Kirk-Othmer Encyclopedia of Chemical Technology.

EXPECTORANTS, ANTITUSSIVES, AND RELATED AGENTS

1. Expectorants

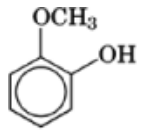
Expectorants enhance the production of respiratory tract fluid and thus facilitate the mobilization and discharge of bronchial secretions. Historically, expectorants have been divided into two classes based on specific mechanisms of action. Stimulant expectorants increase respiratory tract secretion by a direct effect on the bronchial secretory cells. Sedative expectorants act by gastric reflex stimulation. Many compounds classed as expectorants have been inadequately studied and the mechanisms of action are not known with certainty.

The clinical effectiveness of expectorants is a topic of significant controversy. The controversy results from a lack of accepted test methods for evaluating expectorants, with a consequent lack of significant objective data to support effectiveness. For most expectorant products, effectiveness is primarily based on a long history of use and a widespread subjective impression. However, the clinical effectiveness of one expectorant, guaifenesin, is supported by objective data. A randomized, double-blind, placebo-controlled study in 40 patients suffering from chronic bronchitis accompanied by productive cough was submitted to the FDA after this expectorant was classified by the FDA's Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products as Category III, ie, available data insufficient to classify as safe and effective. Statistical data analysis convinced the FDA that guaifenesin loosens and thins sputum and bronchial secretions and makes expectoration easier by increasing sputum volume and reducing sputum viscosity (1). As a result, guaifenesin is the only expectorant permitted for use in U.S. over-the-counter products.

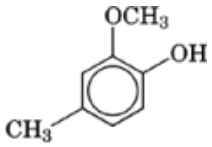
Expectorant preparations have changed dramatically since the 1930s with respect to composition and characterization. For example, in 1941 numerous expectorant formulas were described that contained 20 or more ingredients (2). One such formula, which was recommended for the relief of cough resulting from the common cold, contained thyme herb, horehound herb, grindellia, yerba santa, wild cherry bark, bloodroot, lobelia, squill, pleurisy root, life-everlasting, pipsisewa, mullein, comfrey, elecampane, ammonium chloride, menthol, eucalyptol, gaduol, cascarine, oil of white thyme, glycerol, honey, chloroform, alcohol, and sugar. In the 1990s only a few of the early natural expectorants are in widespread use, and some of these have been chemically modified to improve efficacy or physical characteristics.

1.1. Guaiacols

Cresote, obtained from the pyrolysis of beechwood, and its active principles guaiacol [90-05-1] (**1**) and cresol [93-51-6] (**2**) have long been used in expectorant mixtures. The compounds are usually classed as direct-acting or stimulant expectorants, but their mechanisms of action have not been well studied. Cresol is obtained by the Clemmensen reduction of vanillin (3), whereas guaiacol can be prepared by a number of methods including the mercuric oxide oxidation of lignin (qv) (4), the zinc chloride reduction of acetovanillone (5), and the diazotization and hydrolysis of *o*-anisidine (6).



(**1**)



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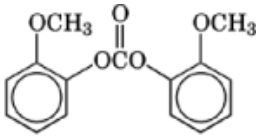
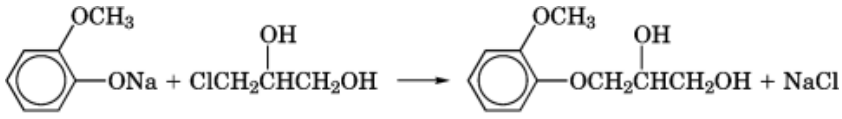


(**3**)

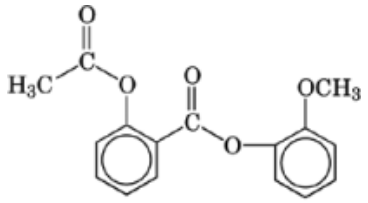
Because of its bitter taste and water insolubility, guaiacol has been chemically modified to improve its properties. Sulfonation provides a mixture of guaiacol-4- and 5-sulfonic acids which, as the potassium salts, is water-soluble, comparatively tasteless, but less active than guaiacol. Treatment of the sodium salt of guaiacol with phosgene provides guaiacol carbonate [553-17-1] (**3**) which also lacks the bitter taste of guaiacol, but is less water-soluble.

Guaifenesin [93-14-1] (**4**), formerly known as glyceryl guaiacolate, is the synthetic guaiacol derivative that has received the greatest acceptance as an expectorant. This compound is widely used, both in single-entity cough preparations and in combination with other active ingredients. Clinical studies carried out in the early 1940s indicated the usefulness of guaifenesin as an expectorant (7, 8). Guaifenesin has also been shown to significantly increase the rate of clearance of inhaled radioactive particles in patients having chronic bronchitis (9). It is the only expectorant permitted for use in U.S. over-the-counter products by the Code of Federal Regulations final monograph on expectorant products (1). Guaifenesin may be prepared by the coupling of sodium guaiacolate and glyceryl monochlorohydrin.



(**4**)

Guacetisal [55482-89-8] (**5**), the acetylsalicylic acid ester of guaiacol, has been shown to retain both antiinflammatory and expectorant activity (10). It is used in Italy for symptomatic relief of painful respiratory disorders.



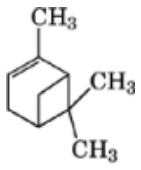
(**5**)

1.2. Volatile Oils

The use of volatile, sometimes called essential, oils as expectorants has been traced back 2000 years to Pliny who used turpentine internally to relieve coughing (11) (see Oils, essential). In spite of long usage, very few objective studies have been carried out to determine their real effectiveness. Limited evidence suggests that the compounds act by direct stimulation of the bronchial secretory cells. Compounds in this category were administered by a number of different routes including oral, topical, by aerosol, as a cream, and sometimes in lozenges. Volatile oils are not permitted for use in U.S. over-the-counter products by the Code of Federal Regulations final monograph on expectorant products (1). Menthol and camphor, however, are permitted in U.S. over-the-counter topical antitussive products, eg, lozenges, chest rubs, vaporizer additives (12).

The volatile oils are isolated from plant sources and are terpenoid in structure. They are purified by a combination of physical and chemical processes. Individual components of the oils are often isolated by crystallization or, in some cases, prepared synthetically.

