PHENYL PROPYL AND PHENYL ISOPROPYL AMINES

Changes in Pharmacological Action on Substitution of Phenyl Nucleus and Amino Nitrogen

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By—the toxicity, pressor, and bronchodilator activities of a group of phenyl propyl amines and of phenyl isopropyl amines have been determined. The changes in these properties resulting from five changes in chemical structure are examined. Definite expectations as to the results of these changes are indicated for the pressor activity in four instances, and in three instances for the toxicity and bronchodilator activity. There is no correlation between any one structural change and all three of the pharmacological activities. More methoxy derivatives possess activity than previous work would indicate.

THE question of variation in pharmacological or bacteriological activity with changes in chemical structure is always of interest to the student of chemotherapy. Great differences in pharmacological activity may result from such slight changes in configuration that the chemical and physical properties differ only slightly from the original material. This makes it hazardous to predict the relation between structure and activity even when only one property is to be followed through a single series of compounds. When a substance may exhibit several types of activity, the problem becomes more complicated.

Examination of the activity of any series of compounds usually has as one object, the finding of substances that appear to have sufficient value to warrant more detailed investigation. If a large number of substances are involved, this preliminary "screening" consists of subjecting these chemical compounds to a few chosen tests. The data obtained may then be examined to see if the properties of unknown substances may be predicted, as if by a periodic table. It is the results of such a procedure that are to be examined, to see what may be "expected" in the way of changes in activity with changes in chemical structure.

Amines having the β-phenethylamine skeleton differ in pharmacological properties from those that do not. The effect of the introduction of various groups into the molecule has been studied extensively, with special emphasis on the pressor effect, but the over-all picture of the changes is still lacking. This paper summarizes the results of three pharmacological tests on a group of seventy-five methoxy and hydroxy phenyl propyl and phenyl isopropyl amines. Since all of the compounds have been synthesized and tested by this laboratory, in the interest of brevity no reference will be made to the work done by others, either in the series under discussion or in related series.

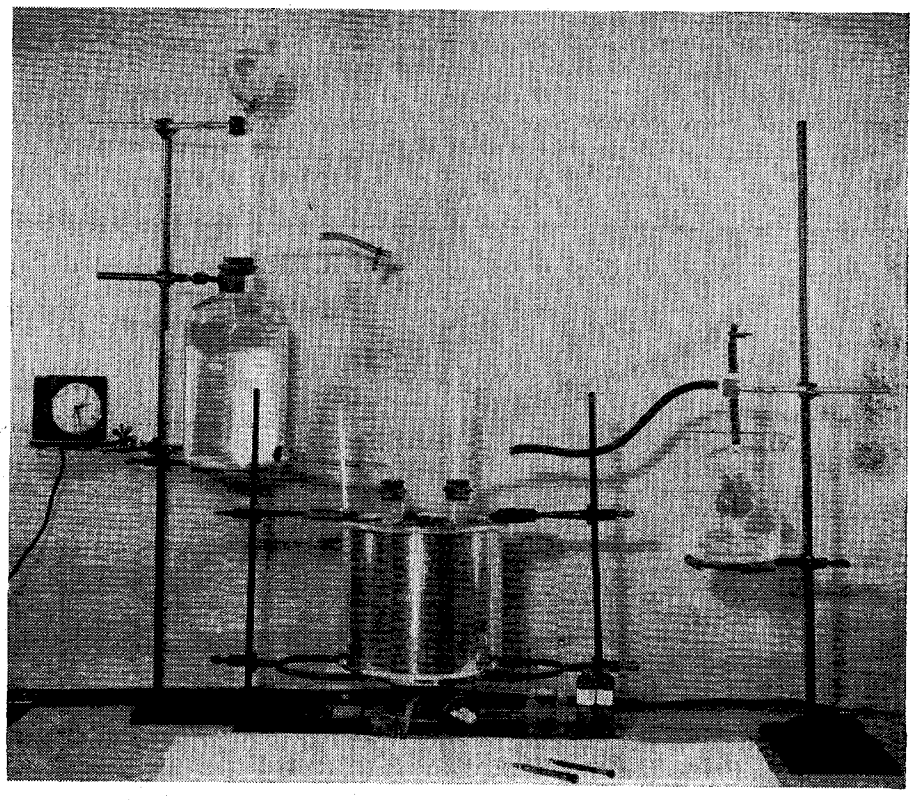
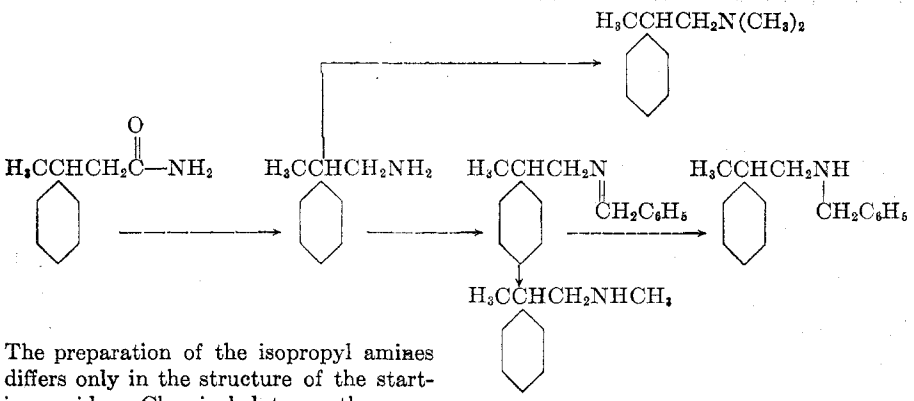


