[CONTRIBUTION OF THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XII. OPTICAL ISOMERS IN THE EPHEDRINE SERIES OF COMPOUNDS (1)

CHARLES JAROWSKI AND WALTER H. HARTUNG

Received September 9, 1943

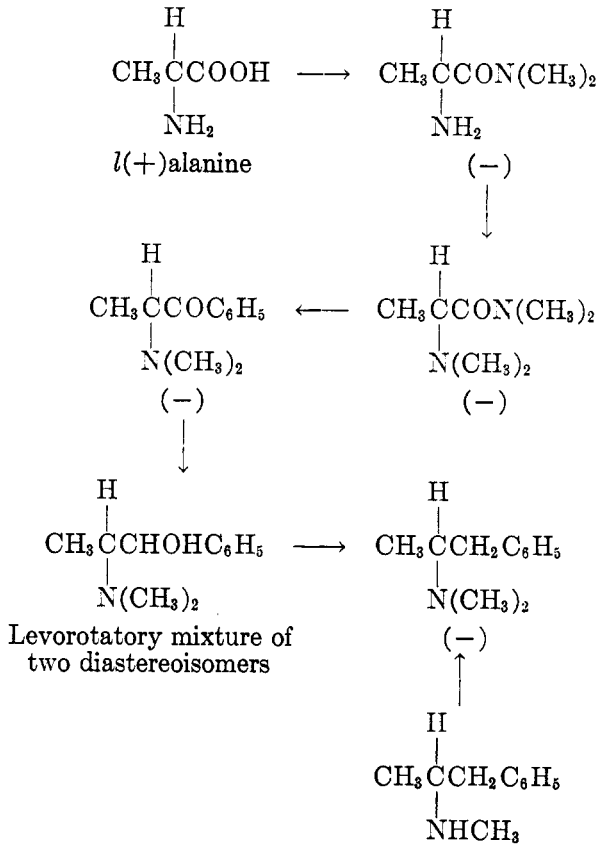
The position isomers and homologs of the ephedrine-epinephrine type of compounds have been extensively studied, and considerable correlation between chemical structure and physiological activity is possible. The chemical and pharmacodynamic properties of the optical isomers are not so well known. (−)Epinephrine possesses about 20 times the circulatory activity of the dextrorotatory isomer (2). (+)Benzedrine is 3 to 4 times more effective as a stimulant for the central nervous system than its (−)isomer (3). The four optical isomers of ephedrine, investigated qualitatively and quantitatively by Chen, Wu, and Henriksen (4), show appreciable variation in their mydriatic properties, effect on isolated tissues and pressor action; the pressor activity apparently decreases with increase in solubility of the (−) mandelate of the four diastereoisomers.

These differences do not appear unexpected if it is remembered that diastereoisomers are in fact different compounds, showing appreciable variations in both physical and chemical properties which are not suggested in the conventional projection formulas.[1] The protoplasmic reaction of the optical isomers with the tissue components undoubtedly increases the diastereoisomeric complexity and is a factor which contributes to their different qualitative and quantitative biological behavior.

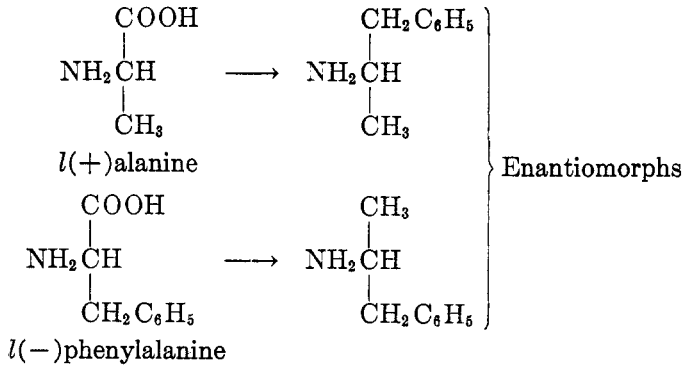
Efforts have been made to establish the relative configuration of the two asymmetric centers in ephedrine, $C_6H_5\underset{H}{\overset{OH}{C}}-\underset{NHCH_3}{\overset{H}{C}}CH_3$. The hydroxyl-bearing carbon atom, which is levorotatory, is placed in the *d*-series by virtue of the following sequence of reactions: *d*(−)mandelic acid → *d*(−)mandelamide $\xrightarrow{CH_3MgI}$ *d*(−)-phenylacetyl carbinol $\xrightarrow[H + CH_3NH_2]{}$ (−)ephedrine (6).

