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Review Article

Structure-Activity Relationships of Drugs Affecting the Lungs

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THE LUNGS can respond to drugs in four different ways: (*a*) there are sensory nerve endings in the lung parenchyma which can be stimulated chemically to influence respiration, (*b*) the smooth muscles of the bronchioles can be contracted or relaxed by drugs and therefore alter the resistance to flow of air during respiration, (*c*) the smooth muscles of the pulmonary vessels can be constricted or dilated by drugs and therefore alter the resistance and pressure of blood flowing in the pulmonary circulation, and (*d*) the total amount of pulmonary blood flow can be reduced or increased by a primary action of drugs on the heart and systemic vessels. This paper will review each of these four types of actions with special emphasis on the relationships of chemical structure to physiological activity as observed on various structures of the lungs.

It should be stated at the outset that no drug has its action limited to only one structure in the lungs. For example, one sympathomimetic amine, like epinephrine, can influence bronchiolar muscle tone, pulmonary vascular tone, and pulmonary blood flow. Another sympathomimetic amine, such as methoxamine, can influence only pulmonary blood flow, but not directly the bronchiolar and pulmonary vascular smooth muscles; however, the consequences of a primary systemic pressor action include reflex increase in vagal tone which can include bronchoconstriction. These examples serve to demonstrate the differences in extent of action of drugs belonging to the sympathomimetic class, and this is true also for xanthines and antihistaminics which will be discussed below. An attempt will be made to explain such differences on the basis of chemical structure. As new compounds are developed, it is possible that some of them may prove clinically useful as selective respiratory stimulants, bronchodilators, and pulmonary vasodilators.

REFLEXES FROM THE LUNGS

Nature of Drug Action.—The respiratory effects of chemical stimulation of receptors in the lungs have been reviewed (1, 2). These receptors are supplied by the vagal innervation of the lungs and, when stimulated, would cause temporary apnea followed by tachypnea. These receptors that influence respiration are believed to be normally functioning as stretch receptors in the lung parenchyma (Hering-Breuer reflex) and baroreceptors in the pulmonary vessels (Bezold-Jarisch reflex). It has not been possible to show any direct response to the latter receptors because isolation from other vagal receptors innervating surrounding structures is difficult.

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Active Compounds.—The following compounds have been shown to increase the activity of the pulmonary stretch receptors: inhalation of ether, trichlorethylene, and chloroform (3); intravenous injection of veratrum alkaloids (4–6), 5-hydroxytryptamine (7), amidines (8), aconitine (9), strychnine (10), and antihistaminic compounds (11). The following compounds have been shown to elicit the reflex from the lungs, but action potential studies are still lacking: nicotine (12), lobeline (13), tributyrin (14), capsaicin (15, 16), andromedotoxin (17), benzofurans (18), and aminoethylisothiuronium (19).

The variety of compounds that elicit a respiratory reflex from the lungs makes it difficult to specify a common pharmacological action to explain the response. It is very probable that the receptors are stimulated in one of three ways: (*a*) direct action of the compound on the sensory nerve ending; (*b*) direct action of the compound on the vessels which will in turn stimulate the baroreceptors; and (*c*) direct action of the compound on the bronchiolar smooth muscle which will in turn influence the sensitivity of the stretch receptors. Although actions (*b*) and (*c*) will be discussed below, it should be stated here that such actions have not been investigated for most of the compounds that elicit the respiratory reflex.

Antihistaminic Compounds.—This group deserves some special attention because it has been adequately studied from several standpoints. Winder and Thomas (20) reported that diphenhydramine caused apnea followed by tachypnea when injected intravenously in the anesthetized dog. Because the effects were eliminated by vagotomy, they postulated that the respiratory effect was due to a central augmentation by the drug of normal vagal proprioceptive impulses from the lungs. Catheterization of the cardiopulmonary circulation showed that this antihistaminic drug was acting not centrally, but peripherally, on receptors in the lungs (21). Takasaki, *et al.* (22), reconfirmed the reflex nature of the response in other animal species (cat and rabbit). Jones (23) showed in such species that the respiratory reflex could not be explained entirely by pulmonary stretch receptors but suggested other receptors in the lungs which have not yet been identified. Unlike most other compounds, the antihistaminics do not stimulate cardiac receptors responsible for bradycardia and hypotension.

Possible Clinical Use.—In the anesthetized animal, the reflex induced by antihistaminic compounds consists of an initial apnea followed by prolonged tachypnea. If the latter response were confirmed in man, it would be possible to develop a new type of respiratory stimulant. Most clinically useful stimulants act centrally and therefore have other undesirable effects (convulsions), so that a stimulant acting exclusively by reflexes would be expected to be free of such central actions.

Structure-Activity Relationships.—Another special feature of the antihistaminic group is that 27 compounds have been tested for reflex respiratory action (21). The results allow the following generalizations in structure-activity relationships: (*a*) Almost all of the antihistaminic compounds tested have a basic ethylamine structure. (*b*) The nature of substitution of the amine partly determines the ability of the compound to elicit the reflex. The most active compounds have either two methyl or two ethyl substituents. (*c*) The nature of aromatic substituents at the β-carbon atom also influences the activity of the compound. The active and inactive substituents are summarized in Fig. 1.

BRONCHODILATATION

Active Compounds.—Hawkins (24) has compiled a series of tables which summarize the effects of several types of compounds on the bronchiolar smooth muscles. It is apparent from such tables that several groups of compounds can be depended upon to relax bronchiolar smooth muscles, particularly after spasm induced by histamine. The groups are as follows: sympathomimetic amines, parasympathetic blocking drugs, local anesthetics, antihistaminics, and a miscellaneous group of compounds with musculotropic action.