Turpentine, one of the most familiar oils to be used in expectorant formulations, is prepared by the process of rectification, which consists of steam distillation of crude turpentine from sodium hydroxide, to remove the acidic and resinous components. The rectified oil contains primarily α-pinene [80-56-8] (**6**) along with small amounts of β-pinene. Two common household oils formerly used as expectorants are oil of lemon and oil of anise. Oil of lemon contains about 90% limonene [138-86-3] (**7**) and oil of anise, obtained by steam distilling the dried ripe fruit of *Pimpinella anisum* L., contains primarily anethole [104-46-1] (**8**). Oil of eucalyptus was first introduced into European medicine during the eighteenth century, but received the greatest attention during the mid-nineteenth century when it was used as a substitute for cinchona alkaloid antimalarials (see Alkaloids; Chemotherapeutics, anticancer). During this period the expectorant properties were recognized. Oil of eucalyptus, prepared by steam distilling the leaves of *Eucalyptus globulus* Labill., generally contains not less than 70% cineole (eucalyptol) [470-82-6] (**9**).



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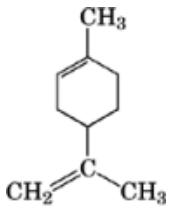

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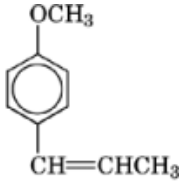

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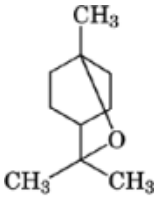
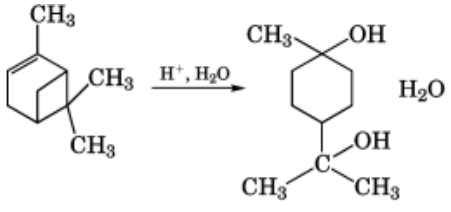


(**9**)

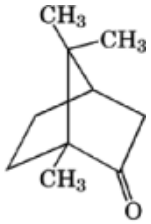
Terpin hydrate [2451-01-6] (**10**), one of the most well-known expectorants, is isolated from crude pine rosin left after the distillation of volatile terpene hydrocarbons and alcohols. It is also manufactured from turpentine (α-pinene) by acid-catalyzed hydration. Terpin hydrate may exist as cis and trans isomers, but only the cis isomer forms a stable, crystalline monohydrate. Terpin hydrate is available in the United States only in prescription products.



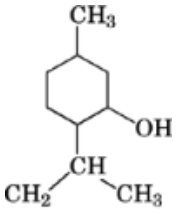
(**10**)

Camphor [126-04-5] (**11**), menthol [89-78-1] (**12**), and thymol [89-83-8] (**13**) are used in topical over-the-counter cough and cold preparations. Camphor is isolated from the camphor tree, *Cinnomomum camphora* T. Nees & Eberneier, or prepared synthetically from α-pinene or isoborneol. About 75% of the camphor sold in the United States is synthetic. Menthol, commercially the most important terpene alcohol, is obtained by crystallization from peppermint oil or prepared synthetically in racemic form by the hydrogenation of thymol. Menthol's local anesthetic activity may contribute to its antitussive properties. Thymol, unlike the other

terpenoids described, contains a fully aromatic ring. It is obtained from the essential oils of *Thymus vulgaris L.* or can be prepared synthetically from *p*-cymene or *m*-cresol.



(**11**)



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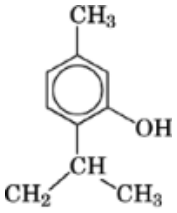
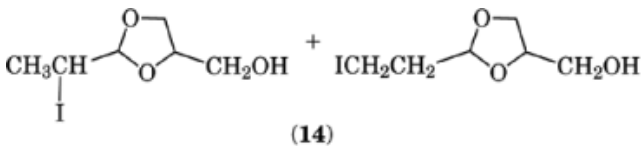


(**13**)

1.3. Iodides and Other Inorganic Compounds

Inorganic compounds such as potassium iodide [7681-11-0], hydriodic acid [10034-85-2], antimony potassium tartrate [28300-74-5], and ammonium chloride [12125-02-9] are thought to act by gastric reflex stimulation. Of these, only the iodides have been studied to any appreciable extent (13). A number of toxic reactions have been associated with both antimony potassium tartrate (14) and inorganic iodides (15, 16). Reaction of iodine with glycerol [56-81-5](qv) produces a stable organic iodide mixture, iodinated glycerol [5634-39-9] (**14**), which has expectorant properties. Formulations of (**14**) contain no free or ionic iodine, but iodine is released metabolically.

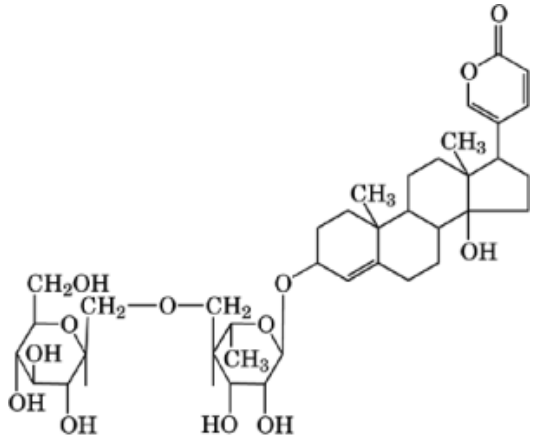


(**14**)

1.4. Miscellaneous Natural Products

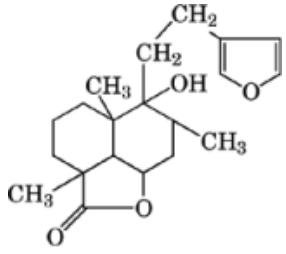
The long list of natural products used in early cough preparations has diminished to the point where only a few are still mentioned. Four natural products still used occasionally outside the United States are squill, horehound, cocillana, and ipecac.

