine, and acetylselenolcholine[9] showed that replacement of its ether oxygen by sulfur or selenium greatly modified the depolarizing action of AcCh in a variety of preparations.[10-13] It was demonstrated by X-ray diffraction studies and by high-resolution nmr spectroscopy that the size and conformation of the acetylthiolcholine and acetylselenolcholine molecules were very similar both in the crystal and in solution.[14,15] Therefore, it may be assumed that the differences in the biological actions of acetylselenolcholine and acetylthiolcholine, which were noted, may be correlated with differences in electron distribution rather than with differences in the abilities of these isosteric molecules to fit receptor sites.

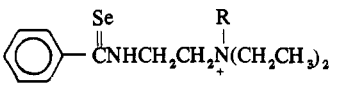
As in the case of AcCh isologs, replacing, with sulfur or selenium, the ether oxygens of esters with local anesthetic activity greatly modifies their potency, as does replacement of their carbonyl oxygens with sulfur.[13,16,17] It should be noted that such chemical modifications alter the blocking activity of local anesthetics in axonal and synaptic preparations in strikingly parallel fashion.[13]

The present study describes the synthesis of the phenylselenocarbonyl ester of choline and of 2-dimethylaminoethanol (I, II). Since these compounds were too unstable for determination of their local anesthetic potency or determination of their ability to block acetylcholinesterase, their selenocarboxamide analogs (III, IV) were also prepared.

Selenocarbonyl esters are normally prepared by the reaction of imino esters with hydrogen selenide in dry pyridine;[18] however, the imino ester required for the synthesis of I and II was not formed when benzonitrile and 2-dimethylaminoethanol were permitted to react. Transesterification proved a satisfactory method for obtaining the desired selenocarbonyl esters.‡ Reaction of the methyl ester of selenocarbonylbenzoic acid with 2-dimethylaminoethanol yielded I which could be quaternized to form II. Attempts to synthesize the selenocarbonyl thiolester and selenocarbonyl selenolester analogs of I and II were unsuccessful. In view of the lack of stability, under physiological conditions, of selenocarbonyl esters, the corresponding selenocarboxamide was synthesized.



1, R = CH_3
II, R = H



III, R = CH_3
IV, R = H

2-Diethylaminoethylbenzamide and 2-diethylaminoethylbenzothiocarboxamide were prepared by the reaction of *N,N*-diethylethylenediamine with benzoyl chloride or thionobenzoyl chloride, respectively. In view of the extreme instability of selenocarbonylbenzoyl chloride, this approach could not be used for the preparation of III. This compound was obtained by the reaction of *N,N*-diethylethylenediamine with selenocarbonylbenzoic acid methyl ester.

Experimental Section

2-Dimethylaminoethyl Selenocarbonylbenzoate Hydrochloride (II). In 5.0 g (0.056 mole) of 2-dimethylaminoethanol was dissolved 0.1 g (0.0043 g-atom) of sodium. A solution of 5.7 g (0.0285 mole) of methyl selenocarbonyl benzoate[18] in 150 ml of toluene was added and the mixture heated to 87° for 1 hr under a slow stream of nitrogen. Flash evaporation at 50° yielded a red residue which was acidified with 5 ml of concd HCl in 70 ml of ice water and filtered to remove precipitated selenium. The filtrate was extracted with ether until the extracts became colorless. The combined ether extracts were dried with $MgSO_4$ and evaporated to dryness; 1.6 g of unreacted selenocarbonyl ester was recovered.

The aqueous layer was treated with 35 ml of ice-cold saturated Na_2CO_3 solution and extracted with three 40-ml portions of ether. The ether extracts were washed with water and dried over anhydrous $MgSO_4$. The solution was filtered, chilled, and treated with dry HCl gas, resulting in the separation of 3.4 g (56.5%) of red product. Three recrystallizations from acetone yielded red needles melting at 135°;§ uv, ethanol: λ_{max} 256, 327 mμ; ϵ_{max} 7020, 10,400. *Anal.*# ($C_{11}H_{16}NOSeCl$) C, H, N, Se.

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‡While the prefix thiono- refers to the thiocarbonyl group, the prefix selenono-, according to Chemical Abstracts nomenclature, refers to the SeO_2^- (SeO_2H) grouping. Therefore, the awkward term selenocarbonyl ester had to be used.

§Mps were determined with a Gallenkamp melting point apparatus and are corrected.

#Analyses were carried out at Schwarzkopf Microanalytical Labs., Woodside, N. Y., or Midwest Microlab Inc., Indianapolis, Ind.

Selenocarbonylbenzoylcholine Bromide (I). A solution of 0.6 g (0.002 mole) of I in 10 ml of water was shaken with 10 ml of ice-cold satd Na_2CO_3 solution, followed by extraction with two 20-ml portions of ether. The organic extracts were washed with water and dried over anhydr $MgSO_4$. Evaporation to dryness yielded a residue which was dissolved in 20 ml of acetone and treated with 2.0 ml of methyl bromide in 20 ml of ether. On standing 0.55 g (78%) of product was obtained. Recrystallization from acetone yielded red needles melting at 158–158.5°; uv, ethanol: λ_{max} 257, 328 mμ; ϵ_{max} 6860, 10,210. *Anal.* ($C_{12}H_{18}NOSeBr$) C, H, N, Se.