The status of the methylamino-bearing carbon atom, which is dextrorotatory, is not definite. By comparing nor-desoxyephedrine (benzedrine) with optically active α-phenethylamine of known relative configuration, Leithe (7) placed this carbon atom in the *d*-series. On the other hand by synthesizing N-methyldesoxyephedrine from *l*(+)alanine through the following series of products:

[1] For a more extended discussion of these phenomena see Jenkins and Hartung (5).



Freudenberg and Nikolai (8) assigned to this carbon atom the *l*-configuration. This confusion is not hard to understand, for it is primarily a question of whether desoxyephedrine is to be looked upon as related to *l*(+) alanine or to *l*(−)phen-



ylalanine, *e.g.*, it at once becomes apparent that if the −COOH of *l*(+) alanine is converted into $-CH_2C_6H_5$ the product is the mirror image of that obtained

when the $-COOH$ of $l(-)$phenylalanine is converted into $-CH_3$. Consequently the relative configuration of the amino-bearing carbon of ephedrine is still unsettled.

A study of the optical isomers of various members of the pressor compounds has been initiated in these laboratories. The resolution and the solubility of the salts of the isomers of propadrine, $C_6H_5CHOHCH(NH_2)CH_3$, benzedrine, $C_6H_5CH_2CH(NH_2)CH_3$, β-phenylpropylamine, $C_6H_5CH(CH_3)CH_2NH_2$, and phenylethanolamine, $C_6H_5CHOHCH_2NH_2$ are now reported.

TABLE I

THE PHYSICAL PROPERTIES OF THE MANDELATES STUDIED

NAME OF COMPOUND	M.P., °C	$(\alpha)_D$	T. °C.	Conc. (water)
1. (−) Ephedrine (−)mandelate	170	−70.6	26.5	2.4056
2. (−)Ephedrine (+)mandelate	78–91	21.3	25.5	2.8180
3. (−)Propadrine (−)mandelate	171.5–172	−70.6	29.0	2.3506
4. (+)Propadrine (−)mandelate	164.5–165	−42.8	29.0	1.2390
5. (+)Propadrine (+)mandelate	171.5–172	70.7	29.5	2.3460
6. *dl*-Propadrine *dl*-mandelate	161–162			
7. (+)ψ-Propadrine (−)mandelate	170	−45.3	32.4	1.1905
8. (−)ψ-Propadrine (−)mandelate	163.5	−41.3	32.4	0.7999
9. *dl*-ψ-Propadrine *dl*-mandelate	162.5–163			
10. (+)Benzedrine (−)mandelate	162–163	−50.0	25.0	2.2368
11. (−)Benzedrine (−)mandelate	166	−68.6	26.0	1.7054
12. (−)Benzedrine (+)mandelate	163	49.8	28.0	1.6045
13. *dl*-Benzedrine *dl*-mandelate	156.5			
14. (−)Isobenzedrine* (−)mand	127.127.5	−57.8	25.6	2.0735
15. (+)Isobenzedrine (+)mand	127–127.5	58.7	29.8	1.5818
16. (+)Isobenzedrine (−)mand	118.5–119	−47.5	29.8	1.2841
17. *dl*-Isobenzedrine *dl*-mand	119.5–120.5			
18. *dl*-Phenylethanolamine *dl*-mand	129.5–130			
19. (−)Phenylethanolamine (−)mand	144–145	−58.3	31.0	0.8916

* Synonym for β-phenylpropylamine.

EXPERIMENTAL

Mandelic acid was resolved according to the method of Roger (9). The reported and observed constants for the enantiomorphs are:

(−)mandelic acid: m.133.8°, $(\alpha)_D$ −178° (reported); observed, m.133–134°, $(\alpha)_D$ −178.4° (conc. 0.6948 in ethanol).

(+)mandelic acid: m.133°, $(\alpha)_D$ 159–173° (reported); observed, m.132–133°, $(\alpha)_D$ 173°, (conc. 0.6907, in ethanol).

