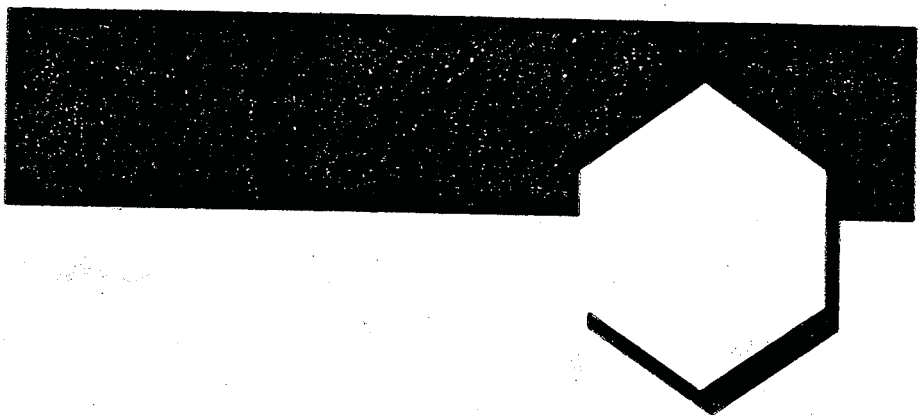

Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry

NINTH EDITION

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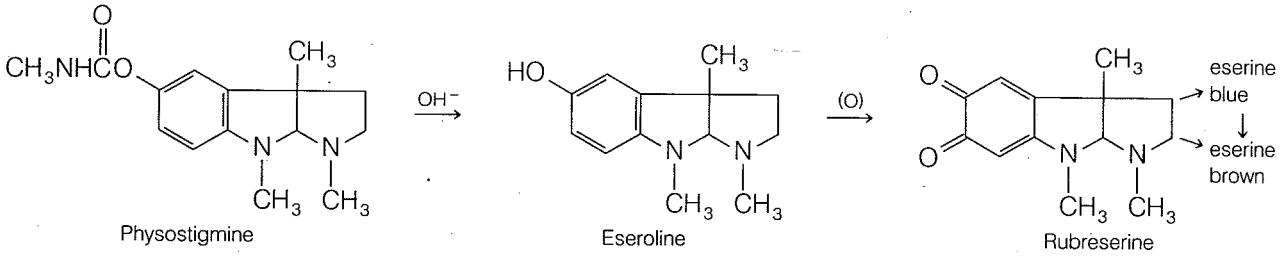
The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

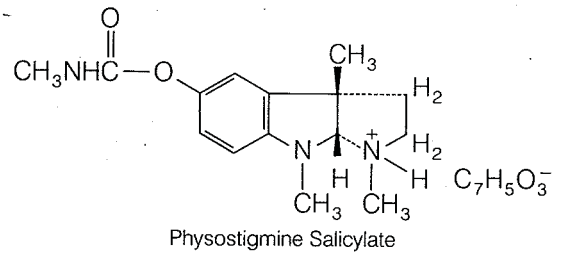
Products

Physostigmine, USP is an alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum*. It occurs as a white, odorless, microcrystalline powder that is slightly soluble in water and freely soluble in alcohol, chloroform, and the fixed oils. This alkaloid as the free base is quite sensitive to heat, light, moisture, and bases, and readily undergoes decomposition. When used topically to the conjunctiva it is better tolerated than its salts. Its lipid solubility properties permit adequate absorption from ointment bases.

Physostigmine is a competitive inhibitor of AChE when ACh is simultaneously present. The mechanism proposed is one of a reversible competition for the active site on the enzyme. A noncompetitive inhibition is observed when the enzyme is preincubated with physostigmine.



Physostigmine Salicylate, USP. Eserine salicylate. The salicylate of physostigmine may be prepared by neutralizing an ethereal solution of the alkaloid with an ethereal solution of salicylic acid. Excess salicylic acid is removed from the precipitated product by washing it with ether. The salicylate is less deliquescent than the sulfate.



Physostigmine salicylate occurs as a white, shining, odorless crystal, or white powder that is soluble in water (1 : 75), alcohol (1 : 16), or chloroform (1 : 6), but is much less soluble in ether (1 : 250). Upon prolonged exposure to air and light, the crystals turn red. The red may be removed by washing the crystals with alcohol, although this causes loss of the compound as well. Aqueous solutions are neutral or slightly acidic and take on a red coloration after a period. The coloration may be taken as an index of the loss of activity of physostigmine solutions.

Solutions of physostigmine salicylate are incompatible with the usual reagents that precipitate alkaloids, alkalies, and with iron salts. Incompatibilty also occurs with benzalkonium chloride and related wetting agents because of the salicylate ion. Physostigmine in solution is hydrolyzed to methylcarbamic acid and eseroline, neither of which inhibits AChE. Eseroline is oxidized readily to a red compound rubreserine[38] and is then converted to eserine blue and eserine brown. The addition of sulfite or ascorbic acid prevents the oxidation of the phenol, eseroline, to rubreserine. Hydrolysis does take place however and the physostigmine is inactivated. Solutions are most stable at *p*H 6 and should never be sterilized by heat, but rather by bacteriologic filtration.