2-Diethylaminoethylbenzoylselenocarboxamide Hydrochloride (IV). A solution of 1.8 g (0.015 mole) of *N,N*-diethylethylenediamine in 10 ml of methylene chloride was treated with 3.0 g of methyl selenocarbonyl benzoate dissolved in 20 ml of the same solvent. The mixture was stirred for 15 min in an ice bath. Selenium was removed by filtration and the filtrate evaporated under vacuum. The residue was washed with ether and recrystallized from ethanol–ether to yield 3.8 g (78.6%) of orange crystals melting at 82°; uv, ethanol: λ_{max} 248, 327 mμ; ϵ_{max} 11,600, 6940. *Anal.* ($C_{13}H_{21}N_2SeCl$) C, H, N, Se.

2-Diethylaminoethylbenzoylthiocarboxamide Hydrochloride. A solution of 1.16 g (0.01 mole) of *N,N*-diethylethylenediamine in 10 ml of methylene chloride was treated with 1.56 g (0.01 mole) of thionobenzoyl chloride[19] in 10 ml of the same solvent. The product was isolated in a fashion analogous to that described above. A yield of 2.2 g (80.5%) of yellow crystals was obtained, mp 96-96.5°; uv, ethanol: λ_{max} 244, 288 mμ; ϵ_{max} 9900, 6630. *Anal.* ($C_{13}H_{21}N_2SCl$) C, H, N, S.

2-Diethylaminoethylbenzamide Hydrochloride. This compound was obtained in 82.6% yield by the reaction of *N,N*-diethylethylenediamine in a mixture of methylene chloride and ether. After recrystallization from acetone it melted at 84–85°. *Anal.* ($C_{13}H_{21}N_2OCl$) C, H, N.

2-Dimethylaminoethylbenzoylselenocarboxamide hydrochloride (mp 120°) and **2-dimethylaminoethylbenzoylthiocarboxamide hydrochloride** (mp 116°) were synthesized in a fashion analogous to that of the diethyl compounds.

Local Anesthetic Studies. The efficacies of the various compounds in blocking the conduction of the nerve impulse were studied using the giant axon of the squid *Loligo pealei*, following the general method of Rosenberg and Podleski.[20] The effects on the action potential of the nerves are summarized in Table I. All compounds were applied in sea water buffered with 1 m*M* Tris at pH 7.5 for 30 min unless complete blockage was observed sooner; recordings were made with extracellular electrodes.

Discussion

As already noted, it has been postulated that local anesthetics may compete with AcCh for attachment to axonal receptors,[3,4] presumably without themselves being able to induce the conformational changes required for altering the excitable membranes' cation permeability. On the other hand, Feinstein has proposed that local anesthetics interfere with the binding of calcium by phospholipids[22,23] and that local anesthetics inhibit nerve conduction by replacing calcium in phospholipid complexes in axonal membranes. Since both AcCh and calcium are likely to be involved in triggering the excitability of nerve and muscle fibers,[24,25] these proposed mechanisms are not incompatible. More recently it was suggested that local anesthetics act as hydrogen-bond donors interacting with the phosphodiester groups of neuronal membrane receptors.[26]

From comparison of the conformation and biological activities[16,17] of our various sulfur- and selenium-containing local anesthetics in axonal and synaptic preparations some conclusions can be drawn.

Local anesthetic blocking activity increases as either the carbonyl or the acyloxy oxygens are replaced by sulfur or by selenium. This observation is *not* compatible with the postulate that hydrogen-bonding ability is of primary importance in the action of these compounds, particularly since these substitutions do not alter the pK_a of the dialkylamino group.[27] It is well known that sulfur is a poorer hydrogen-bond acceptor than is oxygen;**,[28] therefore, the high blocking activity of both 2-dimethylaminoethyl thiolbenzoate and of 2-dimethylaminoethyl thionobenzoate as compared to their ester analog is not compatible with the hydrogen-bonding hypothesis. On the other hand, in a series of benzoylcholine and benzoylthionocholine analogs there appears to be reasonably good agreement between lipid extractibility and local anesthetic potency.[16,**] We had postulated some time ago[11] that in the attachment of cholinergic ligands to membrane receptors "anionic" and "hydrophobic bonding" sites were involved. It is interesting to note that in the series acetylcholine, acetylthiolcholine, acetylselenolcholine depolarizing activity *decreases* progressively, while in the series 2-dimethylaminoethyl benzoate, thiolbenzoate, selenolbenzoate blocking activity *increases* progressively. It seems plausible that excessively strong binding of esters related to AcCh or of local anesthetics to the "hydrophobic bonding site" may interfere with the conformational change within the small-molecule–active site complex required for changes in cation permeability to be induced, thus progressively converting agonists to partial agonists to antagonists.