Separation of the dl- *and* dl-ψ-*propadrine.* A mixture of the four bases prepared by the reduction of phenylnitropropanol, $C_6H_5CHOHCH(NO_2)CH_3$, was obtained through the courtesy of the Commercial Solvents Corporation. The two racemic mixtures were separated from any impurities in the crude product by precipitating them as the hydrochloride from benzene, treating with Norit, basification, extraction, and reprecipitation from benzene as before. The two racemic hydrochlorides were separated by repeated crystallizations from absolute ethanol. The less soluble salt was *dl*-propadrine hydrochloride, m.194. Racemic ψ-propadrine hydrochloride was procured from the mother liquors by the addition of excess ether, m.170.5–171.5°.

Resolution of the bases. *dl*-Propadrine, *dl*-ψ-propadrine, phenylethanolamine, benzedrine, and β-phenylpropylamine were resolved into their optically active components by substantially identical procedures. To a hot ethanol solution of the *dl*-base was added a

TABLE II

PHYSICAL PROPERTIES OF THE ISOMERS STUDIED

NAME OF COMPOUND	M.P., °C	ROTATION		
		$(\alpha)_D$	T., °C	Conc. Abs. EtOH
(−)Ephedrine	34–40	−3.47	27	4.3130
(−)Propadrine	102	−19.90	30	0.2641
(+)Propadrine	102	20.80	32	0.2400
(+)ψ-Propadrine hydrochloride	179	41	29	0.1583
(−)ψ-Propadrine hydrochloride	178	−38.7	32	0.2100
(+)Benzedrine		3.8	25	3.4168
(−)Benzedrine		−3.8	28	2.5633
(−)Isobenzedrine		−18.82	30	2.5492
(+)Isobenzedrine		18.8	30	2.4651
(−)Phenylethanolamine		−20.90	30	0.0956

TABLE III

SOLUBILITY OF THE DIASTEREOISOMERIC MANDELATES

	SOLUBILITY 37°			SOLUBILITY 25°		
	Distilled Water	Normal Saline	Difference	Distilled Water	Normal Saline	Difference
1	6.27	6.99	0.72	6.00	5.95	−0.05
2	80.61	92.34	11.73	77.48	88.68	11.20
3	7.39	7.36	−0.03	6.08	6.30	0.22
4	10.69	10.19	−0.50	7.70	7.26	−0.44
5	8.36	7.34	−1.02	5.58	5.95	0.37
6	8.08	8.14	0.06	5.35	6.00	0.65
7	8.43	9.56	1.13	6.22	6.23	0.01
8	18.74	19.01	0.27	11.95	15.02	3.07
9	11.41	11.06	−0.35	5.67	8.66	−0.01
10	4.63	4.77	0.14	3.93	4.16	0.25
11	7.25	7.56	0.31	5.98	6.24	0.26
12	4.80	4.65	0.05	3.94	4.21	0.27
13	6.98	7.42	0.44	5.73	6.19	0.46
14	25.30	28.08	2.78	14.59	15.59	1.00
15	27.23	31.95	4.72	14.39	15.54	1.15
16	63.46	61.15	−2.31	51.15	48.86	−2.27
17	20.13	18.36	−1.77	11.50	11.31	−0.19
18	18.56	19.79	1.23	11.63	11.76	0.15
19	—	—	—	—	—	—

hot alcoholic solution of an equivalent amount of the optically active mandelic acid. Upon cooling, the less soluble salt crystallized out. The solid product was recrystallized to constant rotation and maximum melting point. The more soluble mandelate was procured by concentration of the mother liquor from the initial crystallization, addition of excess dry ether to the hot ethanolic solution, and adequate cooling. Several recrystallizations from

ether-alcohol yielded the more soluble salt in pure form. Absolute ethanol was used as the solvent in all cases except in the resolution of phenylethanolamine and β-phenylpropylamine in which instances secondary butyl alcohol proved to be more expeditious. The melting points and rotations of the various salts are listed in Table I.

The purified salts, treated with alkali, liberated the optically pure free bases. The properties of the bases are given in Table II.

Solubility measurements. Saturated solutions of the various salts at 25° and 37° in normal saline and distilled water were prepared as follows: To 10 cc. of normal saline or distilled water in a 20-cc. test tube, immersed in a thermostat at the desired temperature, was added an excess of the mandelate. The tubes were stoppered and frequently agitated during the course of six hours. About 3 cc. of solution was pipetted off and weighed. The weight of the residue was then determined after removal of the water on a steam-cone and drying in an electrically heated oven to constant weight. The weight of the residue from the normal saline solutions was corrected in regard to the amount of sodium chloride present. The solubility data are listed in Table III. The numbers in column 1 correspond to the compounds in Table I.