Squill is the dried, sliced bulb of *Urginea maritima* L. Baker and contains the glycosides scillaren A [11003-70-6] (**15**) and scillaren B [1393-22-2], the mixture of glycosides remaining after the separation of scillaren A. It has long been used in cough preparations and, oddly enough, red squill is also used as a rat poison. As an expectorant, squill is usually administered in combination with other ingredients. It is an emetic when given in large doses and this property suggests that the expectorant effect is likely to be caused by reflex stimulation. Toxic effects include nausea, vomiting, and a digitalis-like action on the heart (17).



(**15**)

Horehound is the dried leaves and flowering tops of *Marrubium vulgare* L. Bickerman. It is reported that Serritus, in an early sixteenth century article on cough remedies, recommended the use of syrup of horehound to "purge through the sputa" (18). Although it has frequently been used in cough lozenges, little has been reported concerning its efficacy. The active principle in horehound is the diterpene lactone, marrubiin [465-92-9] (**16**).



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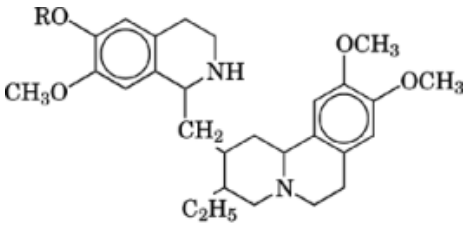


(17) R = CH_3
(18) R = H

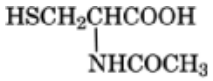
Ipecac is prepared from the dried roots and rhizomes of *Cephaelis ipecacuanha* (Brot.) A. Rich. and contains the alkaloids emetine [483-18-1] (**17**) and cephaeline [483-17-0] (**18**) in a ratio between 2:1 and 4:1. It has been used extensively in cough preparations and is believed to act by gastric reflex stimulation. Toxic effects include vomiting, irritation of the gastrointestinal tract, and cardiac arrhythmias (19). Ipecac syrup is available over-the-counter in the United States only in 30-mL containers for use as an emetic in treating poisonings.

Cocillana, the dried bark of *Guarea rusbyi* (Britt.) Rusby, was probably first used by the natives of the Bolivian Andes as an emetic–cathartic. It is often prescribed as an alternative to ipecac in the treatment of cough, and the emetic side effects at high doses suggest a mechanism of action similar to that of ipecac.

2. Mucolytics

Mucolytics reduce the viscosity of tenacious and purulent mucus, thus facilitating removal. The distinction between mucolytics and other classes of expectorants is frequently blurred. Steam, sometimes in conjunction with surfactants or volatile oils, has long been used to decrease viscosity by physical hydration. However, agents that chemically depolymerize certain components of mucus are available. Trypsin and other proteolytic enzymes have shown good clinical activity because of their ability to cleave glycoproteins. Pancreatic dornase, which depolymerizes DNA found in purulent mucus, also has shown clinical utility.

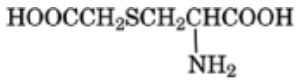
Several mucolytics reduce the viscosity of mucus by cleaving the disulfide bonds that maintain the gel structure. *N*-Acetyl-L-cysteine [616-91-1] (**19**), introduced in 1963, and mesna [19677-45-5] 20, developed in Europe in the early 1970s (20, 21), are effective compounds in this class. Whereas most mucolytics must be administered by aerosol, carbocysteine [638-23-6] (**21**), which contains a derivatized sulfhydryl group, has shown activity by the oral route (22, 23). However, carbocysteine does not reduce mucus viscosity, as does acetylcysteine, but appears to have a direct action on mucus glycoprotein production (24).



(19)

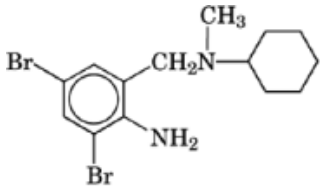
$HSCH_2CH_2SO_3Na$

(20)

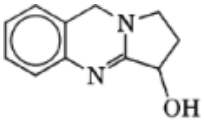


(**21**)

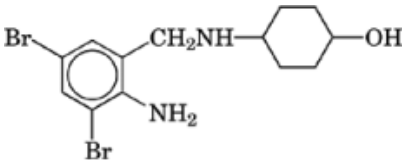
Bromhexine [611-75-6] (**22**), a highly substituted aniline derivative, has been shown to decrease the viscosity and increase the volume of mucus. Part of its activity has been attributed to its ability to fragment mucopolysaccharide fibers. Bromhexine is structurally related to the alkaloid vasicine [6159-55-3] (**23**), the active principle from the plant *Adhatoda vasica* Nees which has been used by the East Indians as an herbal medicine for the relief of cough. The pharmacological and clinical properties of bromhexine have been reviewed (25, 26). The preparation of bromhexine follows standard procedures to *N*-(2-aminobenzyl)-*N*-cyclohexyl-*N*-methylamine which is then brominated to give (**22**) (27).



(**22**)



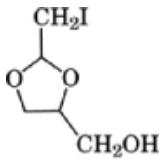
(**23**)



(**24**)

Ambroxol [18683-91-5] (**24**), a metabolite of bromhexine, has also shown potent clinical activity (28). Various esters of ambroxol have been shown to be 1.1 to 1.6 times more active as expectorants than ambroxol (29). The esters also show better gastric tolerability and more rapid absorbtion than ambroxol.

cis-4-Hydroxymethyl-2-iodomethyl-1,3-dioxolane [61508-55-2] (**25**), a compound structurally similar to one component of iodinated glycerol (**14**), was shown to exhibit expectorant activity and mucolytic activity of the same order of magnitude as carbocysteine in rabbits (30). It also had a direct liquefying action on mucus *in vitro*. Acute and chronic toxicity in rats, mice, and dogs was low. The compound was prepared by the reaction of *cis*-4-hydroxymethyl-2-bromomethyl-1,3-dioxolane and sodium iodide. Decasilate [76652-72-7] (**26**) has been shown to possess significant mucolytic activity in rabbits. It also reduces bronchial seizures induced by citric acid in guinea pigs (31).