Sympathomimetic Amines.—This group has been used widely in the treatment of bronchial asthma. The major limitation in the clinical use is the accompanying effects on the cardiovascular system. These side effects have been systematically compared in anesthetized dogs (25), and the pattern of action for each of six bronchodilators are as follows: (*a*) Isoproterenol injected directly into the common carotid, vertebral, superior mesenteric, and external iliac arteries causes vasodilatation. This action is the major cause for the systemic arterial hypotension. It masks the accompanying cardiac stimulation which can be detected as increases in myocardial force of contraction and in pulmonary blood flow. (*b*) Methoxyphenamine and (*c*) isoprophenamine cause systemic vasodilatation similar to that of isoproterenol, but much larger doses are required. The accompanying effect on the heart is a depression of myocardial force of contraction. (*d*) Epinephrine causes vasoconstriction when injected into

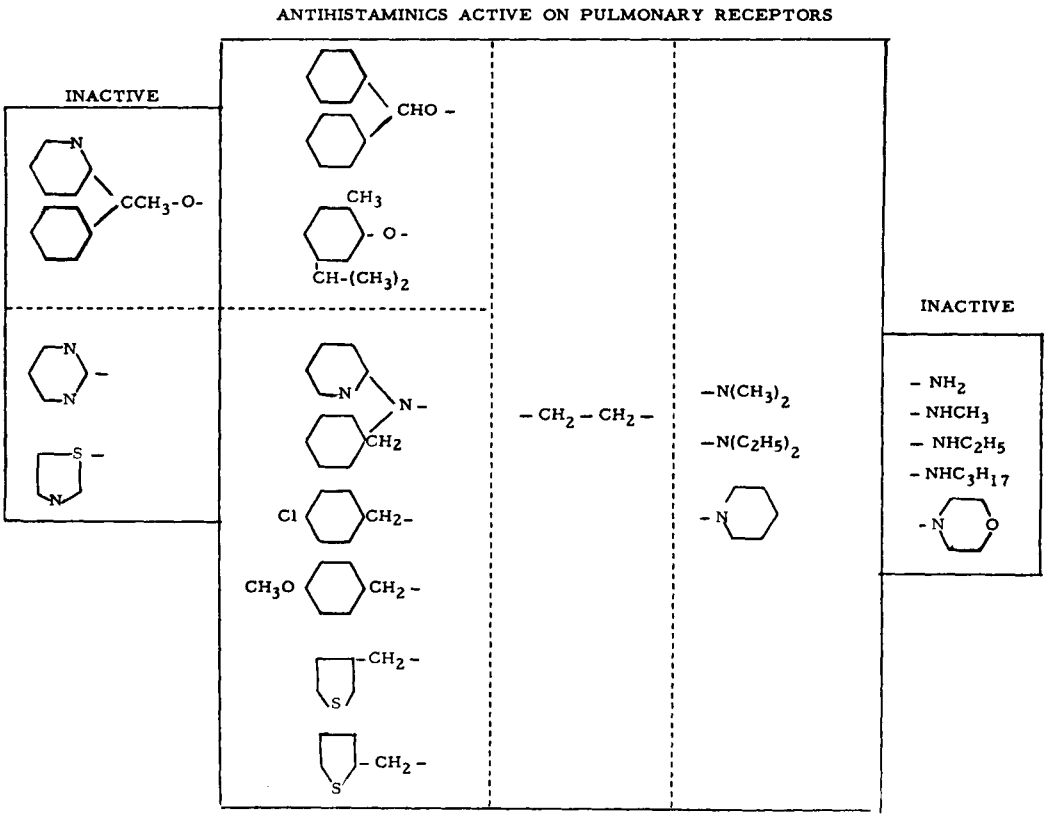


Fig. 1.—Active and inactive substituents associated with stimulation of pulmonary reflexes by antihistaminics.

Sympathomimetic Drugs	Phenyl		Ethyl		Amine	Cardiac stimulant	Vaso-constriction	Vaso-dilatation	Broncho-dilatation
1) Epinephrine	3-OH	4-OH	OH		CH_3	+	+	+	+
2) Levarterenol	3-OH	4-OH	OH			+	+	–	–
3) Isoproterenol	3-OH	4-OH	OH		C_3H_7	+	–	+	+
Cardiac stimulant						+	–	–	–
Bronchodilator						–	–	–	+
4) Metaraminol	3-OH		OH	CH_3		+	+	–	–
5) Phenylephrine	3-OH		OH		CH_3	–	+	–	–
6) Hydroxyamphetamine		4-OH		CH_3		+	+	–	–
7) Nylidrin		4-OH	OH	CH_3	$C_{10}H_{13}$	+	–	+	+
Cardiac stimulant						+	–	–	–
Vasodilator						–	–	+	–
Bronchodilator						–	–	–	+
8) Methoxamine	2-CH_3O	5-CH_3O	OH	CH_3		–	+	–	–
9) B. W. 45-50	2-C_2H_5O	5-C_2H_5O	OH	CH_3		–	+	+	–
10) Methoxyphenamine	2-CH_3O			CH_3		–	–	+	+
11) Isoprophenamine	2-Cl		OH		C_3H_7	–	–	+	+
Vasodilator						–	–	+	–
Bronchodilator						–	–	–	+
12) Ephedrine			OH	CH_3	CH_3	+	+	–	+
13) Methamphetamine				CH_3	CH_3	+	–	+	–
14) Mephentermine				$(CH_3)_2$	CH_3	+	–	+	–
Cardiac stimulant						+	–	–	–
Vasodilator						–	–	+	–
Bronchodilator						–	–	–	+

Fig. 2.—Comparison of chemical structure and side effects of sympathomimetic bronchodilators.

the various systemic arteries. The systemic hypertensive response following its intravenous injection is due both to vasoconstriction and to stimulation of myocardial force of contraction. (*e*) Ephedrine causes vasoconstriction in the various systemic arterial beds and stimulation or depression of myocardial force. (*f*) Pseudoephedrine is a weaker constrictor than ephedrine for the common carotid, external iliac, and superior mesenteric arteries. Unlike ephedrine, pseudoephedrine causes vasodilatation in the area supplied by the vertebral artery. The stimulation and depression of myocardial contraction for both ephedrine and pseudoephedrine are equal in intensity.

Structure-Activity Relationships.—A comparison of the chemical structure of bronchodilator amines has failed to make a distinction between active and inactive substituents (Fig. 2). The 3,4-dihydroxy substitutions common to both epinephrine and isoproterenol are lacking in ephedrine and pseudoephedrine; methoxyphenamine has a 2-methoxy group whereas isoprophenamine contains a 2-chloro substituent in the phenyl ring. The attachment of an hydroxyl or a methyl radical in the ethyl chain is not a normal feature of all bronchodilators. The only common feature is a substitution in the amine and this is true for other sympathomimetic amines that have been proven effective in experimental animals (24). The need for new bronchodilators appears largely to be for a more selective one with minimal activity on the cardiovascular system; the structure-activity relationships for bronchodilatation should be correlated with those for cardiovascular actions discussed below.

