α-Benzyltetrahydrofurfurylamines—A New Series of Psychomotor Stimulants. II.[1] Resolution of Isomers

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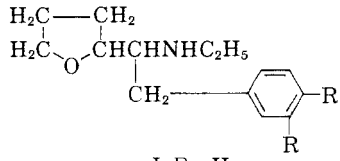
The resolution of *dl-threo-* and *dl-erythro-α*-benzyl-*N*-ethyltetrahydrofurfurylamine (I) is described. The psychomotor stimulatory activity of the separated isomers is reported.

A new series of potent psychomotor stimulants has been discovered which derive from α-benzyltetrahydrofurfurylamine. Paper I of this series[1] reported that the highest level of activity observed was produced by *dl-threo-α*-benzyl-*N*-ethyltetrahydrofurfurylamine (I) and by an unseparated mixture of *dl-threo-* and *dl-erythro-α*-(3,4-dichlorobenzyl)-*N*-ethyltetrahydrofurfurylamine (II).



I, R = H
II, R = Cl

The compounds of this series may be considered to be formally related to amphetamine in that they are *N*-substituted-α-(2-tetrahydrofuryl)-phenethylamines. The basis for assignment of the *threo* and *erythro* configurations to the two forms of I will be published later.

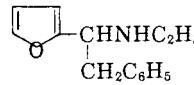
The present paper deals primarily with resolution of *dl-threo-* and *dl-erythro-α*-benzyl-*N*-ethyltetrahydrofurfurylamine (I) and records the stimulatory activity of the resolved forms. Resolution of the *dl-threo* isomer was accomplished most easily through its dibenzoyl-bitartrate salts. The *d-threo* isomer was obtained pure in 96% yield after one recrystallization. Resolution of the *dl-erythro* isomer, however, was most easily achieved through formation of tartrate

(1) Paper I by R. L. Clarke and L. S. Harris, *J. Med. Pharm. Chem.*, **5**, 77 (1962).

salts. The optically active compounds involved in and resulting from these separations are summarized in Table I.

Attention is called to some peculiar optical rotatory relationships which are without obvious explanation. The variation in the optical rotation of the *d*- and *l-threo*-base hydrochlorides when measured in acetic acid and in water is minor and the greater numerical value is found in water. With the *d*- and *l-erythro*-base hydrochlorides, on the other hand, the value in water is less than half of that in acetic acid. Yet, in the case of the *threo* compounds where the above solvent effect is slight, the variation in rotation (in acetic acid) in going from the hydrochloride salt to the free base (acetate salt in solution) involves more than a twofold increase, while in the *erythro* series this change is negligible.

Hydrogenation of α-benzyl-*N*-ethylfurfurylamine (III) afforded the mixture of *threo* and *erythro* forms used in the above experiments. A procedure for separation of these forms which employs a more



III

efficient solvent system than that previously reported[1] is described in the Experimental section. In the five-mole run described here, the yields of pure *threo* and *erythro* isomers were 37% and 41%, respectively. Although the size of the successive crops of the two isomers (collected alternately) decreases with increasing concentration of impurities, their ratio continues to hold nearly constant so it can be concluded with considerable confidence that the isomers are produced in approximately equal quantities in this reaction.

Raney nickel or palladium on charcoal (10%) can be used as hydrogenation catalyst in the reduction under discussion, but platinum apparently causes hydrogenation of the benzene ring also. When the hydrochloride salt of the base is hydrogenated in alcohol, a 60° temperature is necessary to complete the reaction; water as a solvent requires a 60° temperature from the beginning of the reaction.