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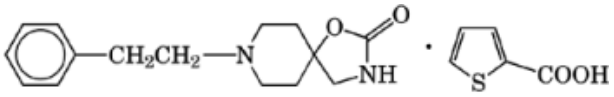


(26)

3. Antitussives

Records from antiquity describe the use of soothing syrups and herbal extracts to control excessive coughing. The use of goat's milk fresh from the udder for acute and chronic cough was reported in a review of ancient Hebrew medicine (32). Galen, in the second century AD, may have been the first to report a truly effective antitussive preparation, camphorated opium tincture (18). Through the centuries, cough remedies have remained a popular item and are found in most medicine cabinets. Over 300 prescription and over-the-counter preparations are available (33), and retail sales of nonprescription cough syrups, expectorants, and cough drops in 1995 are expected to exceed $2 billion (34).

3.1. The Cough Reflex

Coughing is a protective reflex and is one of several important mechanisms for clearing the respiratory tract of excessive secretions and foreign debris, thus ensuring normal gas exchange and minimizing infection. It can be described as occurring in three phases: (*1*) a short deep inspiration of air into the lungs; (*2*) compression of the air by closure of the glottis, and contraction of the thoracic, abdominal, and diaphragmatic muscles; and (*3*) rapid expulsion of the air when the glottis opens. The intensity of the cough varies according to the force behind the expiration. In some cases the expired air moving through the trachea may achieve a linear velocity of >800 km/h (35). The cough reflex can be triggered by chemical, mechanical, or other stimuli to the sensory nerve endings of the respiratory tract. The mechanical receptors generally are confined to the mucosa of the large airway of the upper respiratory tract, especially the lower third of the trachea. The chemical receptors are distributed widely and respond to almost any irritant. Stimulation of the sensory receptors causes impulses to pass along afferent nerve pathways to the cough center in the medulla. Here they are coordinated and transmitted by efferent or motor pathways to abdominal and intercostal muscles, and the diaphragm. Evidence suggests that irritation of the bronchial mucosa may not lead directly to stimulation of the cough receptors. Instead, bronchoconstriction may result first, which then triggers the cough reflex (13, 36). The intensity of the cough is regulated to some extent by the stretch receptors located in the alveolar walls of the lungs.

Coughing can be produced by a number of environmental factors and pathological disorders. The common cold is the most frequent cause of transient cough in children and adults, and cigarette smoking is the most common cause of chronic, persistent cough (37). Changing causative factors from the 1870s to the 1970s are summarized (38).

Other factors that affect cough and the expulsion of irritants from the respiratory tract include ciliary activity and the production and physical characteristics of respiratory tract fluid. Under normal circumstances,

the sweeping action of the cilia propels the demulcent fluid secreted by the goblet cells and the bronchial glands toward the glottis where it is swallowed or expectorated. Respiratory tract fluid is polymeric by nature, containing numerous polysaccharide units attached to a protein core. Large amounts of water and salt can be bound within the matrix, providing an ideal medium for transporting bacteria and debris away from the lungs. Pathological conditions or other factors which alter either ciliary activity, or the composition, amount, and physical properties of respiratory tract fluid may affect the frequency and productivity of coughing. Excellent reviews and monographs dealing with mucociliary clearance (39) and the role and physical characteristics of respiratory tract fluid (40–42) are available.

Theoretically, the act of coughing can be affected directly or indirectly by one or more of the following: (*1*) elimination of the ultimate cause of the cough by treating the responsible pathological condition, or by removing the anatomical or environmental irritant; (*2*) raising the threshold for stimulation of cough peripherally by anesthetizing sensory nerve endings in the respiratory tract; (*3*) interruption of the sensory impulses to the medulla; (*4*) specific depression of the cough center in the medulla; (*5*) interruption of conduction along the motor pathways; (*6*) nonspecific depression of the central nervous system; and (*7*) facilitating bronchial drainage and mucociliary clearance.

The first approach is considered ideal if the necessary relief can be obtained quickly enough. Most therapeutic agents, however, act by one or more of mechanisms (*2*), (*4*), and (*7*). The first pharmacological technique that permitted an objective evaluation of antitussive activity in animals was described in 1938 (43). Since that time, a number of methods have been developed that produce experimental cough by stimulating the respiratory tract, the vagus nerve, or the medulla by chemical, mechanical, or electrical means. Unfortunately, the large number of response criteria, species variation, and other factors reduce the value of these methods for predicting clinical efficacy and potency. Meaningful comparisons of antitussive drugs against pathologic cough in humans are often difficult to obtain owing to varied etiologies and intrinsic variability associated with small patient populations. For this reason, artificially induced cough is frequently used to measure antitussive activity clinically. A number of diverse chemical agents, such as citric acid, acetylcholine, acetic acid, sulfur dioxide, and ammonia have been used as stimulants. Several excellent reviews describe methods for the evaluation of antitussive drugs in animals and humans (44–46).

3.2. Centrally Active Antitussives

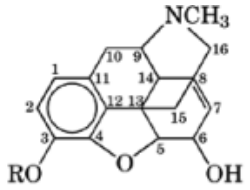
Centrally active antitussives depress the medullary cough center, thus raising the threshold for sensory cough impulses. The most well-known compounds in this category are the narcotics. Unfortunately, many of them have the disadvantage of addiction. Molecular modifications of the morphine skeleton and the synthesis of totally new structures have produced more specific drugs without the disadvantage of addiction. Many of the synthetic compounds also possess other useful properties including local anesthetic and antispasmodic activity (see also Analgesics, antipyretics, and antiinflammatory agents).

3.2.1. Narcotic Antitussives

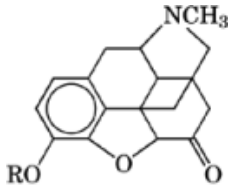
Since its isolation in 1832, codeine [76-57-3] (**27**) has been one of the most widely used and effective compounds for the treatment of cough. Though less potent than morphine [57-27-2] (**28**), it has become the reference against which most antitussives are measured. Codeine, like morphine, is isolated from the opium poppy. However, the low yield of 0.7–2.5% does not provide sufficient material to meet commercial demands. The majority of marketed codeine is prepared by methylating the phenolic hydroxyl group of morphine. Morphine yields from opium poppy are 4–21%. When prescribed for cough, the usual oral dose is 10–20 mg, three to four times daily. At these doses, adverse side effects are very few. Although the abuse potential for codeine is relatively low, the compound can substitute for morphine in addicts (47).

