[Contribution from the Chemistry Laboratory of the State University of Iowa]

# THE STEREOISOMERS OF N,N′-BIS(α-PHENYLETHYL)-FUMARAMIDE

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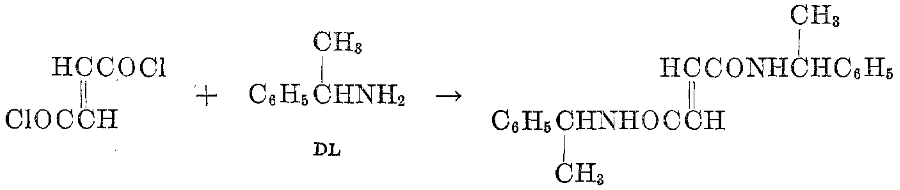
Stereoisomeric principles imply that three optical isomers of N,N′-bis(α-phenylethyl)fumaramide should exist in four forms. This research provided an experimental basis for the D-, L-, DL, and *meso*-modifications of this *trans*-olefinic compound.

The reaction between fumaryl chloride (I) and DL-α-phenylethylamine (II) produced a mixture of two of the substituted fumaramides (III): the DL- and *meso*-modifications. These isomers were separated by first extracting the more soluble isomer from the mixture with ethyl alcohol. Each fraction from this extraction was recrystallized repeatedly from methyl alcohol until the two pure isomers were obtained. One, the less-soluble isomer, melted at 302°; the other, the more-soluble isomer, melted at 281–282°.



$$\underset{\text{ClOCCH}}{\overset{\text{HCCOCl}}{\|}} + \underset{\text{DL}}{C_6H_5\overset{CH_3}{|}{C}HNH_2} \rightarrow \underset{C_6H_5\underset{CH_3}{C}HNHOCCH}{\overset{\text{HCCONH}\overset{CH_3}{C}HC_6H_5}{\|}}$$

I II III

The lower-melting diamide was shown to be the DL-mixture of N,N′-bis(α-phenylethyl)fumaramide. The optically active D- and L-substituted fumaramides were prepared from the respective D- and L-α-phenylethylamines and fumaryl chloride. A mixture of equal amounts of these two was shown to be identical with the isomer melting at 281–282°, and their melting point *vs.* composition curve was a typical one for a racemic mixture. The D- and L-N,N′-bis(α-phenylethyl)fumaramides both melted at 302° and were found to form gels with such organic solvents as methanol.

The isomer melting at 302° obtained from the separation was shown to be identical with the *meso*-N,N′-bis(α-phenylethyl)fumaramide synthesized by an independent method. Methyl N-[(D)α-phenylethyl]fumaramate (VI) was prepared by the reaction between equimolar amounts of methyl fumarate (IV) and D-α-phenylethylamine (V). The *meso*-diamide (VIII) was then isolated from the reaction between this ester-amide (VI) and L-α-phenylethylamine (VII).

The *meso*-N,N′-bis(α-phenylethyl)fumaramide is an interesting example of

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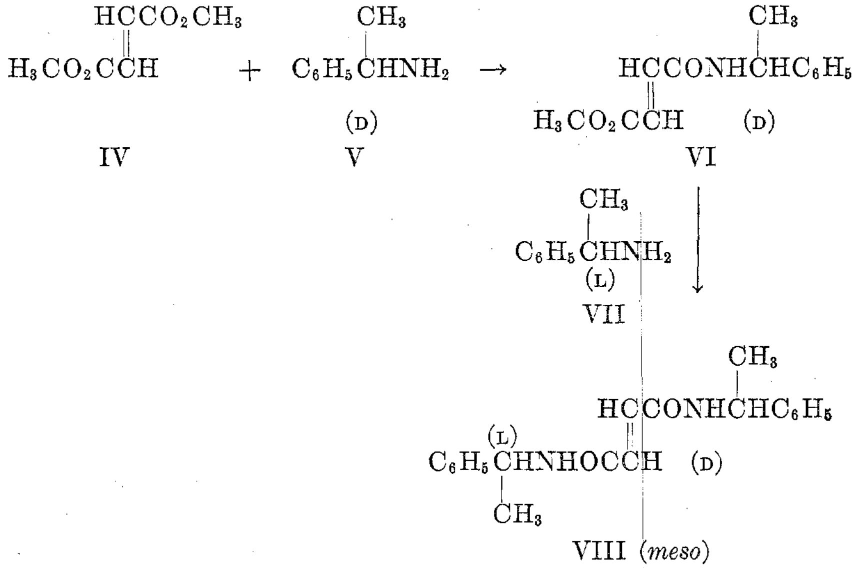
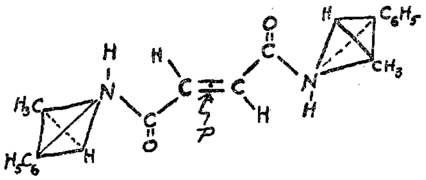
an optically inactive molecule. Inspection of a spatial model of structure VIII shows that it does not have a plane of symmetry, but that when the groups