PULMONARY VASODILATATION

Types of Vasodilators.—The literature on the effects of drugs on the pulmonary vessels has been reviewed recently (26). The vasodilators that have been used clinically to reduce pulmonary hypertension include aminophylline, isoproterenol, and tolazoline. Although each of these three agents is able to dilate the pulmonary vessels, they also dilate the peripheral vessels, and stimulate the heart. The latter action is accompanied usually by an increase in cardiac output or pulmonary blood flow so that the net result of the drug may even be a rise in pulmonary arterial pressure. Derivatives of aminophylline have been examined and these will be discussed next.

Structure-Activity Relationships of Xanthines.—Forty derivatives of aminophylline (theophylline ethylenediamine) were tested in anesthetized dogs to compare the vascular action in the lungs and the extremities (27). All compounds tested revealed either dilatation for both, or constriction for both, but never opposite effects (Fig. 3).

Theophylline (1,3-dimethylxanthine) gave essentially the same results as those described for aminophylline (theophylline ethylenediamine); i.e., pulmonary and femoral vasodilatation. Caffeine (1,3,7-trimethylxanthine) was slightly more powerful than aminophylline in dilating the pulmonary vessels but weaker in dilating the femoral vessels. Theobromine (3,7-dimethylxanthine) was half as active as theophylline in dilating the vessels of the lungs and legs. The following generalizations apply to the correlation of chemical structure of the other xanthines tested for their vascular effect: (*a*) unsubstituted xanthine is a weak dilator (less than one-half the potency of theophylline) for the lung and limb vessels; (*b*) replacement of the oxygen linked to the carbon atoms at positions 2 and/or 6 with sulfur does not affect the dilator action; (*c*) lengthening the carbon chain attached to the nitrogen at position 3 does not alter the dilator effect characteristic of caffeine, theobromine, and theophylline; (*d*) lengthening the carbon chain attached to the nitrogen at position 1 beyond one carbon converts the dilator action of theophylline and caffeine to constriction; (*e*) lengthening the carbon chain at No. 7 nitrogen position beyond the methyl substituent converts the dilator action of theobromine to vasoconstriction; however, if there is an hydroxyl or chlorine attached to the ethyl substituent, the dilator action is restored; (*f*) an additional substitution at No. 8 carbon position either maintains or reverses the dilator action of theophylline or caffeine. Lengthening the carbon chain beyond a methyl group converts the compound to a vasoconstrictor. However, the benzyl and the *p*-aminobenzyl substituted compounds retain their vasodilator effects. Hydroxyl or amino substitution of the methyl carbon results in a vasoconstrictor, as is the carbamyl substituted methylamino compound. An aliphatic or aromatic ether group, and the nitro and sulfhydryl analogs, also give rise to vasoconstrictors. The 4-methylpiperazinyl analog is a vasodilator, whereas the amino substituted compound is a vasoconstrictor.

Patterns of Responses of Sympathomimetic Amines.—Eighty amines have been tested in the anesthetized dog for effects on pulmonary vascular tone and pulmonary blood flow (28). The results of 22 of them which are commercially available are summarized in Fig. 4. It can be

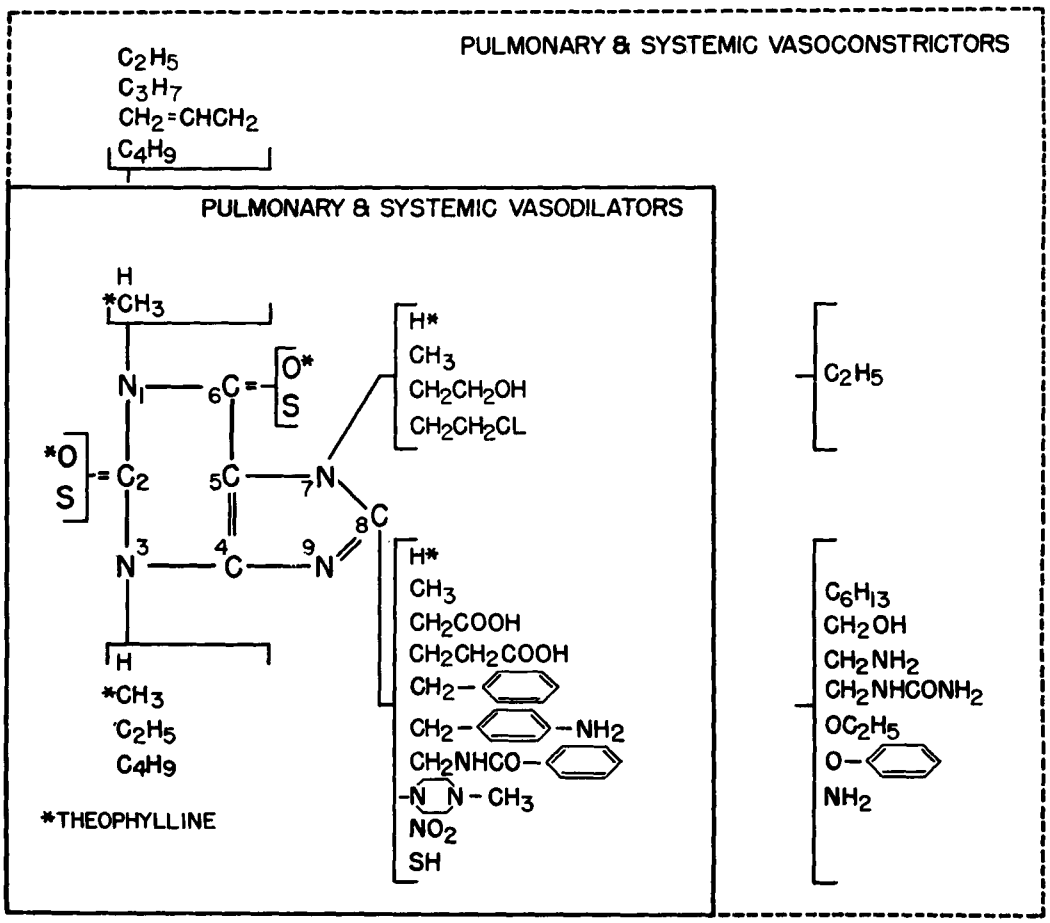


Fig. 3.—Chemical structures of xanthines which cause nonselective vasodilatation or vasoconstriction. Reprinted from reference 27 with the permission of the publishers.

noted that the effects on vessel tone or flow can be grouped into increase, decrease, or variable effect so that there are nine possible combinations of actions. Among the pulmonary vasodilators, the diethoxyl derivative of methoxamine (compounds 45–50) can consistently cause a fall in pulmonary blood pressure because the pulmonary blood flow is reduced. The reduction in flow appears to be related to the substitutions in the 2 and 5 positions of the phenyl ring.