Molecular modifications of the morphine skeleton have produced numerous derivatives with antitussive properties, some of which have become commercially significant. Ethylmorphine [76-58-4] (**29**), a simple

homologue of codeine, is prepared by ethylating morphine. It is pharmacologically similar to codeine but is seldom used clinically. Pholcodine [509-67-1] (**30**), the morpholinoethyl derivative of morphine, is used as an antitussive in a number of European countries. It is about one and a half times as potent as codeine, has little or no analgesic activity, and produces minimal physical dependence. The compound is prepared by the aminoalkylation of morphine (48).



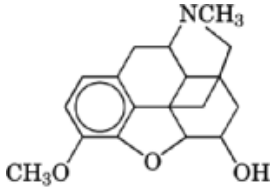
(**27**) R = CH_3
(**28**) R = H
(**29**) R = C_2H_5
(**30**) R = CH_2CH_2N 



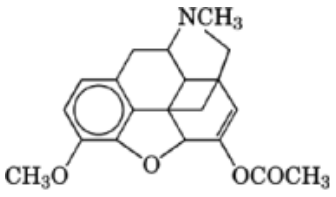
(**31**) R = H
(**32**) R = CH_3

Hydromorphone [466-99-9] (**31**) and hydrocodone [125-29-1] (**32**) are isomers of morphine and codeine, respectively. Hydromorphone can be prepared by catalytic rearrangement of morphine (49) or by oxidation of the aliphatic hydroxyl group of dihydromorphine (50). Hydrocodone can be similarly prepared. As an antitussive, hydromorphone is several times more active than morphine and hydrocodone is slightly more active than codeine. Hydromorphone has a much higher addiction potential than hydrocodone.

Dihydrocodeine [125-28-0] (**33**), introduced in Germany before 1930, and dihydrocodeinone enol acetate [466-90-0] (**34**) both have clinical activity and addiction potential comparable to codeine.

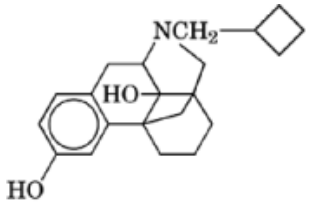


(**33**)

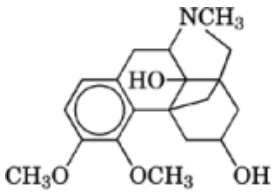


(**34**)

Modifications of the morphine skeleton have produced butorphanol [42408-82-2] (**35**) and drotebanol [3176-03-2] (**36**), which in animal models have demonstrated antitussive activity much greater than that of codeine (51, 52). Butorphanol is also a potent analgetic of the narcotic antagonist type (51). Both compounds possess a unique 14-hydroxyl group.

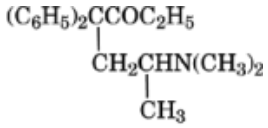


(**35**)

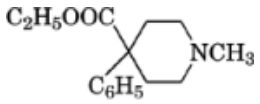


(**36**)

Among the nonopiate narcotics, two compounds, methadone [1095-90-5] (**37**) and meperidine [57-42-2] (**38**) have shown antitussive activity. Methadone is qualitatively morphine-like, and has demonstrated clinical activity against coughing induced by ammonia (53) and citric acid aerosol (54). Meperidine (**38**), although normally not thought of as an antitussive, has been shown to inhibit spasmodic coughing associated with bronchial asthma (55). The addiction potential of both of these agents limits clinical use for treating cough. A convenient synthesis for methadone which avoids the production of undesirable isomeric intermediates has been described (56). Meperidine can be synthesized by a number of different routes, but the method starting with phenylacetonitrile is one of the most practical (57).



(**37**)

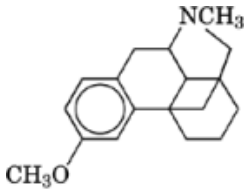


(**38**)

Side effects associated with narcotics include nausea, anorexia, and constipation; most of them also diminish ciliary activity and produce a drying effect on the respiratory tract mucosa.

3.2.2. Nonnarcotic Antitussives

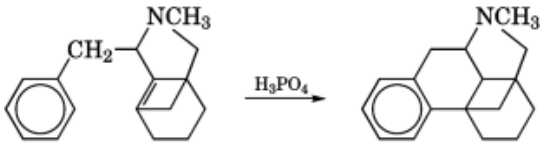
The most centrally active, nonnarcotic antitussive is dextromethorphan [125-71-3] (**39**). It is similar to codeine in terms of potency and mechanism of action, ie, it is a direct depressant of the cough center. It is unique in that even though it is structurally related to codeine, it is not addictive.



(**39**)

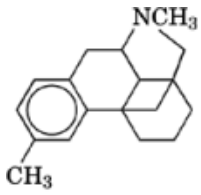
The synthesis of dextromethorphan is an outgrowth of early efforts to synthesize the morphine skeleton. *N*-Methylmorphinan(**40**) was synthesized in 1946 (58, 59). The 3-hydroxyl and the 3-methoxy analogues were prepared by the same method. Whereas the natural alkaloids of opium are optically active, ie, only one optical isomer can be isolated, synthetic routes to the morphine skeleton provide racemic mixtures, ie, both optical isomers, which can be separated, tested, and compared pharmacologically. In the case of 3-methoxy-*N*-methylmorphinan, the levorotatory isomer levorphanol [77-07-6] (levorphan) was found to possess both analgesic and antitussive activity whereas the dextrorotatory isomer, dextromethorphan (**39**), possessed only antitussive activity. Dextromethorphan, unlike most narcotics, does not depress ciliary activity, secretion of respiratory tract fluid, or respiration.

The Grewe synthesis of *N*-methylmorphinan [3882-38-0] (**40**), which paved the way for the preparation of dextromethorphan and numerous analogues, follows standard reactions to 2-methyl-1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. Cyclization of this compound with phosphoric acid gave a mixture of isomers from which *N*-methylmorphinan was separated.