$$\underset{\text{IV}}{\begin{array}{r} HCCO_2CH_3 \\ \| \\ H_3CO_2CCH \end{array}} + \underset{\text{V}}{\begin{array}{c} CH_3 \\ | \\ C_6H_5CHNH_2 \\ (D) \end{array}} \rightarrow \underset{\text{VI}}{\begin{array}{l} \qquad\qquad\quad CH_3 \\ \qquad\qquad\quad | \\ HCCONHCHC_6H_5 \\ \| \\ H_3CO_2CCH \quad (D) \end{array}}$$

$$\xrightarrow{\underset{\text{VII}}{\begin{array}{c} CH_3 \\ | \\ C_6H_5CHNH_2 \\ (L) \end{array}}} \underset{\text{VIII } (meso)}{\begin{array}{l} \qquad\qquad\qquad\qquad CH_3 \\ \qquad\qquad\qquad\qquad | \\ \qquad\quad\;\; HCCONHCHC_6H_5 \\ \quad (L) \qquad\quad \| \\ C_6H_5CHNHOCCH \quad (D) \\ \quad | \\ \quad CH_3 \end{array}}$$

attached to the asymmetric carbon atoms are properly oriented, there is a center of symmetry.



VIII

P = Center of symmetry; no rotation about $\begin{matrix}\diagdown & & \diagup \\ & C{=}C & \\ \diagup & & \diagdown\end{matrix}$ possible rotation about all other single bonds. The asymmetric carbon atoms are mirror images of each other in this *meso*-form. There are, however, many spacial arrangements which possess neither a plane nor a center of symmetry. The puzzling problem of *meso*-configurations and internal compensation have been recently commented on by Noller (1) and by Wright (2). A study was made of the rotatory powers of the optically active fumaramides with the express hope of finding a temperature at which a definite break in the rotation *vs* temperature curve would occur. Measurement of other physical properties of the *meso*-N,N′-bis(α-phenylethyl)fumaramide at such a temperature might provide experimental data which would suggest a satisfactory picture of *meso*-compounds and the explanation of their optical inactivity. However, no significant change in rotatory powers with change in temperature was found.

To aid in the physical chemical study of this *meso*-N,N′-bis($\alpha$-phenylethyl)-fumaramide by x-ray diffraction studies, a model compound with distinctive diffracting atoms was prepared. The analogous DL- and *meso*-modifications of N,N′-bis($\alpha$-*p*-bromophenylethyl)fumaramides were prepared and separated in a manner similar to that used to obtain the unbrominated isomers. The *meso*-isomer was the more insoluble of the two and decomposed at 332–334°, and the DL-modification decomposed at 304–305°.

## EXPERIMENTAL[3, 4]

*Reaction of fumaryl chloride (I) and* DL-*$\alpha$-phenylethylamine* (II). This reaction was investigated under four different laboratory conditions (3). The most suitable procedure found for the synthesis of these isomers was the reaction between fumaryl chloride and the various $\alpha$-phenylethylamines in an inert solvent with a two-mole excess of the amine present.