Figure 1. Equipment for Determination of Bronchodilator Rating

The preparation of the *n*-propyl amines was accomplished by the following procedure:



The preparation of the isopropyl amines differs only in the structure of the starting amide. Chemical data on the compounds under discussion appear in the literature (*2*, *3*, *5–9*).

ACTIONS TESTED

The pharmacological tests chosen were the toxicity, pressor, and bronchodilator actions. Toxicity as determined is the dose (contained in 0.5 to 1.5 cc. of solution injected intravenously at the rate of 0.25 cc. per minute into male white rats weighing between 200 and 300 grams) that will kill 50% of the animals. The pressor effect was determined by the U.S.P. procedure for epinephrine. The values reported are the fractional effectiveness of equipressor doses compared to epinephrine as unity. On account of tachyphylaxis only one determination could be made per dog. The bronchodilator effect is a measure of the relaxing effect upon the bronchial musculature of an isolated rabbit lung following constriction by a chemical agent. In this work the procedure of Sollmann and von Oettingen (*1*, *4*) was used with pilocarpine as the constricting agent. The values in Table I are proportional to the increased rate of flow through the lung. As the liquid flows through the lung shown at the right in Figure 1, air enters the reservoir at the left. Figure 2 shows this in greater detail. By adjusting the difference in fluid level, an initial rate of about thirty bubbles per minute is obtained. On constriction of the lung, the number of bubbles per minute decreases. The amine to be examined is injected; if it is active, an increased rate of flow is observed. The bronchodilator values in Table I refer to the average increase in bubbles per minute upon injection of a 0.5- and 1-cc. dose of a 1 to 100 dilution of the compound. This value is absolute, and we have refrained from giving it as a ratio compared to substances not in this series. The results can be used to compare the effectiveness among the compounds given.

COMPARISON OF CHEMICAL CHANGE WITH ACTIVITY

Many comparisons are possible with the data at hand. Many are either inconclusive, lack a sufficient number of compounds, or require excessive explanation. The comparison between five different structural changes and the three pharmacological properties are collected from Table I and listed in Table II. From these we may find some answer as to what may be expected.

The first structural difference tabulated is that of the position of a methyl group introduced in the ethylamine side chain. It can be so placed as to give either an *n*-propyl or an isopropyl amine. The data show that the isopropyl amines are of equal or greater toxicity in twenty-five of twenty-six pairs. Under pressor activity, four of the nine pairs indicated as having the same activity show zero or depressor action. The isopropyl amine has the greater pressor effect in sixteen of twenty-two active pairs. All three pairs listed as having the same bronchodilator activity are inert or constrictor. It can be stated that one would expect an isopropyl amine to be more toxic and more pressor than a similar *n*-propyl amine. There can be no expectation with respect to the bronchodilator action. It should be noted that certain of the *n*-propyl amines are more pressor than many of the isopropyl derivatives and are well within a useful range. This further complicates any sweeping statement in comparing any two types of structure. The comparisons apply only when two structures identical in all respects but one are compared. This fact should be kept in mind when considering the conclusions drawn from this and other series of compounds.