Physostigmine is a relatively poor carbamylating agent of AChE and is often considered a reversible inhibitor of the enzyme. It has a K_i value (i.e., k_{-1}/k_{+1}) on the order of 10^{-8} M and is considered as a potent inhibitor of the enzyme. Its cholinesterase-inhibiting properties vary with *p*H (Fig. 12-12). The conjugate acid of physostigmine has a pK_a of about 8 and as the *p*H is lowered more is in the protonated form. The inhibitory action is enhanced at lower *p*Hs as shown in Figure 12-12; thus it is

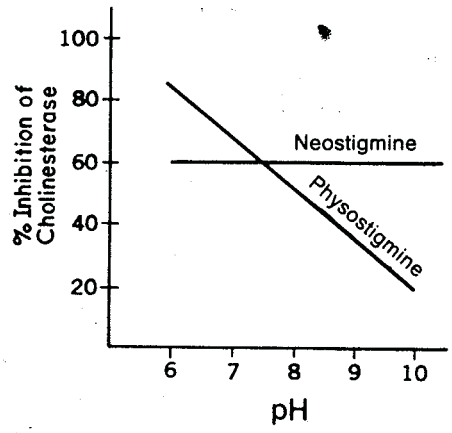


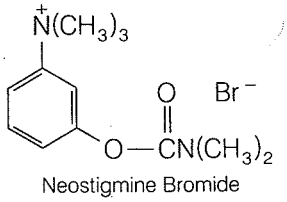
FIG. 12-12.

obvious that the protonated or salt form makes a marked contribution to its activity.

The ophthalmic effect (miotic) of physostigmine and related compounds is due to contraction of the ciliary body. This promotes drainage through the canal of Schlemm and decreases intraocular pressure. Hence, physostigmine is used in the treatment of glaucoma by direct instillation of a 0.1% to 1% solution in the eye. It is directly antagonistic to atropine in the eye, and it is sometimes used to help restore the pupil to normal size following atropine dilatation. Physostigmine also causes stimulation of the intestinal musculature and is used in conditions of depressed intestinal motility. In gaseous distention of the bowel, physostigmine often aids in the evacuation of gas as well as restoring normal bowel movement. It is administered by injection for this purpose. Much research has been done to find synthetic drugs with a physostigminelike action. This has resulted in compounds of the neostigmine type that, at least for intestinal stimulation, are superior to physostigmine.

Physostigmine Sulfate, USP occurs as a white, odorless, microcrystalline powder that is deliquescent in moist air. It is soluble in water 1 : 4, 1 : 0.4 in alcohol, and 1 : 1,200 in ether. It has the advantage over the salicylate salt in that it is compatible in solution with benzalkonium chloride and related compounds.

Neostigmine Bromide, USP. (*m*-Hydroxyphenyl)trimethylammonium bromide dimethylcarbamate; dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium bromide (Prostigmin Bromide). A method of preparation is from dimethylcarbamyl chloride and the postassium salt of 3-hydroxyphenyldimethylamine. Methyl bromide readily adds to the tertiary amine, forming the stable quaternary ammonium salt (see formula for neostigmine bromide). It occurs as a bitter, odorless, white crystalline powder. It is soluble in water (1 : 0.5) and in alcohol. The crystals are much less hygroscopic than are those of neostigmine methylsulfate and thus may be used in tablets. Solutions are stable and may be sterilized by boiling. Aqueous solutions are neutral to litmus.



Neostigmine Bromide

Use of physostigmine as a prototype of an indirect-acting parasympathomimetic drug led to the development of stigmine in which a trimethylamine group was placed *para* to a dimethyl carbamate group in benzene. Better inhibition of cholinesterase was observed when these groups were placed *meta* to each other, giving the drug neostigmine, a more active and useful agent. Although physostigmine contains a methyl carbamate functional group, greater chemical stability toward hydrolysis was obtained with the dimethyl carbamate group in neostigmine.[39,40]

After oral or intravenous administration, neostigmine has a half-life of about 50 minutes. About 80% of a single intramuscular dose of the drug is excreted in urine within 24 hours, approximately 40% as unchanged and the remainder as metabolities. Of the neostigmine that reaches the liver, 98% is metabolized in ten minutes to 3-hydroxyphenyltrimethyl ammonium, which has activity similar to, but weaker than, neostigmine. Its transfer from plasma to liver cells and then to bile is probably passive. Because cellular membranes permit the passage of plasma proteins synthesized in the liver into the bloodstream through capillary walls or lymphatic vessels, they may not present a barrier to the diffusion of quaternary amines such as neostigmine. Possibly the rapid hepatic metabolism of neostigmine provides a downhill gradient for the continual diffusion of this compound.[41] A certain amount is hydrolyzed slowly by plasma cholinesterase.

Neostigmine has a mechanism of action quite similar to that of physostigmine. Neostigmine effectively inhibits cholinesterase at about 10^{-6} M concentration. Its activity does not vary with *p*H, and at all ranges it exhibits similar cationic properties (see Fig. 12-12). There may be a direct action of the drug on tissues innervated by cholinergic nerves, but this has not yet been confirmed.

The uses of neostigmine are similar to those of physostigmine, but they differ in that there is greater miotic activity, fewer and less unpleasant local and systemic manifestations, and greater chemical stability. The most frequent application of neostigmine is to prevent atony of the intestinal, skeletal, and bladder musculature. An important use is in the treatment of myasthenia gravis, a condition caused by an autoimmune mechanism that requires an increase in ACh in the neuromuscular junction to sustain normal muscular activity.

Neostigmine Methylsulfate, USP. (*m*-Hydroxphenyl)trimethylammonium methylsulfate dimethylcarbamate; dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate (Prostigmin Methylsulfate). Neostigmine is prepared as in the method previously described, and the quaternary ammonium salt is made with methyl sulfate. This compound is a bitter, odorless, white crystalline powder. It is very soluble in water and is