The ratio of cyclohexylcarbinol to toluene produced in the hydrogenation of benzyl alcohol was increased by the presence of phenol or diphenylamine and especially of benzene or acetanilide in the reaction mixture.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP & DOHME, INC.]

AMINO ALCOHOLS. VI. THE PREPARATION AND PHARMACODYNAMIC ACTIVITY OF FOUR ISOMERIC PHENYLPROPYLAMINES

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The commoner hypertensive amines are derivatives of β-phenylethylamine, that is, compounds containing the aromatic nucleus separated from the amino group by two carbons of an aliphatic side chain; *e. g.*, tyramine $HOC_6H_4CH_2CH_2NH_2$, epinephrine, $(HO)_2C_6H_3CHOHCH_2NHCH_3$, and ephedrine, $C_6H_5CHOHCH(NHCH_3)CH_3$, all have this common structure.

Recorded pharmacological studies with compounds in which the relative position of these two functional groups is modified are rare.

Barger and Dale,[1] in their classical study on the relationship between chemical structure and sympathomimetic action, included a series of compounds in which the relative position of the amino portion with respect to the phenyl group varied. They found that aniline has no specific action; benzylamine gives a trace of the desired activity, α-phenylethylamine is feebly active, β-phenylethylamine highly active and most active of the series, while γ-phenylpropylamine, $C_6H_5CH_2CH_2CH_2NH_2$, is again much less effective. While no allowance was made for any influence on the physiological activity that might be produced by the successive lengthening of the side chain, they nevertheless advanced the conclusion that "the optimum constitution of a fatty–aromatic amine for the production of sympathomimetic action is, therefore, that which is found in adrenaline itself, *viz.*, a benzene ring with a side chain of two carbon atoms, of which the second bears the amino group."

Concerning the value of the two-carbon side chain these conclusions must, in the light of recent findings, be amended, for it has been amply demonstrated that amino alcohols of the ephedrine type, that is, compounds with three carbons in the side chain, are not only very active pharmacologically but may even possess physiological and therapeutic virtues not resident in the corresponding compounds with but two carbons.[2]

[1] Barger and Dale, *J. Physiol.*, **41**, 19 (1910). *Cf.* Pyman, *J. Chem. Soc.*, **111**, 1103 (1917).

[2] (a) Chen, Wu and Henriksen, *J. Pharmacol.*, **36**, 363 (1929); (b) Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929); (c) Hartung, Munch, Deckert and Crossley, *ibid.*, **52**, 3317 (1930); (d) Piness, Miller and Alles, *J. Am. Med. Assn.*, **94**, 790 (1930).

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Aside from this work of Barger and Dale, comparatively little has been done to substantiate the other part of their conclusion, namely, the necessity for having the aryl and amino groups on adjacent carbons of an aliphatic side chain. Baehr and Pick[3] observed that if in hordenine, *p*-$HOC_6H_4CH_2CH_2N(CH_3)_2$, the dimethylamino group is removed from the aromatic portion by three or four carbons,[4] the pressor potency becomes correspondingly less. Hasama, in comparing the isomeric phenylethanolamines, $C_6H_5CH(NH_2)CH_2OH$ and $C_6H_5CHOHCH_2NH_2$, found the former to have no influence on the blood pressure,[5] whereas the activity of the latter is well established.

Matsuo and Mizuno[6] report that α-phenylethylamine, $C_6H_5CH(NH_2)CH_3$, increased the contraction amplitude of the frog heart and the blood pressure of a rabbit, while the β-compound, $C_6H_5CH_2CH_2NH_2$, showed the opposite effect.

The present investigation was undertaken to determine, if possible, whether in the series of amino alcohols being studied in these Laboratories maximum activity is obtained when the aryl and amino groups are separated by two aliphatic carbon atoms. And in order to confine as nearly as possible any modification in physiological behavior to a corresponding change in the relative positions of these two functional groups, four isomeric phenylpropylamines were prepared and their behavior observed. These four compounds are given in Table I along with a summary of their pharmacological and toxicological behavior. β-Phenylethylamine and phenylpropanolamine are included for comparison.