PULMONARY BLOOD FLOW

In the above discussion of sympathomimetic dilators for the lung vessels it was stated that hemodynamically, a reduction in pulmonary arterial pressure is more likely to occur if the drug reduces pulmonary blood flow or cardiac output. An exception to this would be a relative failure of the left ventricle so that the reduction in output would mean a rise in left atrial pressure, pulmonary venous pressure, and even pulmonary arterial pressure. It is for this reason that the sympathomimetic amines were tested in an attempt to find a pulmonary vasodilator with no reduction of pulmonary blood flow, but with less conspicuous increase in pulmonary blood flow than with isoproterenol and mephentermine. Seven derivatives of mephentermine were tested and the results are reported below.

Methods.—Dogs under morphine (2 mg./Kg., s.c.) and chloralose (70 mg./Kg., i.v.) anesthesia were used. The following procedures were routinely performed in all animals: (*a*) cannulation of the trachea to allow the use of a Starling Ideal pump, (*b*) cannulation of a femoral vein for drug injection, (*c*) catheterization of a carotid artery for recording of aortic blood pressure by a Statham transducer, and (*d*) opening of the chest in the left fifth intercostal space to allow measurements of pressure in the pulmonary artery from a catheter tied into the artery of the left upper lobe. The additional procedures performed in each of two groups of dogs consisted of the following: (*e*) measurement of

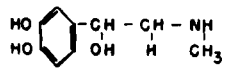
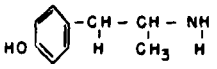
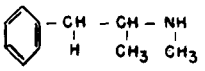
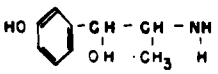
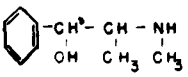
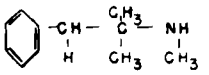
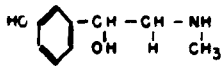
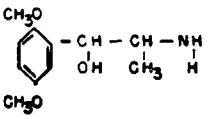
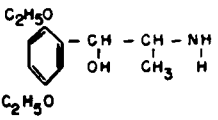
	PULMONARY VASOCONSTRICTOR	VARIABLE OR NONE	PULMONARY VASODILATOR
INCREASED PBF	EPINEPHRINE  LEVARTERENOL (LEVOPHED) TUAMINOHEPTANE (TUAMINE) EPININE TYRAMINE	HYDROXYAMPHETAMINE (PAREDRINE)  PHOLEDRINE (PAREDRINOL) SYNEPHRIN (SYMPATOL)	METHAMPHETAMINE (METHEDRINE)  ISOPROTERENOL (ISUPREL) NYLIDRIN (ARLIDIN)
VARIABLE OR NONE	METARAMINOL (ARAMINE) 	EPHEDRINE  AMPHETAMINE (BENZEDRINE) PHENYLPROPANOLAMINE (PROPADRINE) METHYLAMINOHEPTANE (OENETHYL) NAPHAZOLINE (PRIVINE)	MEPHENTERMINE (WYAMINE)  PHENYLPROPYLMETHYLAMINE (VONEDRINE) CYCLOPENTAMINE (CLOPANE)
DECREASED PBF	PHENYLEPHRINE (NEOSYNEPHRINE) 	METHOXAMINE (VASOXYL) 	B. W. COMPOUND 45-50 

Fig. 4.—Chemical structure of sympathomimetic amines and their effect on pulmonary circulation.

pulmonary venous outflow (28) and force of myocardial contraction by means of a strain gauge arch sutured to the surface of the right ventricle (29), (*f*) inflow perfusion of the left lower lobe (28) combined with measurement of femoral arterial blood flow by insertion of a Shipley-Wilson recording rotameter. All these methods are depicted in Fig. 5 and are briefly described with the results obtained with them. Manuronate (10 mg./Kg., i.v.) was routinely used as the anticoagulant. Aqueous solutions of the compounds were prepared as concentrations such that the total volume of injection did not exceed 0.1 ml. for intra-arterial injection, and 1.0 ml. for intravenous injection.

Results.—The effects of mephentermine and its seven derivatives are summarized in Table I. Each compound was tested on at least three dogs and the comparative activity is expressed in relation to that of mephentermine with an activity ratio of 1.0. The relative potency of the derivative is expressed as either (*a*) the effect of an equivalent dose or (*b*) the dose that elicits an equivalent effect. Thus, the activity ratio of 0.5 signifies that an equivalent dose of the derivative produces half the effect of mephentermine, or twice the dose of the derivative produces an effect equivalent to mephentermine.

Pulmonary Vasodilatation.—The local action of a drug on the lung vessels was investigated by perfusing the left lower lobe at a constant flow with mixed venous blood from the dog's own right atrium (Fig. 5, top). Mephentermine (1 mg./Kg.) injected directly into the perfused pulmonary artery causes an immediate reduction in perfusion pressure. The 4-methoxy derivative

(compound 1364) induces a similar reduction in perfusion pressure when injected in a dose of 1 mg./Kg., indicating that this derivative causes pulmonary vasodilatation. Figure 6 depicts this response and includes the failure of 0.5 mg./Kg. of mephentermine to induce pulmonary vasodilatation. It is on this basis that the potency of the 4-methoxy derivative is expressed as 2.0.

All the other derivatives of mephentermine are weak pulmonary vasodilators (potency of 0.2) with one exception. The nitro derivative (compound 979) instead causes a rise in perfusion pressure, which means that this compound constricts the pulmonary vessels.