The optically active salts have been studied by Dr. K. K. Chen, who will publish elsewhere a more elaborate report of his observations. However through the courtesy of Dr. Chen a summary of the pressure ratios is included here.

DISCUSSION OF RESULTS

From Table I it can be seen that the less soluble salts of (−)mandelic acid from each pair of enantiomorphous bases are: (−)propadrine, (+)ψ-propadrine, (−)phenylethanolamine, (−)β-phenylpropylamine, and (+)benzedrine. The spatial relationships of the asymmetric carbons in the compounds studied show a definite correlation to the solubility of their salts. Thus in those pressor amines possessing only one asymmetric center, the less soluble (−)mandelate is formed by that base whose phenyl-bearing carbon is levorotatory [Example: (−)phenylethanolamine and (−)β-phenylpropylamine] or whose carbinamine carbon is dextrorotatory [Example: (+)benzedrine].

Propadrine and ephedrine each possess two centers of asymmetry. It has been established by the work of Nagai (10), Leithe (11), Freudenberg (12) and others that in (−)ephedrine and (−)propadrine the hydroxyl-bearing carbon is levorotatory while the carbinamine carbon is dextrorotatory. In (+)ψ-propadrine and (+)ψ-ephedrine both centers of asymmetry are exerting their effect in the same direction. Thus of the four possible isomers of these two bases the least soluble is found to be that one answering the specifications mentioned before; namely that the carbinamine carbon be dextrorotatory while the hydroxyl-bearing carbon have a levorotation. In the event both centers of asymmetry are of similar sign it is the dextrorotatory isomer which forms the less soluble mandelate.

Pharmacodynamic information about the sympathomimetic amines studied shows that of the enantiomorphous pairs (−)propadrine, (−)ephedrine, (+)benzedrine, (−)ψ-propadrine, (+)ψ-ephedrine, and (−)β-phenylpropylamine are the more active. Neither quantitative nor qualitative comparisons in the physiological behavior of the optical isomers of phenylethanolamine are available. However from the analogies with the compounds described above the prediction is ventured that the levorotating isomer will prove to be the more active. In

epinephrine, where the hydroxyl-bearing carbon is asymmetric, the levorotatory isomer is more active physiologically. In phenylethanolamine the corresponding carbon atom is asymmetric.

TABLE IV

PHARMACOLOGICAL DATA

NAME OF COMPOUND	AMOUNT PRODUCING THE SAME INTENSITY OF PRESSOR ACTION (AVERAGE) AS 0.01 MG. OF EPINEPHRINE
(−)Benzedrine (−)mandelate	2.82 mg.
(−)Benzedrine (+)mandelate	4.17 "
(+)Benzedrine (−)mandelate	2.70 "
(−)Isobenzedrine (−)mandelate	4.68 "
(+)Isobenzedrine (−)mandelate	5.30 "
(+)Isobenzedrine (+)mandelate	6.73 "
(−)Propadrine (−)mandelate	3.17 "
(+)Propadrine (−)mandelate	4.73 "
(−)Pseudopropadrine (−)mandelate	17.00 "
(+)Pseudopropadrine (−)mandelate	19.00 "
(−)Phenylethanolamine (−)mandelate	5.48 "

TABLE V

COMPARISON OF THE PHYSICAL AND PHYSIOLOGICAL PROPERTIES OF β-PHENYLPROPYLAMINE AND PHENYLETHANOLAMINE

NAME OF COMPOUND	M.P., °C	$(\alpha)_D$	AMOUNT CAUSING THE SAME ACTION AS 0.01 MG. OF EPINEPHRINE
(−)Isobenzedrine (−)mandelate	127–127.5	−57.8	4.68 mg.
(−)Phenylethanolamine (−)mandelate	144–145	−58.7	5.48 "
dl-Isobenzedrine *dl*-mandelate	119.5–120.5		
dl-Phenylethanolamine *dl*-mandelate	129.5–130		
(−)Isobenzedrine		−18.82	
(−)Phenylethanolamine		−20.7	

SOLUBILITY

	37°		25°	
	Distilled Water	Saline	Distilled Water	Saline
dl-Isobenzedrine *dl*-mandelate	20.13	18.36	11.50	11.31
dl-Phenylethanolamine *dl*-mandelate	18.56	19.72	11.63	11.78

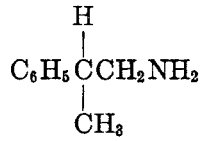
It is interesting to note that the levorotating base of the two ψ-propadrine isomers is the more active physiologically. This is unexpected in view of the fact that *d*-ψ-ephedrine is almost seven times more active as a pressor than is *l*-ψ-ephedrine (4). The explanation of this apparent discrepancy between the ψ-ephedrine bases and their nor-homologs must be left to the future.