The second structural difference to be compared is that of the presence of a methoxyl or hydroxyl group in the ring. The data show that the substance with the methoxyl group is of equal or greater toxicity in twenty-seven of thirty pairs. Of those compounds listed as possessing the same pressor effect, five of the

Table I. Pharmacological Data

Name	—NH2—			—NH.CH3—			—N(CH3)2—			—NH.CH2C6H5—		
	Toxicity	Pressor ratio	Bronchodilator	Toxicity	Pressor ratio	Bronchodilator	Toxicity	Pressor ratio	Bronchodilator	Toxicity	Pressor ratio	Bronchodilator
Phenylisopropyl	20	1/250	−1	20	1/275	2	20	1/500	13	20	1/1000	9
2-Methoxy	60	1/1000	−2	60	Depressor	12	40	Depressor	9	20	Depressor	9
3-Methoxy	40	1/250	6	35	1/500	5	50	1/2000	10	20	1/2000	7
4-Methoxy	30	1/250	4	40	1/225	2	50	1/1600	12	40	1/2000	8
2-Hydroxy	80	1/675	1	90	1/250	3	50	Depressor	7	20	Depressor	6
3-Hydroxy	70	1/300	1	60	1/125	2	...	.....	...	35	1/2000	5
4-Hydroxy	100	1/100	0	100	1/250	3	50	1/250	5	40	1/2000	12
Phenylpropyl	50	1/700	−2	60	1/250	1	80	Depressor	4	30	1/2000	12
2-Methoxy	80	Depressor	0	70	Depressor	10	40	Depressor	8	30	Depressor	4
3-Methoxy	40	1/300	8	70	1/1000	5	70	1/2000	1	40	1/2000	16
4-Methoxy	30	1/3000	3	40	1/1000	12	60	1/2400	8	20	1/4000	16
2-Hydroxy	110	1/9600	3	140	Depressor	0	90	Depressor	9	..	.....	..
3-Hydroxy	90	1/300	−1	90	1/250	6	80	1/2000	3	45	1/2000	6
4-Hydroxy	170	1/1750	−2	170	1/750	1	140	1/2000	6	50	1/2000	12
2,3-Dimethoxy	30	0	0	...	.....	..	...	.....	...	..	.....	..
2,4-Dimethoxy	50	1/3000	8	...	.....	..	...	.....	...	..	.....	..
2,5-Dimethoxy	50	1/1200	5	40	1/650	5	40	Depressor	1	20	Depressor	12
2,6-Dimethoxy	15	Depressor	4	...	.....	..	...	.....	...	..	.....	..
3,4-Dimethoxy	140	1/675	1	130	1/4000	1	80	1/2000	1	40	1/2000	10
3,5-Dimethoxy	70	Depressor	8	...	.....	..	...	.....	...	..	.....	..
2,3-Dihydroxy	120	1/750	0	...	.....	..	...	.....	...	..	.....	..
2,4-Dihydroxy	150	1/1100	0	...	.....	..	...	.....	...	..	.....	..
2,5-Dihydroxy	100	1/4000	0	10	0	5	275	0	1	..	.....	..
2,6-Dihydroxy	90	Depressor	2	...	.....	..	...	.....	...	..	.....	..
3,4-Dihydroxy	40	1/40	−2	...	.....	..	20	Depressor	−1	..	.....	..
3,5-Dihydroxy	?	1/120	−1	...	.....	..	...	.....	...	..	.....	..

Table II. Summary of Data Taken from Table I

Structure	Pairs	Toxicity		Pressor Ratio		Bronchodilator Effect	
		Greater	Same	Greater	Same	Greater	Same
Isopropyl	26	21	4	16	9	13	3
n-Propyl		1		1		10	
OCH_3	32	24	3	5	11	21	3
OH		3		15		7	
NH_2	17	7	5	8	1	4	2
$NH.CH_3$		5		8		11	
$NH.CH_3$	16	5	3	10			1
$N(CH_3)_2$		8		1			
$NH.CH_3$	15	1	2	14	1	0	0
$NH.CH_2C_6H_5$		12		0		15	

eleven are inactive. The hydroxy group therefore appears to confer the greater pressor activity. On the contrary, with regard to the bronchodilator effect the methoxy derivative is of equal or greater activity in twenty-four of thirty-one pairs. It can therefore be expected that the methoxy derivative will be more toxic and less pressor and will have a greater bronchodilator action than the corresponding hydroxy derivative. Several of the methoxy amines have a pressor ratio sufficiently great to indicate that a further investigation of this function is in order.