A solution of 33.8 ml. of DL-$\alpha$-phenylethylamine (4) in 100 ml. of dry toluene was cooled in an ice-bath and 10 g. of fumaryl chloride (5) was added dropwise with stirring. After an hour a heavy white precipitate formed. A 200-ml. portion of dry toluene was then added and the stirring continued for four hours longer. The heavy white slurry was poured into a separatory-funnel and shaken with 25 ml. of concentrated hydrochloric acid in 200 ml. of water. The entire contents of the separatory-funnel were poured onto a Büchner funnel. The filtrate was saved for the recovery of the excess amine. The amide was washed with 3 l. of water and dried in an oven at 80° for four hours. After drying the yield of amide was found to be greater than theoretical and chloride ion was still present in the solid. The crude amide was then washed in a beaker with 700 ml. of boiling distilled water and again filtered. The filter press cake was washed with boiling distilled water (about 9 l.) until the filtrate showed no trace of chloride ion. The white amorphous solid was then dried in an oven at 80°. The yield of the mixture of diamides was 18.2 g. (87%), melting at 250–274°.

When the reaction was carried out by a modified Schotten-Baumann procedure, a yield of only 37.3% of the diamides was obtained. Conducting the reaction in acetone with the addition of solid potassium carbonate gave a 42% yield. A black tarry mass was obtained when the reaction was attempted in a toluene solution of pyridine. The isolation of a black powdery product from the reaction of pyridine and fumaryl chloride definitely indicated that this procedure could not be used for the preparation of these substituted fumaramides.

*Separation of the* DL- *and meso-N,N′-bis($\alpha$-phenylethyl)fumaramide.* A survey of the solubility of the product obtained from the reaction of fumaryl chloride and DL-$\alpha$-phenylethylamine provided the basis of the scheme which was devised for the separation of the DL- and *meso*-fumaramides.

The crude mixture of diamide (8.5 g.) from the reaction of fumaryl chloride and DL-$\alpha$-phenylethylamine was stirred for 3 hours at 40° with two successive 600-ml. portions of absolute ethyl alcohol. From these extractions there remained 3.4 g. of diamide which was mostly the more insoluble form. This residue was fractionally crystallized first from 1200 ml. of absolute ethyl alcohol and then three succeeding times from 1000-ml. portions of methyl alcohol. The yield of this form was 2.6 g., m.p. 302°. This product was the *meso*-N,N′-bis($\alpha$-phenylethyl)fumaramide (VIII).

*Anal.* Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69.
Found: C, 74.56; H, 6.67; N, 8.68.

The two 600-ml. ethyl alcohol extracts were combined and placed in a refrigerator overnight. Any crystals which had separated from the solution were removed and returned to the original crude mixture of diamide. The filtrate was evaporated to dryness yielding a

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[3] All melting points reported in this paper are corrected except those taken on the Maquenne Block.

[4] Carbon, hydrogen, and nitrogen analyses by E. C. Steinle and J. Kozikowski.

white powdery product melting at 263–270°. This material was then fractionally crystallized six times from methyl alcohol. About 200 ml. of methyl alcohol per gram of diamide was used each time. Each crystallization required about two weeks' standing in the refrigerator. The product was a white amorphous precipitate rather than a crystalline one. The yield of this more-soluble isomer was 0.9 g. It melted at 281–282°. This product was the DL-N,N′-bis(α-phenylethyl)fumaramide.

*Anal.* Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69.
Found: C, 73.99; H, 6.60; N, 8.69.

D-*N,N′-Bis(α-phenylethyl)fumaramide.* A solution of 2.13 ml. of fumaryl chloride in 50 ml. of purified Skellysolve[5] C was added dropwise, with stirring, over a period of two hours to 8.0 ml. of D-α-phenylethylamine (6) in 100 ml. of Skellysolve C at room temperature. A fine white slurry was formed which was stirred and refluxed on a steam-bath for 30 minutes after all of the acid chloride had been added. After cooling, the crude diamide was collected and washed by stirring in a beaker with 250 ml. of 5% hydrochloric acid. The diamide was again collected and the hydrochloric acid solution was saved for the recovery of the excess amine. The diamide was then successively washed by stirring in a beaker with 1-l. portions of hot distilled water and filtered until the filtrate was free from chloride ion. Five washings were necessary. The yield of the crude diamide was 5.0 g. (100%) and the product melted at 299–300°.