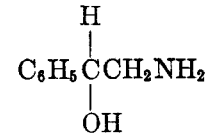
From these results one is led to believe that the optimum configuration for activity is found in those isomers in which the phenyl-bearing carbon atom, if asymmetric, is dextrorotatory (*d*-series if referred to phenylalanine, *l*-series if referred to alanine).

Other correlations between solubility and physiological effects do not appear in the data thus far procured. It is not unlikely, however, that as more information about the physical and physiological properties becomes available that further correlations may be found.

This study reveals a striking parallelism of properties between β-phenylpropylamine and phenylethanolamine as may be seen from Table V.

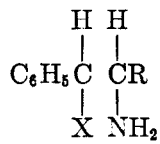
This suggests an unusual type of isosterism,





in which a hydroxyl group of a physiologically active compound may be replaced by a methyl and only relatively minor changes in physical properties are produced. This isosteric analogy apparently holds for physiological properties both quantitatively and qualitatively. When given parenterally both are effective pressors; on the other hand oral administration shows no activity. Furthermore both compounds exert only a slight stimulant action on the central nervous system (13).

These correlations suggest the desirability of comparing the physical and physiological properties of an active molecule of the type:



in which X represents the first elements in groups IV, V, VI, and VII of the periodic table joined by a single bond to the remainder of the molecule, the other valences being satisfied with hydrogen atoms, thus

—CH_3	—NH_2	—OH	—F
(m.w. 15)	(m.w. 16)	(m.w. 17)	(a.w. 19)

The molecular weights of the four isosters would be nearly the same and there should be little difference in electronic structure and molecular size.

SUMMARY

1. Mandelic acid was separated into *dextro* and *levo* components by the use of (−)ephedrine.

2. Phenylethanolamine, β-phenylpropylamine, benzedrine, propadrine, and ψ-propadrine were resolved by means of *d*- and *l*-mandelic acids, and a study of

the solubility of the mandelates at 25° and 37° in distilled water and normal saline was made.

3. From the data procured one is led to believe that the optimum configuration for activity is found in those isomers in which the phenyl-bearing carbon atom, if asymmetric, is levorotatory, and in which the carbinamine carbon, if asymmetric, is dextrorotatory. In all cases except that of the ψ-propadrines, the isomer forming the less soluble mandelate was the more active physiologically.

4. An interesting isosteric analogy between β-phenylpropylamine and phenylethanolamine is pointed out.

BALTIMORE, MD.

REFERENCES

(1) For Amino Alcohols, XI, see LEVIN AND HARTUNG, *J. Org. Chem.*, **7**, 408 (1942).
(2) TAINTER, *J. Pharmacol.*, **40**, 43 (1930).
(3) ALLES AND PRINZMETAL, *Am. J. Med. Sci.*, No. 5, **200**, 665 (1940).
(4) CHEN, WU, AND HENRIKSEN, *J. Pharmacol.*, **36**, 363 (1929).
(5) JENKINS AND HARTUNG, "The Chemistry of Organic Medicinal Products", John Wiley and Sons, Inc., New York, **1943**, pp. 569–615.
(6) FREUDENBERG, SCHÖFFEL, AND BRAUN, *J. Am. Chem. Soc.*, **54**, 234 (1932).
(7) LEITHE, *Ber.*, **65**, 660 (1932).
(8) FREUDENBERG AND NIKOLAI, *Ann.*, **310**, 223 (1934).
(9) ROGER, *J. Chem. Soc.*, 1544 (1935).
(10) NAGAI, *J. Pharm. Soc. Japan*, **121**, 200 (1892).
(11) LEITHE, *Ber.*, **64**, 2827 (1931).
(12) FREUDENBERG, BRAUNS, AND SIEGEL, *Ber.*, **56**, 193 (1923).
(13) HAUSCHILD, *Arch. exptl. Path. Pharmakol.*, **195**, 647 (1940).