(**40**)

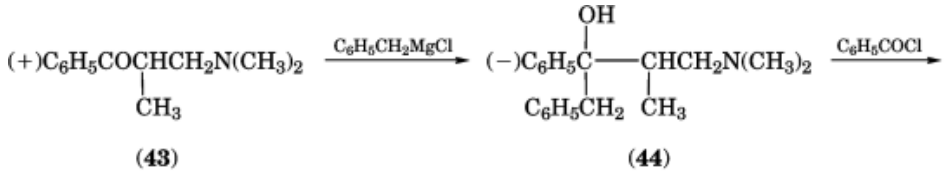
The synthesis (60) and potent antitussive activity (61) of dimemorfan [36309-01-0] (**41**), D-3-methyl-*N*-methylmorphinan, have been reported. This compound, prepared by a modification of the Grewe process, differs from dextromethorphan only by having a methyl group, rather than a methoxy group, in the 3 position.



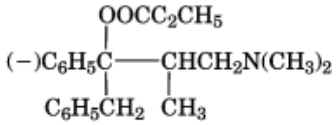
(**41**)

Included in the nonnarcotic class of antitussives are many compounds that do not possess a morphine skeleton and which vary widely from each other with respect to structural features and pharmacologic profiles.

Levopropoxyphene [2338-37-6] (**42**), the optical antipode of the dextrorotatory analgetic propoxyphene, is an antitussive without analgetic activity. The 2-naphthalenesulfonate salt has a less unpleasant taste than the hydrochloride salt, and is widely used. Clinical effectiveness has been demonstrated against pathological and artificially induced cough, but the potency is somewhat less than codeine. The compound is reported not to cause addiction. Levopropoxyphene can be prepared (62) by first resolving β-dimethylamino-α-methylpropiophenone with dibenzoyl-(+)-tartaric acid. The resolved (+)-propiophenone [93-55-0] (**43**) is then treated with benzylmagnesium chloride to give (**44**), which is converted by acylation to levopropoxyphene.

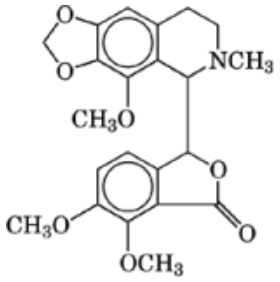


(**43**) (**44**)



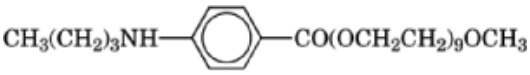
(**42**)

Noscapine [128-62-1] (**45**) is the second most abundant alkaloid found in opium. Unlike most opium alkaloids, however, it has an isoquinoline rather than a phenanthrene ring system. Noscapine was first isolated in 1817 but its antitussive activity was not demonstrated pharmacologically until 1952 (63). Clinical studies have confirmed its effectiveness. It is not a narcotic and has a wide margin of safety when given orally. Death could be produced in rats only with doses > 800 mg/kg (64). Noscapine is isolated from the water-insoluble residue remaining after processing opium for the manufacture of morphine.

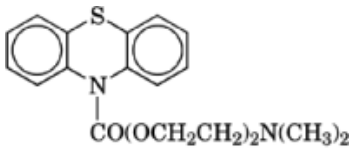


(45)

Benzonatate [104-31-4] (**46**) is a unique compound which appears to have both central and peripheral antitussive effects. Structurally it is a derivative of *p*-aminobenzoic acid and contains a long poly(ethylene glycol) side chain. The peripheral effects are the result of local anesthetic action on the pulmonary stretch receptors. Clinical activity was first reported in 1955 (65).



(46)



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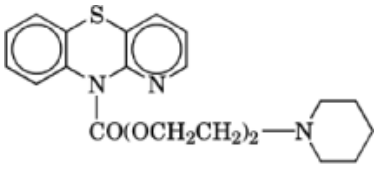
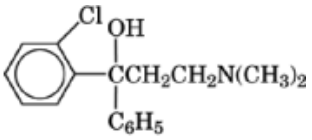


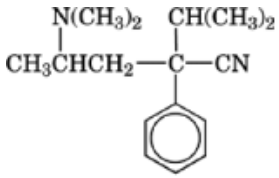
(48)

Dimethoxanate [477-93-0] (**47**) and pipazethate [2167-85-3] (**48**) are related phenothiazine derivatives that have shown antitussive activity. Unlike many phenothiazines, these do not produce central nervous system depression or analgesia at therapeutic doses. They are both somewhat less potent than codeine. It has been suggested that the unique side chain that is similar to, but shorter than, the one on benzonatate, may be at least partly responsible for the antitussive effects. Both dimethoxanate and pipazethate are the result of molecular modifications of classical phenothiazines, such as promethazine [60-87-7], which possess antitussive activity in addition to central nervous system depressant activity. Dimethoxanate can be prepared by the reaction of phenothiazine-10-carboxylic acid chloride with β-dimethylaminoethoxyethanol (66).

Chlophedianol [791-35-5] (**49**) is the most potent antitussive in a series of compounds originally synthesized as potential antispasmodics. It is about one-third as active as codeine and has weak antispasmodic and local anesthetic activity. Although the onset of antitussive activity is slow, the duration is prolonged. Chlophedianol can be prepared from 2-chlorophenylphenylmethanone (67).



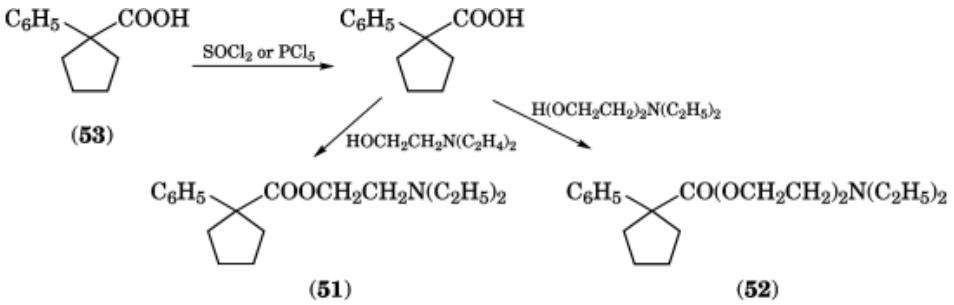
(**49**)



(**50**)

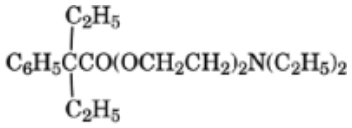
The citrate salt of isoaminile [77-51-0] (**50**) is a nitrile used as an antitussive in numerous European countries. In clinical trials it was shown to be as effective as codeine or chlophedianol, with few mild side effects. Isoaminile citrate is longer acting than chlophedianol and does not cause the respiratory depression of codeine (68).