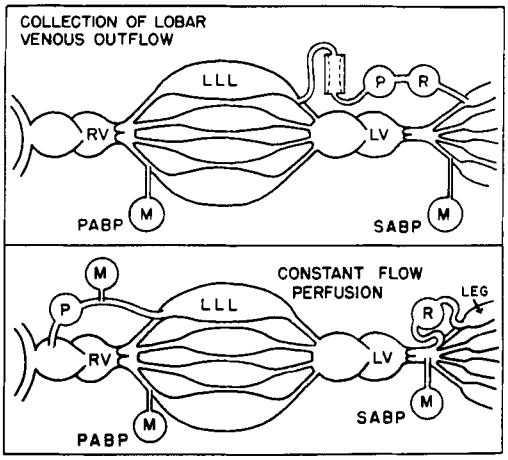


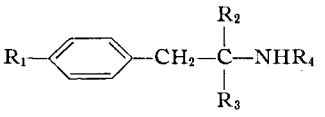
Fig. 5.—*Top.*—Collection of lobar venous outflow in a closed collapsible rubber reservoir, emptied by a Dale-Schuster pump (*P*), measured by a Shipley-Wilson rotameter (*R*), and returned to the animal's own femoral artery. Pulmonary arterial blood pressure (PABP) and aortic blood pressures (SABP) are measured by Statham transducers (*M*) recording on a Sanborn Poly Viso. *Bottom.*—Constant inflow perfusion of left lower lobe with mixed venous blood derived from the animal's own right atrium. Femoral arterial blood is shunted through a Shipley-Wilson rotameter (*R*). Perfusion pressure, arterial pressure of intact lobes, and aortic pressure are registered by Statham transducers (*M*).

Femoral Vasodilatation.—The same group of dogs that were subjected to lung perfusion were also utilized for the investigation of the femoral vascular bed by insertion of a rotameter for measuring arterial blood flow (Fig. 5). It can be noted in Fig. 6, *A* and *C*, that mephentermine and its 4-methoxy derivative, in a dose of 0.1 mg./Kg. injected directly into the femoral artery, cause an immediate increase in femoral blood flow. The responses as femoral vasodilatation induced by both compounds are equivalent in intensity (potency for both expressed as 1.0). The six other derivatives are uniformly able to dilate the femoral vascular bed, although most of them are weaker than mephentermine.

Pulmonary Venous Outflow.—Because of the various objections to the indirect methods of measuring cardiac output, it was decided to measure pulmonary venous outflow by a direct and unequivocal method (Fig. 5). A glass cannula was inserted into the vein of the left lower lobe. All the effluent blood was collected in a collapsible rubber reservoir at the same horizontal level as the cannula. The blood was instantaneously returned by means of a Dale-Schuster pump to the animal's own left atrium or femoral vein. The pump was set to empty the reservoir continuously so that pressure between the lobar vein and the reservoir was never allowed to increase. A Shipley-Wilson rotameter was inserted into the outflow side of the pump to obtain a graphic recording of the rate of blood flowing from the pulmonary vein. Although the pulmonary venous outflow measured by this method represents only one lobe, it is felt that it can be regarded as a reasonable criterion of flow in all lobes and of cardiac output.

The intravenous injection of mephentermine

TABLE I.—DERIVATIVES OF MEPHENTERMINE[a] AND THEIR PULMONARY VASCULAR EFFECTS BASED ON ACTIVITY OF MEPHENTERMINE EXPRESSED AS 1.0



Compound No.	R_1	R_2	R_3	R_4	Activity Ratios: Pulmonary Vaso-dilatation	Femoral Vaso-dilatation	Increased Pulmonary Blood Flow	Stimulation Myocardial Contraction
Mephentermine	...	CH_3	CH_3	CH_3	1.0	1.0	1.0	1.0
1364	4-CH_3O	CH_3	CH_3	CH_3	2.0	1.0	0.3	Variable
979	4-NO_2	CH_3	CH_3	CH_3	Constrict	1.0	Variable	Variable
1035	4-NH_2	CH_3	CH_3	CH_3	1.0	0.5	Variable	Variable
1420	...	CH_2OH	CH_2OH	CH_3	0.2	0.2	Variable	Variable
1239	...	CH_3	CH_3	CH_3—CH_2CH_2—CH_2	0.2	0.2	Variable	Variable
1240	...	CH_3	CH_3	$(CH_3)_2$—CH—CH_2	0.2	0.2	Variable	Variable
609	...	CH_3	CH_3	[b]	0.2	0.2	Variable	Variable

[a] Supplied by Dr. G. E. Farrar, Wyeth Laboratories, Radnor, Pa.
[b] Tertiary amine = CH_3 and $HOCH_2CH_2NHCH_2CO$.