Another approach to the four resolved tetrahydrofurfurylamine isomers involved resolution of the furfurylamine III, then saturation of the furan ring of each enantiomer and separation of the resulting diastereoisomeric mixtures. *dl*-α-Benzyl-*N*-ethylfurfurylamine was

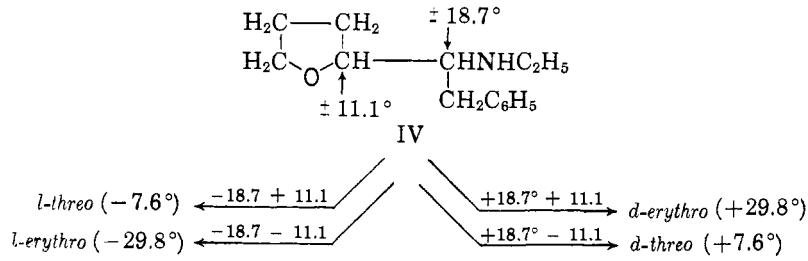
TABLE I

Compound	Optical form	Salt	$[\alpha]^{25}D$ HOAc	$[\alpha]^{25}D$ H_2O	M.p., °C.
threo-α-Benzyl-*N*-ethyl-tetrahydrofurfuryl-amine	*d*	Dibenzoyl-D-bitartrate	−66.2		163–164 dec.
	l	Dibenzoyl-L-bitartrate	+66.5		162–164 dec.
	d	Hydrochloride	+ 7.5	+ 8.7	126–128
	l	Hydrochloride	− 7.7	− 8.9	126.5–128.5
	l	Free base	−17.5[a]		
erythro-α-Benzyl-*N*-ethyltetrahydro-furfurylamine	*d*	D-Tartrate	+24.9	+20.8	134–135.5
	l	L-Tartrate	−26.2	−20.8	133–135
	d	Hydrochloride	+29.4	+12.5	130–130.6
	l	Hydrochloride	−30.3	−12.6	128–129
	l	Free base	−33.1[a]		
α-Benzyl-*N*-ethyl-furfurylamine	*l*	Dibenzoyl-D-tartrate	−92.6		181–182 dec.
	d	Dibenzoyl-L-tartrate	+93.2		182.5–183.5 dec.
	l	Free base	−66.9[a]		
	d	Free base	+68.1[a]		
	l	Hydrochloride		−54.9	210–212 (uncorr.)
	d	Hydrochloride		+56.9	210–212 (uncorr.)
α-Benzyl-*N*-methyl-furfurylamine	*l*	Dibenzoyl-D-tartrate	−94.9		214–215 dec.
	d	Dibenzoyl-L-tartrate	+94.8		212–212.5 dec.
	l	Hydrochloride	−60.6	−58.0	164–165.5
	d	Hydrochloride	+60.2	+57.4	163.5–165.5

[a] In acetic acid solution, the base would be present as its acetate salt.

resolved through its dibenzoyltartrate salts. Table I contains a summary of the optically active compounds derived from this separation.

Hydrogenation of *d*-α-benzyl-*N*-ethylfurfurylamine introduced the second asymmetric center. The rotation of the hydrochloride salt of the resulting unseparated diastereoisomeric mixture (88% yield) was +18.2° (glacial acetic acid.) From the optical rotatory values of the resolved *threo* and *erythro* forms (as hydrochloride salts in acetic acid and using averaged numerical values of 7.6° and 29.8° for these rotations), it can be calculated that one center of asymmetry contributes ±18.7° and the other, ±11.1°.[2] A nearly 1:1 ratio of *threo:erythro* mixture can be assumed. If the original *d*-asymmetric center had contributed +18.7°, the reduced mixture should have shown the average of the extremes of +29.8° and +7.6°, *i.e.*, +18.7°. If the original center had contributed +11.1°, the reduced product should have shown the average of the extremes of +29.8° and −7.6°, *i.e.*, + 11.1°. The observed value of 18.2° indicates strongly that a *d-threo–d-erythro* mixture was produced and that the rotational contributions shown in IV are essentially correct. This conclusion



is supported by biological data described below. It was of particular interest to be able to prepare a *d-threo-d-erythro* mixture (containing the two most active enantiomers) without having to perform the *dl-threo-dl-erythro* separation.

Hydrogenation of *l*-α-benzyl-*N*-ethylfurfurylamine gave a presumed 1:1 mixture of *l-threo-* and *l-erythro*-α-benzyl-*N*-ethyltetrahydrofurfurylamine with $[\alpha]^{25}D$ − 25.7° (acetic acid). The mean of the values for the *l-threo*-base in acetic acid (−17.5°) and the

(2) These values are approximations as shown by M. A. Rosanoff, *J. Am. Chem. Soc.*, **28**, 525 (1906), who demonstrated that the optical rotatory power of an asymmetric carbon atom is affected by the configuration of an attendant asymmetric carbon atom.

l-erythro-base in acetic acid (−33.1°) is −25.3°, a value in very good agreement with that found.