The third difference in structure is the addition of a methyl group on the amino nitrogen, to give a secondary amine. Table II shows the effect on the toxicity and pressor ratio of this change to be unpredictable. The methyl group does by a ratio of about 3 to 1 increase the bronchodilator action. The effect of the addition of a methyl group to the amino nitrogen can be expected to increase the bronchodilator activity but there can be no expectation with regard to toxicity and pressor effect.

The fourth structural change is the introduction of a second methyl group on the amino nitrogen, giving a tertiary amine. The effect of this change on the toxicity and bronchodilator effect is inconclusive. In four of the five pairs where the pressor action is reported as the same, both members are inactive. This indicates that, if the methyl amine is pressor, it is more pressor than the dimethyl. With the introduction of the second methyl group therefore, it is expected that the pressor ratio will decrease but there can be no expectation with regard to the toxicity and bronchodilator action.

The last change to be discussed is the effect of introducing a large group, such as benzyl, on the amino nitrogen as compared with the introduction of a small group, such as methyl. From the data it is to be expected that a benzyl amine will be more toxic, less pressor, and a better bronchodilator than the corresponding methyl amine.

The toxicities show definite trends in three of the five cases examined, the pressor effect in four of the five, and the bronchodilator effect in three of the five comparisons. On this basis it would appear easier to predict the effect of structural changes on the pressor ratio than either of the other two properties. Upon the introduction of a methyl in the amino group it is a 50-50 chance as to whether the pressor ratio will increase or decrease. This accounts for the conflicting reports concerning the effect of this change. It is remarkable, in view of the considerable activity possessed by many of the methoxy derivatives, that they have received comparatively little attention. The lack of correlation between any one chemical change and all three pharmacological properties indicates that it is impossible to determine all types of activity with one test.

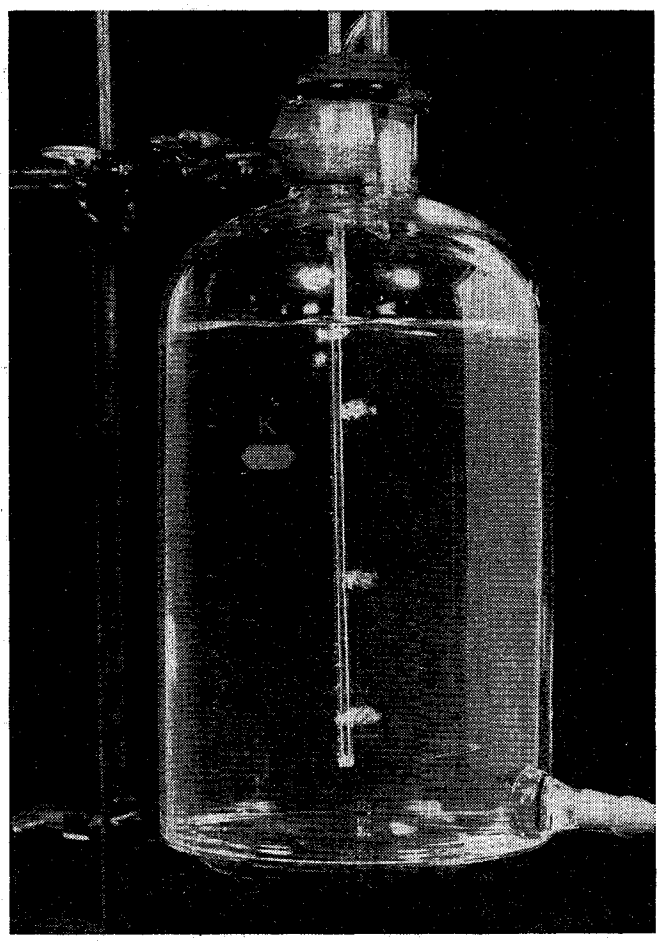


Figure 2. An Enlarged View of Reservoir, Showing the Entrance of Air Bubbles

Conclusions such as those drawn here are merely guide posts in an attempt on the part of the chemist to indicate a possible line of attack. The chemist is not interested in seats of physiological action or mechanism of action. He asks only a method that will keep him from straying too far from the road toward his goal. Results are sometimes twisted beyond their true or original meaning, but if their natural limitations are kept in mind, data of the type presented are of value.

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