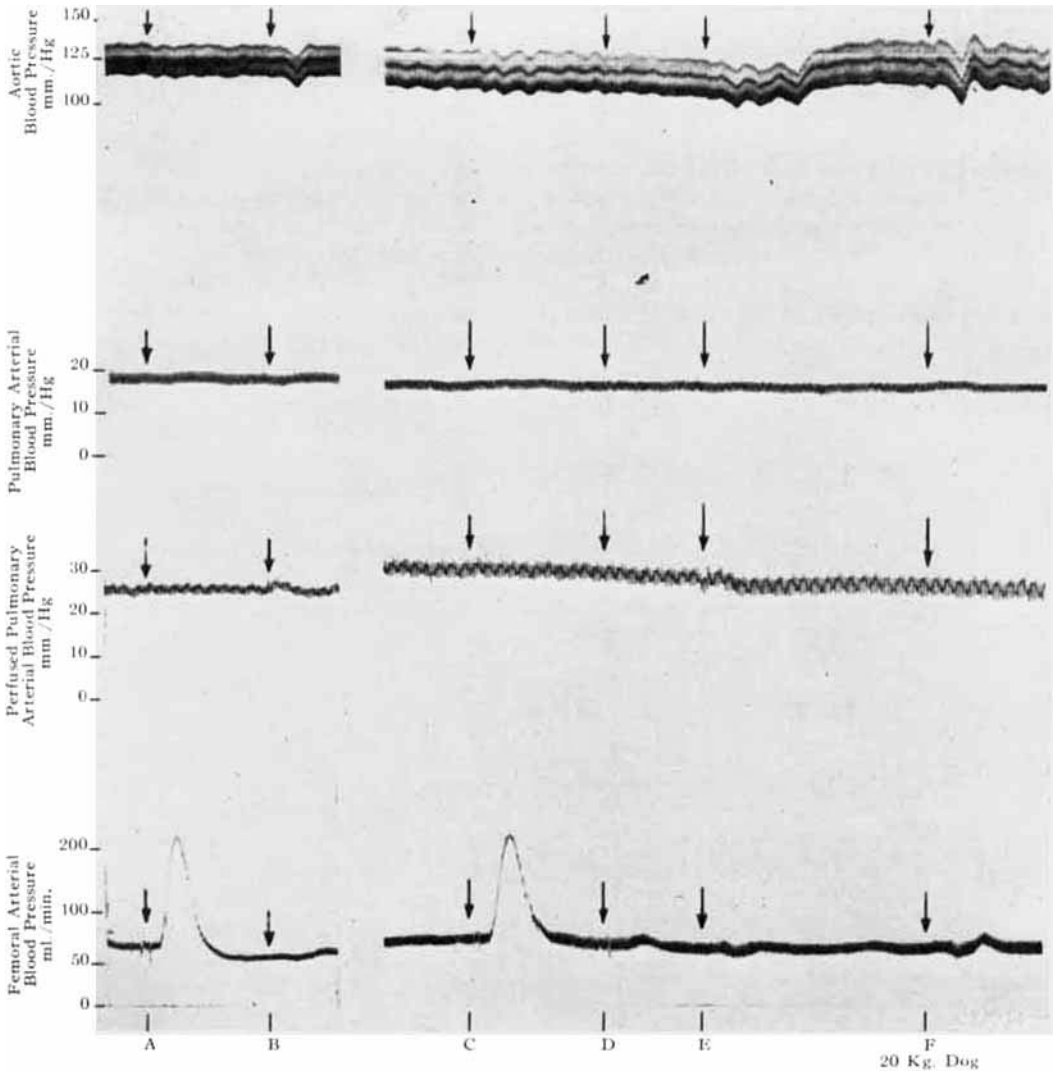


Fig. 6.—Comparative effects of mephentermine and 4-methoxy derivative. *A*, Mephentermine 0.1 mg./Kg. into femoral artery; *B*, mephentermine 0.5 mg./Kg. into perfused pulmonary artery (elapsed time between *B* and *C*, 20 min.); *C*, 4-methoxy derivative 0.1 mg./Kg. into femoral artery; *D*, saline 0.2 ml. into femoral artery; *E*, 4-methoxy derivative 0.5 mg./Kg. into perfused pulmonary artery; *F*, 4-methoxy derivative 1.0 mg./Kg. intravenously.

(1 mg./Kg.) causes an increase in pulmonary venous outflow (Figs. 7, *B*, and 8, C). The corresponding effect of the 4-methoxyderivative is a less intense increase in pulmonary venous outflow, with an activity ratio of 0.3 (Figs. 7, *A*, and 8, *A*). The other derivatives have variable effects on pulmonary venous outflow, either an increase or a decrease, and both may even appear in the same dog after repeated injections of the same compound. This variability is related to the biphasic action on the heart muscle which is described in the following paragraph.

Force of Myocardial Contraction.—The known stimulant action on the myocardium for mephentermine can be demonstrated by means of the Walton strain gauge. An intravenous injection (1 mg./Kg.) causes an increase in force of myocardial contraction, and this occurs simultaneously with the increase in pulmonary venous outflow (Figs. 7, *B*, and 8, *C*). An equivalent amount of the 4-methoxy derivative causes either an equally intense or less intense stimulation. After repeated injection of this compound, the stimulation may be converted to a temporary depression (Fig. 8, *D*). The variable effect on myocardial depression is related to the less intense increase in pulmonary venous outflow. The other derivatives have variable effects on myocardial force.

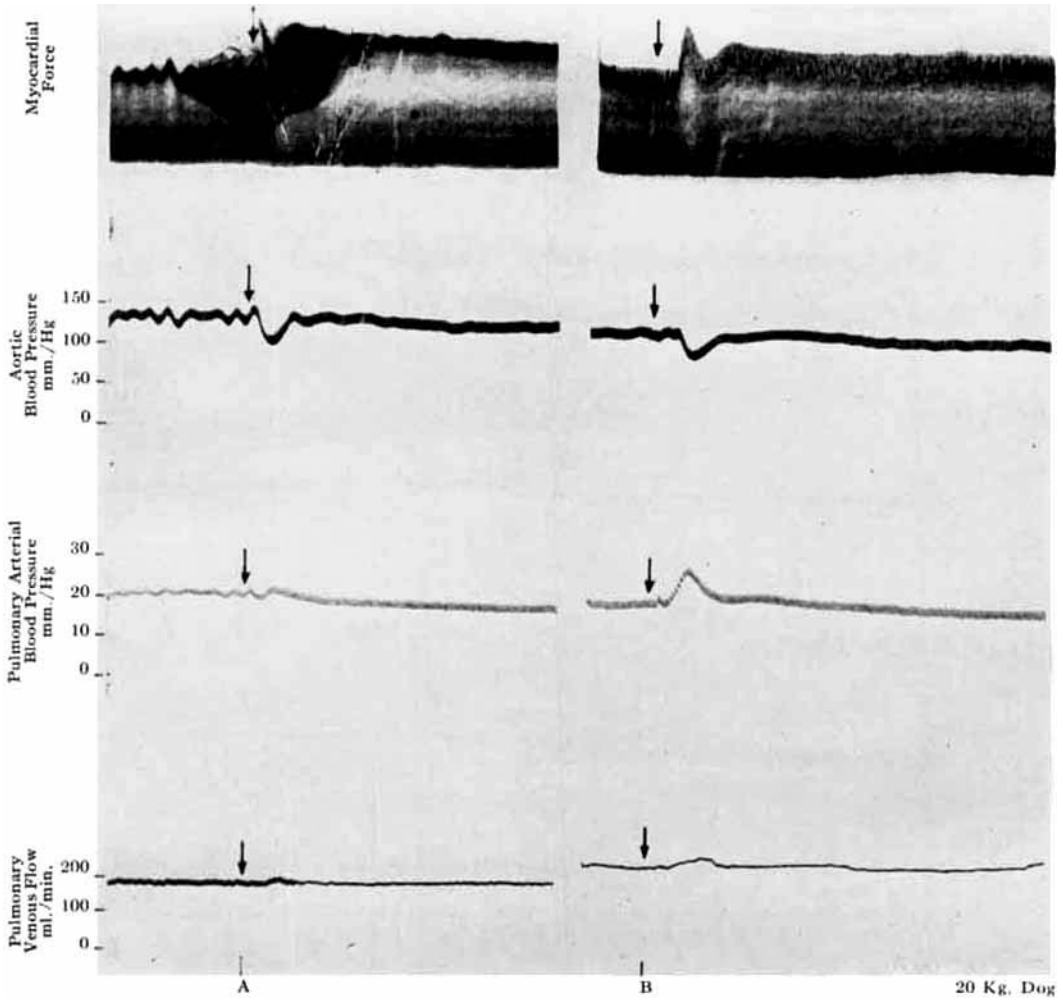


Fig. 7.—Comparative effects of mephentermine and 4-methoxy derivative on myocardial force, aortic blood pressure, pulmonary arterial blood pressure, and pulmonary venous outflow. *A*, 4-Methoxy derivative 1 mg./Kg. intravenously; *B*, mephentermine 1 mg./Kg. intravenously.