The purification of this isomer proved to be difficult. When 0.1 g. of the crude D-diamide was dissolved in 50 ml. of boiling methyl alcohol and allowed to cool overnight in a refrigerator it would form a gel which was stable enough to cling to the bottom of a 125-ml. Erlenmeyer flask when inverted. The D-diamide was also found to form a gel with the following solvents:

Ethyl alcohol
Isopropyl alcohol
Isobutyl alcohol
Cyclohexyl alcohol
Acetic acid
Dioxane
Acetonitrile
Cyclohexanone
Acetone
*p*-Chlorotoluene
*o*-Cholorotoluene
Chlorobenzene
Chloroform

With nitromethane, both the optically active isomers and the diamide formed from the DL-amine formed a gel.

The D-diamide was found to be soluble in phenol and pyridine, but all attempts to crystallize the material from these solvents failed. After the numerous attempts to crystallize this optically active diamide from a simple solvent had failed, the precipitation of the material from a methyl alcohol solution with water was investigated. The crude product (3 g.) was dissolved in 800 ml. of hot methyl alcohol and the solution filtered. This hot methyl alcohol solution of the diamide was then poured into 2 l. of hot distilled water which was stirred vigorously. The purified diamide was then collected and washed with 2 l. of hot distilled water. This purification procedure was repeated four times in order to obtain a product with the constant m.p. 302°.

*Anal.* Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69.
Found: C, 73.90; H, 6.62; N, 8.60.

*Rotation:* 0.0973 g. made up to 50 ml. with *n*-Butyl Cellosolve gave $[\alpha]^{30}_{D}$ +175°.

*Molecular weight:* $\Delta T$ for 0.1190 g. of acetanilide in 10.4317 g. of phenol: 0.603°. $\Delta T$ for 0.1901 g. of D-N,N′-bis (α-phenylethyl)fumaramide in 10.4317 g. of phenol: 0.405°. $K_f$ from acetanilide: 7.15; Calc'd molecular weight of D-diamide: 321.7. Literature value of $K_f$ for phenol: 7.27 (7); Calc'd molecular weight of D-diamide: 326.6. Theoretical for $C_{20}H_{22}N_2O_2$: 322.4.

L-*N,N′-Bis(α-phenylethyl)fumaramide.* This isomer was prepared by the method described for the D-diamide except that 100 ml. of dry benzene was used for the reaction solvent of L-α-phenylethylamine (6) and fumaryl chloride. This isomer also melted at 302°.

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[5] One liter of Skellysolve C was shaken three times with 100-ml. portions of concentrated sulfuric acid in a separatory funnel and once with 200 ml. of distilled water. It was then dried over calcium chloride and redistilled; the fraction boiling from 85° to 95° was collected.

*Anal.* Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69.
Found: C, 74.75; H, 6.77; N, 8.97.

*Rotation:* 0.1058 g. made up to 50 ml. with *n*-Butyl Cellosolve gave $[\alpha]_D^{30}$ −189°.

*Characterization of* DL-*N,N'-bis(α-phenylethyl)fumaramide.* A 0.100-g. sample of D-N,N'-bis(α-phenylethyl)fumaramide along with a 0.100-g. sample of the L-isomer was dissolved in 60 ml. of warm methyl alcohol. The solution was filtered and placed in a refrigerator for two weeks. The white amorphous precipitate was isolated on a sintered glass crucible. This "synthetic" DL-modification was dried overnight in an oven at 80°; m.p. 282–283°. The melting point of a mixture of this sample with a sample of the lower-melting, more-soluble isomer, m.p. 281–282°, obtained from the separation of the DL- and *meso*-isomers was 281–282°, indicating that both were the DL-modification. The melting point of a mixture of this sample and the *meso*-isomer, m.p. 302°, obtained from the separation was 259–265°.