Separation of the diastereoisomeric *d-threo-d-erythro* mixture by means of dibenzoyl-L-tartaric acid was unsatisfactory as was the separation of the *l-threo-l-erythro* mixture with dibenzoyl-D-tartaric acid. In retrospect, it is apparent that reversal of the tartrate forms used on the two mixtures should have afforded much better separation.

In the *N*-methyl series, *dl*-α-benzyl-*N*-methylfurfurylamine[1] was resolved in a manner identical with that used for the *N*-ethyl homolog. The rotations and melting points of the optically active compounds derived from this separation are shown at the bottom of Table I. Hydrogenation of the free bases and separation of the components of the resulting diastereoisomeric mixtures was not entirely satisfactory and is not described here.

The degree of psychomotor stimulation produced by the resolved *threo* and *erythro* isomers described above was measured by the frequency with which a transverse light beam was broken by medicated mice confined in a cylindrical cage. This method is described in detail in ref. 1. Data on the four isomers are summarized in Fig. 1, where it is evident that the *d-threo* isomer is the most potent stimulant. With either enantiomeric pair, the *d* form is more active than the *l* form. The lines for the *l* forms are short because the animals fail to respond to higher doses of these isomers with further increases in activity. For comparison purposes the dose-response curve for *dl*-amphetamine is given.

Medication of the mice with the *d-threo-d-erythro* mixture described above, obtained by reduction of *d*-α-benzyl-*N*-ethylfurfurylamine (III), produced a dose-response curve which would lie midway between the curves in Fig. 1 for the *d-threo* and *d-erythro* isomers. These test data thus support the identity of this mixture.

Experimental[3]

Resolution of *dl-threo*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine.—A solution of 285 g. (1.11 mole) of *dl-threo*-α-benzyl-*N*-ethyltetrahydrofurfurylamine hydrochloride in 400 ml. of water was treated with 100 ml. of 35% aqueous sodium hydroxide solution and the liberated base was extracted with three 250-ml.

(3) All melting points are corrected unless otherwise noted. Optical rotations are in acetic acid (1%) except where indicated. Appreciation is extended to Mrs. G. A. Snyder, Miss J. R. Dembinski and Miss D. A. Henderer for technical assistance, to Dr. F. C. Nachod and staff for the optical rotational data and to Mr. K. D. Fleischer and staff for the analytical data.

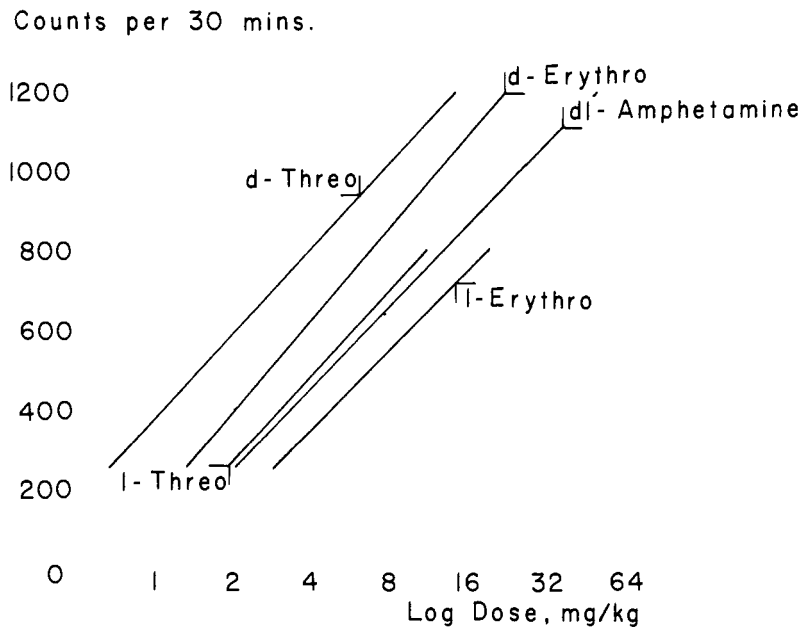


Fig. 1.—A comparison of the psychomotor stimulation produced by resolved isomers of *threo-* and *erythro-α*-benzyl-N-ethyltetrahydrofurfurylamine and by *dl*-amphetamine.

portions of benzene. The combined extracts were dried over "Drierite" and concentrated to an oily residue (245 g.).