Studies of the conformations of thio and seleno isologs of AcCh and of thio and seleno isologs of local anesthetics have been carried out both in the crystal and in solution. In the crystal, replacement of the acyloxy oxygen of AcCh with sulfur and with selenium transformed the gauche conformation of the NCCO grouping[29] to the trans conformation for the NCCS (Se) grouping.[14] Studies of the conformation of local anesthetics such as procaine,[30,31] or of 2-dimethylaminoethyl benzoate and its sulfur and selenium isologs,[32] show that in the benzoates, as in the acetates, replacement of the acyloxy oxygen by sulfur or by selenium converts the gauche conformation of the OCCN grouping to the fully extended trans conformation for the resulting molecules. Nuclear magnetic resonance studies in D_2O solution have shown that, for both acetates[33-35] and benzoates,[36] the conformations observed in the crystal are also the conformations predominating in solution.

In the case of both acetates and benzoates, replacement of the carbonyl oxygen by sulfur leaves the gauche conformation substantially unaltered.

It was concluded by Sundaralingam[37] and by Baker, *et al.*,[38] that the gauche conformation is fundamental to the ability of cholinergic ligands to initiate a nerve impulse. Similarly it has been proposed[31] that the gauche conformation of the NCCO grouping in local anesthetics may be "an important feature necessary for effective effector-receptor

Table I. Reduction of the Height of the Action Potential in Squid Axons. The Number of Experiments Is Shown in Parentheses

$$C_6H_5-\overset{\overset{A}{\|}}{C}-B-CH_2-CH_2-N(C_2H_5)_2$$

		% reduction				
		Concentration, *M*				
A	B	1×10^{-4}	3×10^{-4}	1×10^{-3}	2×10^{-3}	3×10^{-3}
O	O		5 (2)	25 (3)	60 (2)	80 (2)
O	NH		10 (1)	60 (4)		100 (1)
S	NH	50 (4)	70 (4)	90 (2)		
Se	NH	25 (2)	50 (5)	100 (1)		
Procaine[a]						20

[a] This value was taken from ref 21 where essentially the same procedures as ours were employed.

**G. R. Hillman and H. G. Mautner, unpublished data.

interaction" in blocking conduction of the nerve impulse. In contrast, our biological data show no consistent correlation between conformation and biological activity. Rather it seems that differences in electron distribution[39] and differences in hydrophobic bonding ability may be more important than the conformations of the molecules. It should be emphasized[34] that the conformers seen in the crystal and in D_2O solution may not necessarily be the conformers predominating at the active site.

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N-Phenyl-2-indolinones and *N*-Phenylindolines. A New Class of Antidepressant Agents†

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Biological activity of an adrenergic-potentiating type in animals indicative of antidepressant action in man is displayed by compounds of formula II, especially 3-methyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (Amedalin) and 3-methyl-3-(3-methylaminopropyl)-1-phenylindoline (Daledalin). They do not possess the antihistaminic and anticholinergic side effects shown by other antidepressant drugs. The syntheses of compounds depicted by formula II (X = O or H_2; R_1 = alkyl; R_2, R_3 = H or alkyl) are described together with structure-activity relationships.

A number of 3-(ω-aminoalkyl)-1-phenyl-2-indolinones and the corresponding 1-phenylindolines have been synthesized and evaluated pharmacologically as potential antidepressant agents. These series were designed to incorporate the main structural characteristics of the established antidepressants (*e.g.*, imipramine) in a nontricyclic framework. Pharmacological evaluation of these two groups of compounds showed widespread biological activity of an adrenergic-potentiating type. The properties of the most potent compounds, indolinone **11** (Amedalin‡) and indoline **44** (Daledalin‡), are compared with those of the standard antidepressant drugs. Two side reactions which gave X and XI were encountered in the synthetic work and these are discussed briefly.

Imipramine is the prototype of a series of structurally closely related drugs usually referred to as the tricyclic antidepressants.[2] All members of the series cause varying degrees of side effects which are believed to originate from inherent anticholinergic and antihistaminic properties,[3-7] and our objective was to synthesize an antidepressant which lacked these side effects. We decided to investigate substances incorporating the main structural features of imipramine and its congeners in a nontricyclic chemical framework. This is readily achieved in phenyl-substituted bicyclic systems of general formula I. Substances derived from *N*-phenylindole seemed particularly attractive in view of the well-documented involvement of indole compounds in brain function (*e.g.*, tryptophan,[8-11] 5-HT,[12-18] and bufotenine[19]). We here report the structure-activity relationships of two series of

†A preliminary account of this work has appeared,[1a] and preparation of the compound has been described in ref 1b. After completion of this manuscript, compounds 1, 2, 6, 12, and 66 were reported in another context.[1c]

‡USAN Council approved name.