TABLE I

DATA ON COMPOUNDS

	Base	M. L. D. of hydrochloride, mg./kg. Rats, subcutaneous	Rabbits, intravenous	Pressor activity of hydrochloride (Intravenous to dogs)
I	$C_6H_5CH_2CH_2NH_2$	..	60	1 Mg./kg. gave good rise that persisted about 20 min.
II	$C_6H_5CH(NH_2)CH_2CH_3$	1000	50	1 Mg./kg., very slight rise
III	$C_6H_5CH_2CH(NH_2)CH_3$	25	25	1 Mg./kg. gave rise equal to that of I. Effect persisted longer. Orally active[2d]
IV	$C_6H_5CH_2CH_2CH_2NH_2$	100	50	1 Mg./kg. gave medium transitory rise
V	$C_6H_5CH(CH_3)CH_2NH_2$	500	50	Good pressor; also active after oral administration.
VI	$C_6H_5CHOHCH(NH_2)CH_3$	..	75–90	Equals ephedrine

[3] Baehr and Pick, *Arch. exptl. Path. Pharmakol.*, **80**, 161 (1912).

[4] V. Braun, *Ber.*, **47**, 492 (1914).

[5] Hasama, *Arch. exptl. Path. Pharmakol.*, **153**, 165 (1930).

[6] Matsuo and Mizuno, *Acta Schol. Med. Univ. Imp. Kioto*, [1] **7**, 11 (1924); *Chem. Abst.*, **19**, 2705 (1925).

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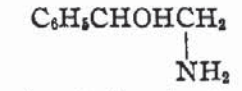
The data on comparative pressor potencies are not yet satisfactorily quantitative, but the information thus far obtained is very illuminating. For instance, it is readily seen that Barger and Dale are substantially correct in ascribing the optimum constitution for producing a rise in blood pressure to compounds containing at least a β-phenylethylamine skeleton. If any deviation is made from this elementary structure either by moving the amino closer to the phenyl (II) or by removing it farther away (IV), the degree of physiological response is very greatly diminished. But if this minimum skeleton is left unchanged (III, V and VI), substitutions in the other portions of the molecule may modify the nature of the pharmacodynamic behavior, but the ability to produce a rise in blood pressure is not diminished.

Chen, Wu and Henriksen[2a] attribute the oral efficacy of ephedrine to the presence of the third carbon in the side chain; thus, for instance, phenylpropanolamine (VI) is active when taken by mouth whereas phenylethanolamine, $C_6H_5CHOHCH_2NH_2$, is not.

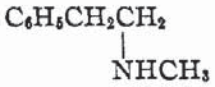
Piness, Miller and Alles,[2d] who are interested clinically in phenylethanolamine, were desirous of determining what it lacked structurally to make it active when administered orally. Since phenylethanolamine differs from ephedrine by two methyl groups, one in the side chain and the other on the



Phenylethanolamine

Ephedrine

amino group, they investigated two methyl substituted derivatives of β-phenylethylamine, one in which the methyl was substituted on the nitrogen and the other in the side chain. They found the former ineffective when



given by mouth and the latter, with three carbons in the side chain, very active when so administered. Hence, they also conclude that it is the three-carbon side chain that makes for oral activity.

Our results show that in extending the side chain of β-phenylethylamine, the entering methyl may be substituted on either of the two aliphatic carbons and in either case (III and V) oral activity is conferred. While quantitative values for pressor activity of these two isomers have not yet been determined, the wide differences in toxicity are very well defined and very striking indeed.

Phenylpropanolamine (VI) is included in the table in order to emphasize the importance of the alcoholic hydroxyl. Its elimination, which gives III, increases the intravenous toxicity to rabbits by 300% or more, a very significant extent.

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Procedure

All the amines were prepared by the catalytic hydrogenation of an appropriate intermediate by the process already described.[7]

Experimental

Phenyl-1-amino-1-propane.—Propiophenone oxime[8] was dissolved in absolute alcohol containing three equivalents of hydrogen chloride and smoothly reduced to the corresponding amine, isolated as the hydrochloride. The salt melted at 189.5° (corr.) and the base distilled at 100–105° at 35 mm.; a benzoyl derivative melted at 115–116° (corr.).[9]

Phenyl-1-amino-2-propane was obtained by reducing phenyl-1-chloro-1-amino-2-propane. Sixteen grams of phenylpropanolamine was heated in a bomb tube with 130 ml. of concentrated hydrochloric acid at 110–115° for four hours. No pressure developed. The solution was then chilled in an ice-salt bath and the hydrochloride of phenyl-1-chloro-1-amino-2-propane which settled out was filtered off, dried and recrystallized from absolute alcohol. The crystals melted at 201° (corr.); 8.5 g., a yield of 48%. Calcd. for $C_9H_{12}NClHCl$: Cl, 34.4. Found: Cl, 33.3. The organic chlorine seems to be very labile and further recrystallization gives a product with even less chlorine.