A solution of 420 g. of dibenzoyl-D-tartaric acid monohydrate[4] and the 245 g. of *dl-threo* base in 2.8 l. of absolute ethanol at 60° was scratched (or seeded) to initiate crystallization and allowed to cool slowly to 25° with stirring. The mixture was kept for 4 hr. at 25°, filtered and the filter cake washed with a small quantity of cold absolute alcohol and then with dry acetone. The solid was air-dried overnight at 40° to give 335 g. of *d-threo-α-benzyl-N-ethyltetrahydrofurfuryl-amine dibenzoyl-D-bitartrate*, m.p. 161–161.5° dec. Recrystallization from 2 l. of 95% ethanol gave 310 g. (96%) of salt, m.p. 163–164° dec., $[\alpha]^{25}D$ −66.2°.

Anal. Calcd. for $C_{32}H_{35}NO_9$: C, 66.54; H, 6.11; neut. eq., 577.6. Found: C, 66.9; H, 6.5; neut. eq., 562.

Concentration of the filtrate from separation of the *d-threo*-base dibenzoyl-D-bitartrate and treatment of the residue with excess 2 *N* sodium hydroxide liberated the crude *l-threo*-base which was extracted with ether. The ether extracts were dried over sodium sulfate and concentrated to a residue. This residue was

(4) C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, **55**, 2605 (1933).

treated with dibenzoyl-L-tartaric acid monohydrate[5] in absolute alcohol in a manner identical with that for the preparation of the enantiomorphic salt described above. *l-threo-α-Benzyl-N-ethyltetrahydrofurfurylamine dibenzoyl-L-bitartrate* melts at 162–164° dec., $[\alpha]^{25}D$ +66.5°.

Anal. Calcd. for $C_{32}H_{35}NO_8$: C, 66.54; H, 6.11; neut. eq., 577.6. Found: C, 67.0; H, 5.8; neut. eq., 566.

***d-threo*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine Hydrochloride.**—*d-threo*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine dibenzoyl-D-bitartrate (20.9 g., 0.036 mole) was treated with 50 ml. of 2 *N* sodium hydroxide solution and the liberated base was extracted with two portions of ether. The ether extracts were washed with saturated salt solution, dried over sodium sulfate and concentrated to a residue. Treatment of this oily residue with 4.5 ml. of 8.3 *N* alcoholic hydrogen chloride with cooling, dilution with ether and filtration afforded 8.25 g. (90% yield) of the *d*-base hydrochloride, m.p. 126–128°. Recrystallization of this solid from 100 ml. of ethyl acetate with concentration of the solution to a 50-ml. volume afforded 7.85 g. of white, massive prisms, m.p. 126–128°, $[\alpha]^{25}D$ +7.5° (a 5% solution in water showed +8.7°).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.76; H, 8.67; Cl, 13.87. Found: C, 65.4; H, 8.5; Cl, 14.1.

***l-threo*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine Hydrochloride.**—*l-threo*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine was liberated from its dibenzoyl-L-bitartrate salt in the manner described for the *d-threo* compound immediately above. The free base distilled at 83.5–84.5° (0.05 mm.), $n^{25}D$ 1.5149, $[\alpha]^{25}D$ −17.5°.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.38. Found: C, 76.5; H, 9.4; N, 6.3.

The hydrochloride salt of this base formed massive prisms, m.p. 126.5–128.5°, $[\alpha]^{25}D$ −7.7° (a 5% solution in H_2O showed −8.9°).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.76; H, 8.67; Cl, 13.87. Found: C, 65.5; H, 8.6; Cl, 13.9.