Pulmonary Blood Pressure.—The most usual response of pulmonary arterial blood pressure following the intravenous injection of 4-methoxy derivative is a fall. This fall most probably is related to the vasodilatation demonstrable in the perfused lung, which appears to be more important than the increase in pulmonary blood flow. In some instances the pulmonary arterial pressure is unchanged, and this can be explained by both increased flow and vasodilatation occurring to equalize each other. The pulmonary arterial pressure responses of mephentermine and the six derivatives (other than 4-methoxy) are variable, and are related to the effects on pulmonary blood flow and pulmonary vasomotor tone reported above.

Aortic Blood Pressure.—The aortic pressor response of mephentermine can be elicited by the intravenous injection of 1 mg./Kg. This has been explained by cardiac stimulation which has been documented by reports of various investigators (29–34). The pressor response is converted to a depressor response after the injection of the 4-methoxy derivative (Fig. 7) and this indicates that the systemic vasodilator action of mephentermine becomes of primary importance. The basic mechanism for this predominance induced by the 4-methoxy derivative is not known but may be an indication of cross-tachyphylaxis between the two compounds.

The behavior of aortic blood pressure following the intravenous injection of 4-methoxy derivative (1 mg./Kg.) is variable even in a dog receiving this compound for the first time. In a group of 6 dogs, a fall was encountered in 3, a rise in 1, and no change in 2. The fall can be explained by the

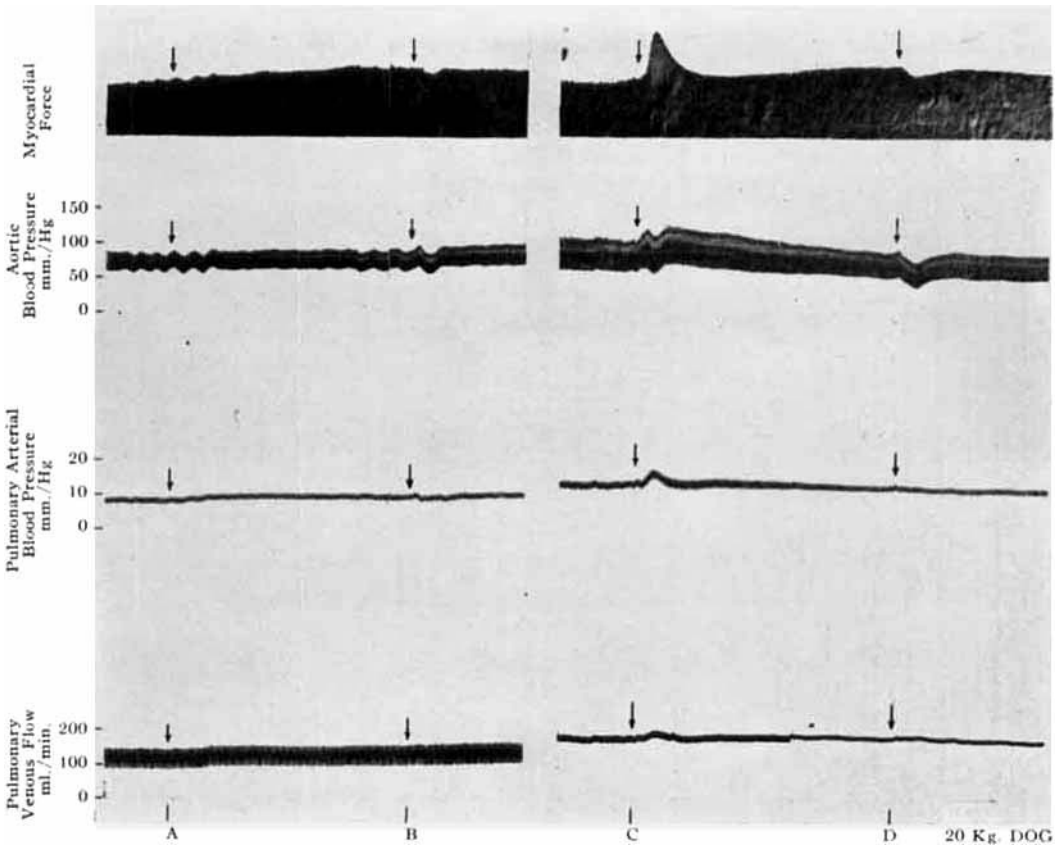


Fig. 8.—Comparative effects of mephentermine and 4-methoxy derivative on myocardial force, aortic blood pressure, pulmonary arterial blood pressure, and pulmonary venous outflow. *A*, 4-Methoxy derivative 1 mg./Kg. intravenously; *B*, 4-methoxy derivative 1 mg./Kg. intravenously; *C*, mephentermine 1 mg./Kg. intravenously; *D*, 4-methoxy derivative 2 mg./Kg. intravenously.

systemic vasodilatation, but final proof must await studies on systemic vascular beds other than the femoral.

Correlation of Chemical Structure to Pulmonary Vascular Action.—The effects of seven derivatives of mephentermine suggest the following generalizations. (*a*) The addition of a 4-methoxy radical in the phenyl ring to mephentermine causes an exaggeration of pulmonary vasodilator action but a reduction in the ability to increase pulmonary blood flow. The addition of a 4-amino radical does not reduce the pulmonary vasodilator action but reduces the systemic dilator action. (*b*) The substitution of a nitro radical converts the compound into a pulmonary vasodilator, the activity which is reduced by conversion of the methyl substituent in the terminal nitrogen to a longer aliphatic chain. A similar reduction in activity can be induced by substituting both methyl radicals in the α-carbon to two carbinol groups. All of these alterations reduce the vasodilator potency not only for the femoral vessels but also for the pulmonary vessels. (*c*) The ability to stimulate myocardial force is a feature common to all the derivatives tested, although this action is not a consistent one since depression may be encountered.