Caramiphen [125-86-0] (**51**) and carbetapentane [77-23-6] (**52**) are structurally related antitussives which, like chlophedianol, also possess antispasmodic and local anesthetic activity. Caramiphen is also a potent anticonvulsant (69) (see Hypnotics, sedatives, and anticonvulsants). These compounds differ in that the ester side chain of carbetapentane is lengthened by an ethyleneoxy unit. Caramiphen is usually administered for antitussive activity as an ethanedisulfonate salt. It is comparable to codeine in potency but appears to have a longer duration of action. Experimentation has provided evidence that caramiphen has a central rather than a peripheral site of antitussive action (70). Carbetapentane is slightly less active than codeine. Both caramiphen and carbetapentane produce typical atropine-like side effects including dryness of the mouth and visual disturbances. They can be synthesized (71, 72) from a common intermediate, 1-phenylcyclopentanecarboxylic acid [77-55-4] (**53**).



(**53**) (**51**) (**52**)

Oxeladin [468-61-1] (**54**), an antitussive developed in the UK, is structurally related to carbetapentane in that the cyclopentane ring has been broken at the 3,4-bond. It is also similar pharmacologically. Extensive clinical studies using cough drops and syrup containing oxeladin are described (73). The compound can be synthesized from phenylacetonitrile (74).

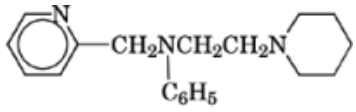


(**54**)

Diphenhydramine [58-73-1] 55 was originally developed as an antihistamine and was first used clinically for this purpose in 1946 (see Histamine and histamine antagonists). In addition to this primary effect, however, central antitussive activity has also been demonstrated in animals (75, 76) and in humans (77). Its antitussive activity is about half that of codeine. Drowsiness is the most frequent side effect. Diphenhydramine can be prepared as follows (78):

$$(C_6H_5)_2CHBr + HOCH_2CH_2N(CH_3)_2 \xrightarrow{Na_2CO_3} (C_6H_5)_2CHOCH_2CH_2N(CH_3)_2 + HBr \qquad (55)$$

Another antitussive with weak antihistaminic activity is the Japanese compound picoperine [21755-66-8] (**56**). This compound is a structural isomer of the well-known antihistamine tripelennamine and is more potent than codeine. The chemistry (79) and pharmacology (80) of picoperine have been reported.



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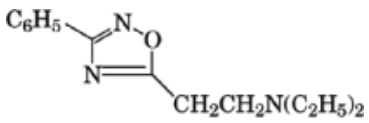
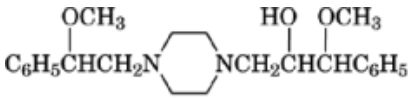


(**57**)



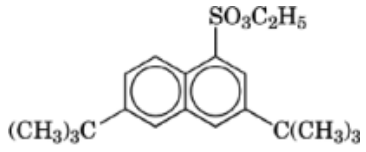
(**58**)

Oxolamine [959-14-8] (**57**) is sold in Europe. It is an oxadiazole, and its general pharmacological profile is described (81). The compound possesses analgesic, antiinflammatory, local anesthetic, and antispasmodic properties, in addition to its antitussive activity. Although a central mechanism may account for some of the activity, peripheral inhibition of the cough reflex may be the dominant effect. The compound has been shown to be clinically effective, although it is less active than codeine (82, 83). The synthesis of oxolamine is described (84).

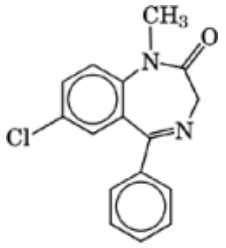
Zipeprol [34758-83-3] (**58**) is another European antitussive with a wide range of pharmacological effects, including antispasmodic, antihistaminic, and local anesthetic activities (85, 86). It has been reported that zipeprol has been abused in Italy because high doses cause hallucinations (87). Spontaneous withdrawal symptoms similar to those of opiates have been observed; withdrawal symptoms can also be precipitated by naloxone.

Zipeprol can be prepared from 1-(2-methoxy-2-phenylethyl)piperazine and 3-methoxy-3-phenylpropylene oxide (88).

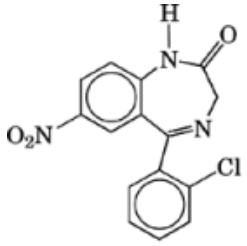
Ethyl dibunate [5560-69-0] (**59**), which is sold in Canada, is the ethyl ester of 3,6-(*tert*-butyl)-1-naphthalenesulfonic acid. It is structurally unrelated to most of the classical antitussives and is a selective central inhibitor of the cough reflex. Also significant is its low toxicity. The oral LD_{50} is greater than 5000 mg/kg in the rat. The clinical and pharmacological profile of this compound has been reviewed (89).



(**59**)



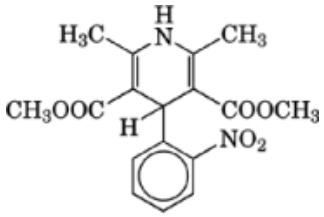
(**60**)



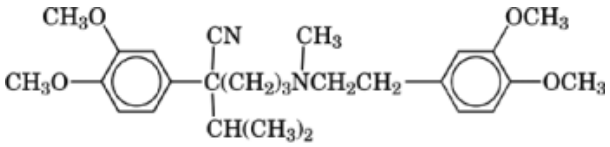
(**61**)

Diazepam [439-14-5] (**60**) and clonazepam [1622-61-3] (**61**) suppress cough induced by electrical stimulation of the lower brainstem of cats (90). Clonazepam and diazepam administered intravenously are about thirty-five times and six times more potent than codeine, respectively. Nevertheless, the compounds have not been widely used as antitussives in humans. Diazepam is used in the treatment of anxiety, and clonazepam as an anticonvulsant.