Resolution of *dl-erythro*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine.—*dl-erythro*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine hydrochloride was converted to the free base in the manner described for the *dl-threo* hydrochloride. A solution of 44 g. (0.2 mole) of the *dl-erythro* base and 15.0 g. (0.100 mole) of D-tartaric acid in 60 ml. of 95% ethanol was cooled to 5° and scratched to induce crystallization. The mixture was allowed to stand for 20 hr. at 5°, filtered and the filter cake was washed with 5 ml. of cold 95% alcohol and with ether. Drying overnight at 60° afforded 25 g. (85% of the theoretical yield) of *d-erythro-α-benzyl-N-ethyltetrahydrofurfurylamine* D-*tartrate*, m.p. 130–133°. A single recrystallization of the product from 50 ml. of 95% ethanol gave 18 g. of material, m.p. 134–135.5°, which was unchanged by further recrystallization, $[\alpha]^{25}D$ +24.9° (a 5% solution in H_2O showed +20.8°).

Anal. Calcd. for $C_{32}H_{48}N_2O_8$: C, 65.28; H, 8.22; N, 4.76. Found: C, 68.3; H, 8.5; N, 4.7.

Concentration of the filtrate from separation of the *d-erythro* base D-tartrate by

(5) Prepared by the method of ref. 4, but using L-tartaric acid instead of D-tartaric acid.

warming *in vacuo* and treatment of the residue with excess 2 *N* sodium hydroxide liberated the crude *l-erythro* base which was extracted with ether. The ether extracts were dried over sodium sulfate and concentrated to a residue. A solution of this residue (24 g.) and 8.16 g. of L-tartaric acid in 50 ml. of 95% alcohol was scratched to initiate crystallization and the mixture was cooled at 5° for 2 hr. The precipitate was collected, washed with 5 ml. of cold 95% ethanol and dried at 70° to give 18.3 g. (62%) of *l-erythro-α-benzyl-N-ethyltetrahydrofurfurylamine* L-*tartrate*, m.p. 131–134°. Two recrystallizations of the product from 95% ethanol afforded 13.0 g. of pure material, m.p. 133–135°, $[\alpha]^{25}D$ −26.2° (a 5% solution in H_2O showed −20.8°).

Anal. Calcd. for $C_{32}H_{48}N_2O_8$: C, 65.28; H, 8.22; N, 4.75. Found: C, 65.5; H, 8.6; N, 4.7.

***d-erythro*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine Hydrochloride.**—*d-erythro-α*-Benzyl-*N*-ethyltetrahydrofurfurylamine D-tartrate (16 g.) in 100 ml. of water was treated with an excess of sodium hydroxide solution and the liberated base was extracted with ether. The ether extracts were washed with saturated salt solution, dried over "Drierite" and concentrated to a residue. The residual oily base was dissolved in 50 ml. of isopropyl alcohol and treated with 5 ml. of concentrated hydrochloric acid. All solvent was removed by warming *in vacuo*, the viscous residue was dissolved in 30 ml. of acetone, a residual cloudiness was removed by filtration and the solution was cooled to 5° for several hr. The solid was collected, washed with cold acetone and with ether and dried overnight at 70° to give 10.5 g. (75% yield) of the *d*-base hydrochloride, m.p. 130–130.6°, $[\alpha]^{25}D$ + 29.4° (a 5% solution in H_2O showed +12.5°).

Anal. Calcd. for $C_{14}H_{22}ClNO$: Cl, 13.87; % Base, 85.7. Found: Cl, 13.7; % Base, 86.1.

***l-erythro*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine Hydrochloride.**—This salt was prepared from *l-erythro-α*-benzyl-*N*-ethyltetrahydrofurfurylamine L-tartrate in a manner identical with that described above for the *d-threo* hydrochloride. The product, obtained in 84% yield, melted at 128–129°, $[\alpha]^{25}D$ −30.3° (a 5% solution in H_2O showed −12.6°).

Anal. Calcd. for $C_{14}H_{22}ClNO$: Cl, 13.87; % Base, 85.7. Found: Cl, 14.1; % Base, 86.1.