By shaking the chloro compound, dissolved in absolute alcohol, with palladium catalyst in an atmosphere of hydrogen, the chlorine was completely replaced by hydrogen; the resulting amine was isolated as hydrochloride, the salt melting at 144–147° and the base distilling at 200–201° (uncorr.).[10]

Phenyl-1-amino-3-propane.—An impure cinnamaldoxime[11] was reduced in an absolute alcoholic solution containing three equivalents of hydrogen chloride. Reduction ceased when 90% of the hydrogen calculated as required by the pure oxime had been taken up. The catalyst was removed and the filtrate evaporated to dryness on a steam-bath; the residue was taken up in water and an insoluble dark oily impurity removed by extraction with ether. The aqueous solution was treated with excess alkali, the liberated base extracted with ether, dried over sodium sulfate and distilled, boiling at 216–220° (uncorr.). For $C_6H_5CH_2CH_2CH_2NH_2$ the following boiling points are recorded: 215°,[12] 215–216°,[13] 221.5°.[14] The hydrochloride was precipitated from an ethereal solution of the base by addition of an absolute alcoholic solution of hydrogen chloride. The salt melted at 218° (corr.). From 11.6 g. of cinnamaldoxime 8.1 g. of the salt was obtained, a yield of 60%.

Phenyl-2-amino-1-propane was obtained from a-phenylpropionitrile. This intermediate nitrile was prepared from the sodium derivative of phenylacetonitrile and methyl iodide according to the directions of Victor Meyer[15] and Freund and König.[16]

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[7] Hartung, THIS JOURNAL, 50, 3370 (1928).

[8] "Beilstein," 4th ed., Vol. VII, p. 301.

[9] Busch and Leefhelm, *J. prakt. Chem.*, [2] **77**, 7 (1908), describe $C_6H_5CH(C_2H_5)NH_2 \cdot HCl$ as melting at 194°, the free base as distilling at 99–100° at 16 mm., and the benzoyl derivative as melting at 115–116°.

[10] Hey, *J. Chem. Soc.*, 18 (1930).

[11] Ref. 8, p. 351.

[12] Lasch, *Monatsh.*, **34**, 1658 (1913).

[13] Tafel, *Ber.*, **19**, 1924 (1886).

[14] Tafel, *ibid.*, **22**, 1854 (1889).

[15] Meyer, *Ann.*, **250**, 118 (1889).

[16] Freund and König, *Ber.*, **26**, 2874 (1893).

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However, the good yields they report, as high as 79%, have not been duplicated; our yields were 10–14%.

The reduction of α-phenylpropionitrile dissolved in absolute alcohol containing three equivalents of hydrogen chloride proceeded smoothly and completely, although about a third as rapidly as for the oximes, and the product was isolated as its hydrochloride salt, melting at 123–124° (corr.). Freund and König, by reducing the nitrile with sodium and absolute alcohol, obtained the base $C_6H_5CH(CH_3)CH_2NH_2$, whose hydrochloride melted at 124°.

Summary

Four isomeric phenylpropylamines were prepared by catalytic hydrogenation of an appropriate intermediate. A preliminary pharmacological examination of these compounds indicates that:

(1) The optimum skeleton for pressor compounds is β-phenylethylamine.

(2) A shift in the relative positions of the phenyl and amino groups very greatly decreases pressor potency.

(3) Substitution of a methyl on either of the two carbons in the side chain of this skeleton confers oral activity.

(4) The presence of the secondary alcoholic hydroxyl in phenylpropanolamine serves to decrease the toxicity to a degree that becomes significant therapeutically.

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THE PREPARATION OF ALIPHATIC AMIDES

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The most satisfactory methods of preparing amides have involved dehydration of the ammonium salt of the corresponding acid. Hofmann[1] prepared various amides by heating ammonium salts of aliphatic acids for five or six hours at 230° under pressure. Kundig[2] prepared acetamide by the rapid distillation of ammonium acetate and by heating an alcoholic solution of acetic acid and ammonia in a sealed tube for a long time at 100°. He also obtained a yield of amide greater than 25% by passing dry ammonia through acetic acid and then heating to boiling. Grant and James[3] have prepared amides by saturating the acid with dry ammonia and boiling. Dunlap,[4] Keller[5] and Verley[6] have modified the procedure by heating sodium acetate and ammonium chloride at 240°.

[1] Hofmann, *Ber.*, **15**, 977 (1882).
[2] Kundig, *Ann.*, **105**, 277 (1858).
[3] Grant and James, THIS JOURNAL, **39**, 933 (1917).
[4] Dunlap, *ibid.*, **24**, 762 (1902).
[5] Keller, *J. prakt. Chem.*, [2] **31**, 364 (1885).
[6] Verley, *Bull. soc. chim.*, [3] **9**, 691 (1893).

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