CONCLUDING REMARKS

The structure-activity relationships of antihistaminics, xanthines, and sympathomimetic amines have been reviewed. These drugs are able to (*a*) influence respiration by activation of pulmonary vagal receptors, (*b*) relax bronchiolar tone, (*c*) dilate pulmonary vessels, and (*d*) either decrease or increase pulmonary blood flow. The major shortcoming of active agents is their lack of selectivity for a specified structure in the lungs. They usually affect two or more reactive areas in the lungs and usually influence the heart and the systemic vessels.

REFERENCES

(1) Dawes, G. S., and Comroe, J. H., Jr., *Physiol. Revs.*, 34, 167(1954).

(2) Aviado, D. M., and Schmidt, C. F., *ibid.*, **35**, 247 (1955).
(3) Whitteridge, D., and Bulbring, E., *J. Pharmacol. Exptl. Therap.*, **4**, 85(1946).
(4) Dawes, G. S., Mott, J. C., and Widdicombe, J. G., *Brit. J. Pharmacol.*, **6**, 675(1951).
(5) Meier, R., and Bein, H. J., *Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's*, **112**, 119(1952).
(6) Meier, R., Bein, H. J., and Helmick, H., *Experientia*, **5**, 484(1949).
(7) Schneider, J. A., and Yonkman, F. F., *J. Pharmacol. Exptl. Therap.*, **111**, 84(1954).
(8) Dawes, G. S., and Comroe, J. H., Jr., *Physiol. Revs.*, **34**, 167(1954).
(9) Keller, C. J., and Loeser, A., *Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's*, **145**, 146(1929).
(10) Creed, R. S., and Hertz, D. H., *J. Physiol.*, **78**, 85(1933).
(11) Jones, J. V., *Brit. J. Pharmacol.*, **8**, 352(1953).
(12) Takasaki, K., *Kurume Med. J.*, **3**, 146(1956).
(13) Bevan, J. A., and Verity, M. A., *J. Pharmacol. Exptl. Therap.*, **132**, 42(1961).
(14) Wretlind, A., *Acta Physiol. Scand.*, **40**, 59(1957).
(15) Toh, C. C., Lee, T. S., and Kiang, A. K., *Brit. J. Pharmacol.*, **10**, 175(1955).
(16) Porszasz, J., Such, G., and Porszasz-Gibiszer, K., *Acta Physiol. Acad. Sci. Hung.*, **12**, 189(1957).
(17) Moran, N. C., Dresel, P. E., Perkins, M. E., and Richardson, A. P., *J. Pharmacol. Exptl. Therap.*, **110**, 415(1954).
(18) Schmitt, H., *Arch. intern. pharmacodynamie*, **109**, 251(1957).
(19) DiStefano, V., Leary, D. E., and Little, K. D., *J. Pharmacol. Exptl. Therap.*, **126**, 158(1959).
(20) Winder, C., and Thomas, R. W., *ibid.*, **91**, 1(1947).
(21) Aviado, D. M., Pontius, R. G., and Li, T. H., *ibid.*, **99**, 425(1950).
(22) Takasaki, K., Nakano, T., and Nagasaki, N., *Kurume Med. J.*, **4**, 43(1957).
(23) Jones, J. V., *Brit. J. Pharmacol.*, **7**, 450(1952).
(24) Hawkins, D. F., "Handbook of Respiration," W. B. Saunders Co., Philadelphia, Pa., 1958, pp. 202–252.
(25) Aviado, D. M., Wnuck, A. L., and DeBeer, E. J., *J. Pharmacol. Exptl. Therap.*, **122**, 406(1958).
(26) Aviado, D. M., *Pharmacol. Revs.*, **12**, 159(1960).
(27) Quimby, C. W., Jr., Aviado, D. M., Jr., and Schmidt, C. F., *J. Pharmacol. Exptl. Therap.*, **122**, 396(1958).
(28) Aviado, D. M., and Schmidt, C. F., *ibid.*, **120**, 512 (1957).
(29) Boniface, K. J., Brodie, O. J., and Walton, R. P., *Proc. Soc. Exptl. Biol. Med.*, **84**, 263(1953).
(30) Glassman, J. M., and Seifter, J., *J. Pharmacol. Exptl. Therap.*, **112**, 364(1954).
(31) Goldberg, L. I., Cotton, M. deV., Darby, T. D., and Howell, E. V., *ibid.*, **108**, 177(1953).
(32) Binion, J. T., Morgan, W. J., Jr., Welch, G. H., and Sarnoff, S. J., *Circulation Research*, **4**, 705(1956).
(33) Freiheit, H. J., *Intern. Record Med.*, **170**, 510(1957).
(34) Welch, G. H., Jr., Braunwald, E., Case, R. B., and Sarnoff, S. J., *Am. J. Med.*, **24**, 871(1958).

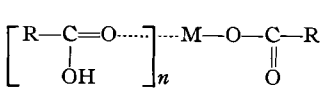
Research Articles

Complexation of Organic Acids and Bases with Their Salts in Aqueous Solution

By MICHAEL R. VALINOTI and SANFORD BOLTON

The solubilization of certain organic acids in aqueous solutions of their salts has been attributed to a complexation between the acid and anion species. In the present investigation solubility studies were used in an effort to ascertain the factors influencing such complexation and to determine the nature of the complexes formed. Benzoic acid, salicylic acid, *p*-hydroxy-, 2,4-dihydroxy-, 2,5-dihydroxy-, 2,6-dihydroxy-, and 3,4-dihydroxybenzoic acids, phenylacetic acid, adipic acid, barbituric acid, barbital, phenobarbital, and saccharin showed substantial increases in solubility in the presence of their sodium salts. Studies with atropine and procaine in solutions of their salts showed that similar complexes occurred in these systems. In some cases insoluble complexes were formed at high salt concentrations. Addition of hydroxyl groups to benzoic acid favors complexation. Quantitative evaluation of equilibrium constants could not be determined because of a concurrent salting out effect.

THE APPARENT increase in solubility of various organic acids in aqueous solutions of their alkali or alkaline earth metal salts has been attributed to the formation of an acid-anion complex (1–6). Ross and Morrison (1) have described solubility curves for various mandelic acid-metal mandelate systems and have noted the formation of complexes of acid-salt ratios of 1:1, 2:1, and 3:1. They proposed the following formula as the most favorable representation of the complex species



where n can be either 1, 2, or 3. Hoitsema (2) investigated the salicylic acid-sodium salicylate and hippuric acid-potassium hippurate systems

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