***l-erythro*-α-Benzyl-*N*-ethyltetrahydrofurfurylamine** (free base) boiled at 108° (1 mm.), $n^{25}D$ 1.5149, $[\alpha]^{25}D$ −33.1°.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.38. Found: C, 76.5; H, 9.5; N, 6.3.

Separation of *dl-erythro* and *dl-threo* Forms of α-Benzyl-*N*-ethyltetrahydrofurfurylamine.—To 1100 g. (5.02 moles) of a mixture containing approximately equal quantities of *dl-erythro* and *dl-threo-α*-benzyl-*N*-ethyltetrahydrofurfurylamine was added 300 ml. of 8.3 *N* alcoholic hydrogen chloride (one-half the calculated amount) with vigorous stirring and cooling. Seed crystals of pure *dl-erythro* salt were added and the mixture was stirred at 5° until heavy precipitation had occurred (several hr.). Dry ether (2 l.) was added with stirring, the mixture was filtered and the filter cake was washed with ether to give 650 g. of crude *dl-erythro* salt, m.p. 140–153°. Recrystallization of this salt from 2 l. of isopropyl alcohol gave 330 g. of *dl-erythro* salt, m.p. 156–159° (m.p. of pure salt, 159.5–161°).

The mother liquor from the recrystallization was added to the first liquor and this solution was neutralized with approximately 300 ml. of 8.3 *N* alcoholic hydrogen chloride. The solution was concentrated to a residue by warming *in vacuo*. At the first signs of crystal formation, the residue was dissolved in 750 ml. of boiling 95% isopropyl alcohol and the solution cooled to 25°. The mixture was filtered and the filter cake was washed with isopropyl alcohol and acetone to give 110 g. more of the *dl-erythro* salt, m.p. 152–156°.

Concentration of the combined filtrate and washings by warming *in vacuo* to the point of initial crystallization, addition of 1 l. of boiling acetone, stirring, cooling to room temperature, filtration and washing of the filter cake with acetone gave 300 g. of *dl-threo* salt, m.p. 145–148° (m.p. of pure salt, 151–152.5°).

Repetition of this process of concentration, crystallization from isopropyl alcohol to give the *dl-erythro* salt, concentration of the filtrate and crystallization from acetone to give the *dl*-threo salt furnished 520 g. (41% yield) of *dl-erythro* salt, m.p. 152–156°, and 475 g. (37% yield) of *dl-threo* salt, m.p. 145–150°. A single further recrystallization of each salt from isopropyl alcohol afforded pure material.

Resolution of *dl*-α-Benzyl-*N*-ethylfurfurylamine.—*dl*-α-Benzyl-*N*-ethylfurfurylamine (24.4 g., 0.113 mole) was added with stirring to a solution of 20.3 g. (0.057 mole) of dibenzoyl-D-tartaric acid monohydrate in 100 ml. of absolute ethanol. The precipitate which formed was collected, dissolved in 1.5 l. of hot absolute ethanol and the solution was concentrated to *ca.* 600 ml. Cooling to 30° and filtration afforded 14.1 g. (64%) of needle clusters, m.p. 179–181° dec., of nearly pure *l-α-benzyl-N-ethylfurfurylamine dibenzoyl-D-tartrate*. This product was recrystallized again from absolute ethanol to give 11.6 g. of pure salt, m.p. 181–182° dec., $[\alpha]^{25}D$ −92.6°.

Anal. Calcd. for $C_{46}H_{48}N_2O_{10}$: C, 70.04; H, 6.13; neut. eq., 394.4. Found: C, 70.2; H, 6.3; neut. eq., 388.

The original reaction liquor and the filtrate from the first recrystallization step above were combined and concentrated to a residue. This residue was treated with an excess of 2 *N* sodium hydroxide solution and the liberated base was extracted with two portions of ether; the extracts were washed with saturated salt solution, dried over potassium carbonate and concentrated to an oily residue; this was treated with a solution of 15.0 g. (0.079 mole) of dibenzoyl-L-tartaric acid monohydrate in 70 ml. of absolute ethanol and the precipitated solid was collected. It was recrystallized by dissolving it in 1.5 l. of absolute ethanol, concentrating the solution to a 650-ml. volume and cooling it to 30°. Filtration afforded 16.3 g. (74% of the theoretical amount) of white needles, m.p. 182–183° dec., of *d-α-benzyl-N-ethylfurfurylamine dibenzoyl-L-tartrate*. This product was recrystallized again from absolute ethanol to give 13.8 g. of salt, m.p. 182.5–183.5° dec., $[\alpha]^{25}D$ +93.2°.