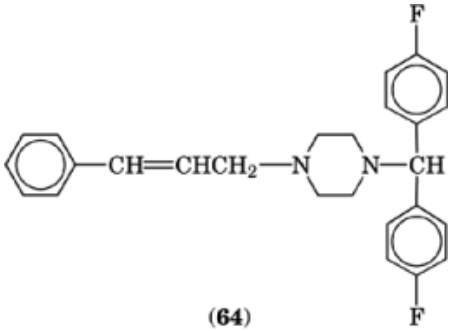
The calcium ion antagonists nifedipine [21829-25-4] (**62**), verapamil [52-53-9] (**63**), and flunarizine [52468-60-7] (**64**) exhibit antitussive effects in a dose-dependent manner in guinea pigs (91). Pretreatment with a subthreshold dose of nifedipine also markedly increased the antitussive effects of morphine, dihydrocodeine, and dextromethorphan. However, none of the calcium ion antagonists are used clinically as antitussive agents. They are used in the treatment of angina and hypertension (see Cardiovascular agents).



(**62**)

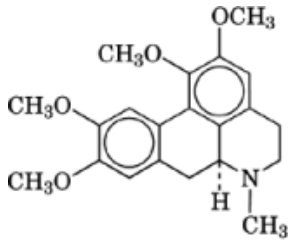


(**63**)

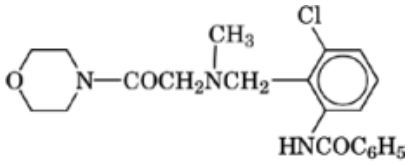


(**64**)

Glaucine [475-81-0] (**65**) has been compared against codeine for antitussive and toxic effects (92). In cats and dogs, the antitussive effect was 0.2 to 0.8 that of codeine, depending on the route of administration. The respiratory and cardiovascular effects of glaucine are similar to those of codeine but are generally less marked. Other studies concluded that glaucine appears to be safe for clinical use as an antitussive (93) and that the drug appears to exert its effect directly on the cough center (94).



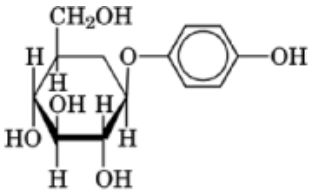
(**65**)



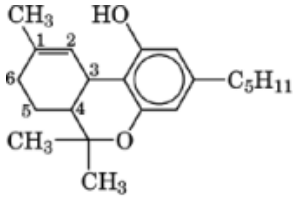
(66)

Fominoben [18053-31-1] (**66**) is another nonnarcotic drug which has shown antitussive activity comparable to codeine when administered both orally or parenterally in a variety of animal species (95).

Arbutin [497-76-7] (**67**) has been suggested as a potential antitussive (96). Both oral and intraperitoneal administration of arbutin to mice in a range of 50 to 200 mg/kg showed a concentration-dependent activity against ammonia induced cough.



(67)



(68)

Among the long list of diverse structures reported to possess central antitussive activity is Δ^1-tetrahydrocannabinol (THC) [1972-08-3] (**68**), the principal psychoactive component of marijuana (see Psychopharmacological agents). This compound was found to be comparable to codeine against electrically induced cough in the anesthetized cat (90). Two other naturally occurring cannabinoids, cannabidiol and cannabinol, are inactive.

Except for the addiction liability of some of the narcotic antitussives, side effects for most of the centrally acting compounds are relatively few and mild at therapeutic doses. Qualitative comparisons of both side effects and pharmacological profiles have been summarized for many of the compounds described above (97).

3.3. Peripherally Active Antitussives

Peripherally active antitussives act by raising the threshold for cough at the sensory nerve endings, or by facilitating bronchial drainage, mucociliary clearance, or both. Agents that act by the first mechanism include local anesthetics that desensitize the mucosa of the respiratory tract, and antispasmodics that relax the smooth muscles of the bronchi (see Neuroregulators). Most of these compounds also have a central antitussive component as a part of their pharmacological profile and have been previously discussed. Expectorants and mucolytics act primarily by the second mechanism.

Table 1. Shipment Values for Cough or Cough–Cold Preparations, $ × 10^6

Product	1967	1977	1991
cough preparations and expectorants[a]			
narcotic	27.4	56.7	133.1
nonnarcotic	15.9	40.2	30.1
cough–cold combinations[a]	7.3	11.6	132.0
cough–cold preparations[b]			
cough syrups	44.5	84.0	365.2
capsules and tablets	38.3	98.6	409.5
lozenges	14.8	25.8	51.1
topical preparations	0.9	[c]	[c]
cough drops		[c]	90.6
other preparations	23.1	98.8	224.3

[a]Prescription products.
[b]Over-the-counter products.
[c]Shipment value combined with value for other preparations.

4. Economic Aspects

Sales figures for expectorants and antitussives are usually combined under the general headings of cough preparations or cough and cold preparations. Antitussives and expectorants are frequently formulated together for the treatment of cough, or formulated with antihistamines and bronchodilators for the treatment of cold symptoms. Department of Commerce figures for the total value of manufacturer's shipments of cough or cough and cold preparations are shown in Table 1 (98–100).

At the retail level, sales of nonprescription cough syrups, elixirs, and expectorants at all outlets were $365.2 million in 1991 compared to $304.8 million in 1978 (100, 101). Sales of prescription cough preparations and expectorants were $163.1 million in 1991 (100). Among narcotic antitussives, codeine (**27**) is by far the leading product. However, sales of codeine-containing cough preparations have declined in recent years, probably because of the increased acceptance of nonnarcotic antitussives such as dextromethorphan (**39**). U.S. figures show drugstore and hospital purchases of codeine for antitussive use declining from 7.71 t in 1972 to 6.38 t in 1977, with a projected decline to 5.77 t in 1981 (102).

5. Health and Safety

Safety and efficacy data on a number of antitussives and expectorants have been reviewed by the FDA's Advisory Review Panel on Over-the-Counter (OTC) Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Products. The conclusions and recommendations regarding the effectiveness, safety, labeling, and suitability for marketing of over-the-counter preparations have been reported (103). After review of these recommendations, FDA has issued final monographs for over-the-counter antitussives (12) and for expectorants (1). LD_{50} data for most of the compounds described have been reported (104, 105).

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