The melting points of varying compositions of the D- and L-diamides were then observed. The plot of the data obtained is given in Figure 1.

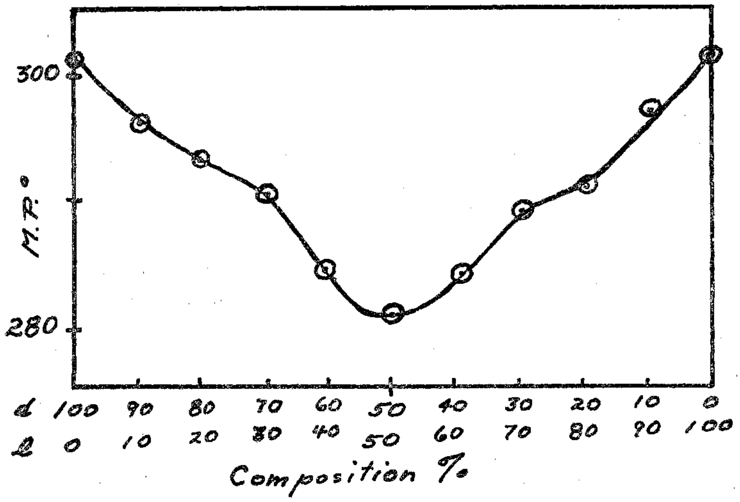

FIG. 1. MELTING POINT—COMPOSITION DIAGRAM, D- AND L-N,N'-BIS(α-PHENYLETHYL)-FUMARAMIDES

*Methyl N-*[(D)*α-phenylethyl*]*fumaramate* (VI). A modification of the procedure of Dermer and King (8) was followed. A mixture of 6.18 g. of dimethyl fumarate (IV) (9), 5.53 ml. of D-α-phenylethylamine (V), 0.3 g. of ammonium chloride, and one small drop of concentrated hydrochloric acid was refluxed for 30 hours. After heating, the reaction mixture was transferred into 100 ml. of 5% hydrochloric acid. The solid product was isolated and washed with 2 l. of distilled water. It was then stirred with 250 ml. of ether for two hours and the mixture was filtered. A small amount of ether-insoluble D-diamide was isolated. The ethereal filtrate was immersed in a Dry Ice-isopropyl alcohol cooling bath, and almost at once a white crystalline precipitate was formed. By carefully stirring and cooling the ethereal solution, 1.2 g. of dimethyl fumarate was recovered and removed. The filtrate was cooled and stirred for four hours in the Dry Ice-bath, but no precipitate was formed. The ether was then evaporated leaving 1.9 g. of a white powdery product, m.p. 264–271°. The white powdery product was then recrystallized four times from 15-ml. portions of methyl alcohol to yield 1.1 g. (11%) of the amide-ester *melting* at 273–274°. Further recrystallizations did not raise the melting point.

*Anal.* Calc'd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01.
Found: C, 66.51; H, 6.49; N, 6.33.

*Rotation:* 0.0362 g. made up to 25 ml. with *n*-Butyl Cellosolve; $[\alpha]_D^{24}$ +76°.

*meso-N,N′-Bis(α-phenylethyl)fumaramide* (VIII). Methyl N-[(D)α-phenylethyl]fumaramate (VI) (1 g.) and 0.55 ml. of L-α-phenylethylamine (VII) with one small drop of concentrated hydrochloric acid was refluxed on a steam-bath for 34 hours. The sticky brown product which was formed was washed with 50 ml. of 2% hydrochloric acid and three 50-ml. portions of distilled water. The sticky mass was then extracted four times with 25-ml. portions of boiling ether. A nice white solid product was left after the ether extractions. Two recrystallizations of this residue from 400-ml. portions of methyl alcohol gave 0.8 g. (58%) of the diamide, m.p. 302°. The melting point of a mixture of this product and the higher-melting isomer isolated from the product of the reaction between fumaryl chloride and DL-α-phenylethylamine was also 302°. The over-all yield of *meso*-diamide based upon dimethyl fumarate was 6.4%. The observed rotation of 0.1427 g. of this sample of the *meso*-form made up to 50 ml. with *n*-Butyl Cellosolve was zero.