Anal. Calcd. for $C_{46}H_{48}N_2O_{10}$: C, 70.04; H, 6.13; neut. eq., 394.4. Found: C, 70.5; H, 6.2; neut. eq., 388.

***l*-α-Benzyl-*N*-ethylfurfurylamine.**—*l*-α-Benzyl-*N*-ethylfurfurylamine dibenzoyl-D-tartrate (11.1 g., 0.014 mole) was treated with an excess of 2 *N* sodium hydroxide solution and the liberated base was dissolved in ether. The ether solution was washed with saturated salt solution, dried over sodium sulfate and

concentrated to an oily residue. Distillation of the oil afforded 5.68 g. (94% yield) of product, b.p. 85–85.5° (0.24 mm.), $[\alpha]^{25}D$ −66.9°, $n^{25}D$ 1.5289.

Anal. Calcd. for $C_{14}H_{17}NO$: N, 6.52; Found: N, 6.4.

The *hydrochloride salt* of this base melted at 210–212° (uncorr.), $[\alpha]^{25}D$ −54.9° (5% in H_2O).

Anal. Calcd. for $C_{14}H_{18}ClNO$: Cl^-, 14.1. Found: Cl^-, 14.0.

***d*-α-Benzyl-*N*-ethylfurfurylamine.**—*d*-α-Benzyl-*N*-ethylfurfurylamine dibenzoyl-L-tartrate (13.3 g., 0.017 mole) was treated with an excess of 2 *N* sodium hydroxide solution in the manner described immediately above and the base distilled to give 6.48 g. (90%) of product, b.p. 78.5–80.5° (0.04 mm.), $[\alpha]^{25}D$ +68.1°, $n^{25}D$ 1.5290.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.1; H, 8.2; N, 6.4.

The *hydrochloride salt* of this base melted at 210–212° (uncorr.), $[\alpha]^{25}D$ +56.9° (5% in H_2O).

Anal. Calcd. for $C_{14}H_{18}ClNO$: Cl^-, 14.1. Found: Cl^-, 14.0.

Hydrogenation of *d*-α-benzyl-*N*-ethylfurfurylamine (22 g., 0.10 mole) was accomplished in 200 ml. of 95% ethanol in the presence of 1 teaspoonful of Raney nickel under 3.5 kg./cm.^{2} (gauge) of hydrogen at room temperature. The reaction mixture was filtered and the filtrate was treated with 8.5 ml. of concentrated hydrochloric acid and concentrated to a residue by warming *in vacuo*. The oily residue was dissolved in 30 ml. of ethyl acetate. This solution was scratched to initiate crystallization, cooled, diluted with an equal volume of ether and filtered to give 23.0 g. (88% yield) of a mixture of *d-erythro-* and *d-threo-α-benzyl-N-ethyltetrahydrofurfurylamine hydrochloride*, m.p. 101–108.5°, $[\alpha]^{25}D$ +18.2°.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.76; H, 8.67; Cl, 13.88. Found: C, 65.7; H, 8.5; Cl, 14.1.

Hydrogenation of *l*-α-benzyl-*N*-ethylfurfurylamine (5.45 g., 0.0253 mole) in the presence of 140 ml. of 95% ethanol, one-third teaspoonful of Raney nickel and hydrogen under 107 kg./cm.^{2} (gauge) for 3.25 hr. at 25° caused saturation of the furan ring. The resulting mixture of *l-threo-* and *l-erythro-*α-benzyl-*N*-ethyltetrahydrofurfurylamine boiled at 87.5–88° (0.1 mm.) (3.85 g.), $n^{25}D$ 1.5150, $[\alpha]^{25}D$ −25.7°.

Resolution of *dl*-α-Benzyl-*N*-methylfurfurylamine.—*dl*-α-Benzyl-*N*-methylfurfurylamine (45.4 g., 0.226 mole) was added with stirring to a solution of 40.5 g. (0.108) mole of dibenzoyl-D-tartaric acid monohydrate in 350 ml. of absolute ethanol. A pasty mixture resulted which was allowed to stand overnight and filtered. The collected solid was boiled with 3.5 l. of methanol and the insoluble portion collected (28.5 g.). Cooling the filtrate precipitated 11.8 g. of solid. Portionwise recrystallization of the 40.3 g. of solid at hand from 3.5 l. of methanol with final concentration of the liquors afforded 37.7 g. (92% of the theoretical amount) of *l*-α-benzyl-*N*-methylfurfurylamine dibenzoyl-D-tartrate. The seven crops of crystals which constituted this product showed $[\alpha]^{25}D$ from −94.3° to −96.0°. A 1-g. sample was recrystallized again from methanol to give an analytical sample, m.p. 214–215° dec., $[\alpha]^{25}D$ −94.9°.

Anal. Calcd. for $C_{44}H_{44}N_2O_{10}$: C, 69.45; H, 5.83; neut. eq., 380.4. Found:

C, 69.2; H, 5.5; neut. eq., 380.

The original reaction liquor and the filtrate from the first recrystallization step above were combined and concentrated to a residue. This residue was treated with 100 ml. of 2 *N* sodium hydroxide solution and the liberated base was extracted twice with ether; the extracts were washed with saturated salt solution, dried over potassium carbonate and concentrated to residue. Treatment of a solution of this oily residue (18 g.) in 100 ml. of absolute ethanol with 17 g. of dibenzoyl-L-tartaric acid in 100 ml. of absolute ethanol produced a precipitate which was collected, washed with 100 ml. of absolute ethanol and recrystallized portionwise from 3 l. of methanol with final concentration of the liquors to give 28.1 g. (69%) of *d*-α-benzyl-*N*-methylfurfurylamine dibenzoyl-L-tartarate, m.p. 210–212.5° dec., $[\alpha]^{25}D$ +93.6° to 94.8° for the various crops. The analytical sample, crop 1, melted at 212–212.5° dec., $[\alpha]^{25}D$ +94.8°.

Anal. Calcd. for $C_{44}H_{44}N_2O_{12}$: C, 69.45; H, 5.83; neut. eq., 380.6. Found: C, 69.2; H, 5.6; neut. eq., 379.

***l*-α-Benzyl-*N*-methylfurfurylamine.**—*l*-α-Benzyl-*N*-methylfurfurylamine dibenzoyl-D-tartrate (36.7 g., 0.048 mole) was treated with 100 ml. of 2 *N* sodium hydroxide solution and the liberated base was extracted with ether. The ether extract was washed with saturated salt solution, dried over potassium carbonate and concentrated to an oily residue. Distillation of the oil afforded 18.5 g. (96%) of *l*-α-benzyl-*N*-methylfurfurylamine, b.p. 99–101° (0.04 mm.) $n^{25}D$ 1.5390. The *hydrochloride salt* was prepared and recrystallized from acetonitrile to give massive prisms, m.p. 164–165.5°, $[\alpha]^{25}D$ −60.6° (a 5% solution in H_2O showed −58.0°).

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.4; H, 6.5; N, 6.0.

***d*-α-Benzyl-*N*-methylfurfurylamine.**—*d*-α-Benzyl-*N*-methylfurfurylamine dibenzoyl-L-tartrate (26.8 g., 0.035 mole) was treated with sodium hydroxide in the manner described immediately above and the free base distilled to give 12.0 g. (85%) of *d*-α-benzyl-*N*-methylfurfurylamine, b.p. 84–89° (0.02 mm.), $n^{25}D$ 1.5382. The *hydrochloride salt* was prepared and recrystallized from acetonitrile to give massive prisms, m.p. 163.5–165.5°, $[\alpha]^{25}D$ + 60.2° (a 5% solution in H_2O showed +57.4°).

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.9; H, 6.9; N, 6.0.