*Rotary powers of the* D- *and* L-*N,N′-bis(α-phenylethyl)fumaramides at temperatures from 1° to 92°.* A 0.1058-g. sample of the L-diamide was made up to 50 ml. with *n*-Butyl Cellosolve; a 0.0973-g. sample of the D-diamide was made up to 50 ml. with *n*-Butyl Cellosolve. One-decimeter jacketed polarimeter tubes were used. The solutions in the polarimeter tubes were maintained at constant temperature. The observed rotations, taken at 10°-intervals, were +0.32° ± 0.05 for the *d*-diamide and −0.37° ± 0.06 for the L-diamide with no definite trend for either an increase or decrease in rotation.

*Preparation of* DL- *and meso-N,N′-bis(α-p-bromophenylethyl)fumaramide.* A solution of 7.04 ml. of DL-α-*p*-bromophenylethylamine (10) in 50 ml. of purified Skellysolve C was added dropwise, with stirring, over a period of one hour to 1.49 ml. of fumaryl chloride in 100 ml. of purified Skellysolve C. Then an additional 50 ml. of solvent was added to rinse the dropping-funnel used to add the amine. The heavy white slurry was stirred continuously and heated on a steam-bath intermittently for two hours. The slurry was cooled and the solid product collected. The white amorphous product was first washed by stirring in a beaker with 250 ml. of 5% hydrochloric acid. The diamide was again collected and the acid wash solution was saved for the recovery of the excess amine. The product was successively washed by stirring with four 800-ml. portions of hot distilled water. The yield of the crude N,N′-bis(α-*p*-bromophenylethyl)fumaramide was 5.5 g. (80.5%) and it melted at 275–290°.

The crude product (4 g.) from the reaction of fumaryl chloride and DL-α-*p*-bromophenylethylamine was stirred with 300 ml. of methyl alcohol for eight hours while heating on a steam-bath. This extraction process was repeated with a second 300-ml. portion of methyl alcohol, and finally with a 500-ml. portion of methyl alcohol. After these three extractions, there remained 1.4 g. of the more-insoluble isomer. This portion of the bromo diamide was then recrystallized three times from 3-l. portions of absolute ethanol. The final yield of the *meso*-isomer was 1.0 g. and its decomposition point was 332–334°.

*Anal.* Calc'd for $C_{20}H_{20}Br_2N_2O_2$: C, 50.02; H, 4.19; N, 5.83; Br, 33.28.
Found: C, 49.81; H, 4.24; N, 5.82; Br, 33.37.

The combined methyl alcohol extracts of the crude bromodiamide were placed in a refrigerator overnight. The precipitate which had formed was removed and the filtrate was evaporated to dryness. The dried residue weighed 1.1 g. This isomer was then recrystallized three times from 1-l. portions of methyl alcohol. This material behaved like the unbrominated DL-mixture in that each crystallization required about two weeks' standing in the refrigerator. The final yield of the DL-N,N′-bis(α-*p*-bromophenylethyl) fumaramide was 0.98 g. and its decomposition point was 304–305°.

*Anal.* Calc'd for $C_{20}H_{20}Br_2N_2O_2$: C, 50.02; H, 4.19; N, 5.83; Br, 33.28.
Found: C, 49.89; H, 4.14; N, 6.04; Br, 32.77.

## SUMMARY

The reaction of an excess of DL-α-phenylethylamine with fumaryl chloride has been found to produce the DL- and *meso*-modifications of N,N′-*bis*(α-phenylethyl)fumaramide.

The constitution of the DL-modification was shown by the fact that it was identical with a sample obtained by mixing equal amounts of the D- and L-isomers, each of which was independently synthesized.

The *meso*-modification was also synthesized by treatment of methyl N-[(D)α-phenylethyl]fumaramate with L-α-phenylethylamine.

The analogous DL- and *meso*-modifications of N,N′-*bis*(α-*p*-bromophenylethyl)fumaramide were also prepared.

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