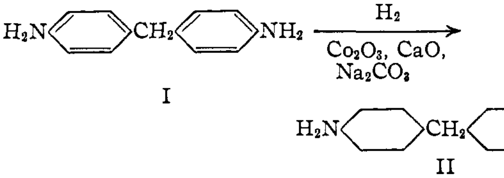
[CONTRIBUTION NO. 277 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

# Alicyclic Diamines: The Geometric Isomers of Bis-(4-aminocyclohexyl)-methane

BY A. E. BARKDOLL, H. W. GRAY AND W. KIRK, JR.

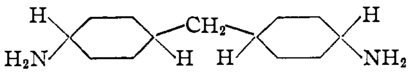
Catalytic hydrogenation of bis-(4-aminophenyl)-methane (I) gives bis-(4-aminocyclohexyl)-methane (II).[1,2] This dialicyclic diamine should exist in



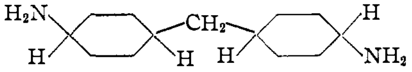
I

II

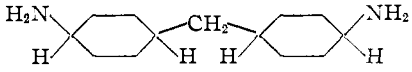
three geometrically isomeric forms, namely, *trans–trans* (III), *cis–trans* (IV) and *cis–cis* (V).



III, *trans–trans*



IV, *cis–trans*



V, *cis–cis*

In this communication the isolation and identification of the three possible geometric isomers are described. The properties of the isomers and their derivatives are summarized in Table I. The general scheme followed in the isolation procedure is shown in Tables III and IV. Configurations have been assigned to the three isomers by comparison of their melting points with those of analogous systems (Table II) and by consideration of the probable effects of the catalyst and hydrogenation conditions on isomer composition.

TABLE I

PROPERTIES OF GEOMETRIC ISOMERS OF BIS-(4-AMINOCYCLOHEXYL)-METHANE

| Isomer | | *cis–cis* | *cis–trans* | *trans–trans* |
|---|---|---|---|---|
| B. p. | °C. | 141 | 127–128 | 130–131 |
| | Mm. | 2 | 1.2 | 0.8 |
| M. p., °C., cor. | | 60.5–61.9 | 35.7–36.9 | 64–65.4 |
| F. p., °C., cor. | | ....... | ....... | 65.39 |
| $n^{25}D$ | | ....... | 1.5046 | ....... |
| $d^{25}_4$ | | ....... | 0.9608 | ....... |

The alicyclic diamine (II) was prepared by hydrogenation of I at 210–220° and 2000–3200 lb./sq. in. in the presence of a catalyst[1,2] comprised of cobaltic oxide ($Co_2O_3$), freshly ignited CaO and anhydrous $Na_2CO_3$, the yields being as high as 71% for autoclave runs and somewhat higher (*ca.* 86%) for hydrogenations conducted on a smaller scale. On isolation by distillation, II was obtained as a colorless sirupy liquid which spontaneously solidified at room temperature to a soft, white, crystalline paste.

TABLE II

ASSIGNED GEOMETRIC CONFIGURATIONS AND MELTING POINTS OF SOME COMPOUNDS ANALOGOUS TO BIS-(4-AMINOCYCLOHEXYL)-METHANE

| Compound | Geometric isomer, m. p., °C. *trans–trans* | *trans–cis* | *cis–trans* | *cis–cis* |
|---|---|---|---|---|
| 5-(3′,4′-Methylenedioxyphenyl-2,4-pentadienoic acid | 216<br>Piperic | 148–149<br>Isopiperic | 138–139<br>Isochavicic | 200–202<br>Chavicic |
| Cinnamalacetic acid | 165–166 | 138 | 128 | .... |
| α-Bromomuconic acid, dimethyl ester | 89 | ..... | 55 | 68 |
| α-Bromomuconic acid, diamide | 235 | ..... | 156 | 197 |
| 1,4-Diphenyl-1,3-butadiene | 149-150 | oil | | 70–70.5 |
| Benzildioxime | 238<br>*anti* | 163<br>*amphi* | | 207<br>*syn* |
| Bis-(4-Aminocyclohexyl)-methane | 64–65.4 | 35.7–36.9 | | 60.5–61.9 |

Differences in solubilities were utilized to advantage in effecting separation, the solubilities of the isomers and their derivatives being in the order *cis–trans* > *cis–cis* > *trans–trans*. Thus, the fractionation scheme shown in Table III led first of all to separation of the *trans–trans* isomer from its mixture with the remaining two isomers. Also, the preponderance of this isomer over the other two isomers facilitated its isolation. While the *trans–trans* isomer can be readily obtained by fractional crystallization and centrifugation of the anhydrous diamine, the separation is by no means quantitative so that other means must be employed to remove the residual *trans–trans* isomer before proceeding to the isolation of the remaining isomers. Precipitation as the diformyl derivative was employed for removal of the residual *trans–trans* isomer. Pure *trans–trans* II, melting at 64–65.4°,[3] was readily obtained from the diformyl derivative upon recrystallization and hydrolysis.

The formylated mixture of the *cis–cis* and *cis–trans* isomers remaining after removal of the *trans–trans* isomer was concentrated to a sirup which resisted all attempts at crystallization. Therefore, the mixture was hydrolyzed to the diamine (Table IV), which was then acetylated and the crystalline mixture of diacetyldiamines fractionally recrystallized to yield the pure *cis–cis* and *cis–trans* isomers in the form of their diacetyl derivatives. The pure isomers obtained upon hydrolysis melted at 60.5–61.9° and 35.7–36.9°, respectively.[3] The diacetyl derivatives were quite resistant to hydrolysis in comparison with the diformyl derivatives.

## Discussion

The stereochemical equivalence of double bonds

---

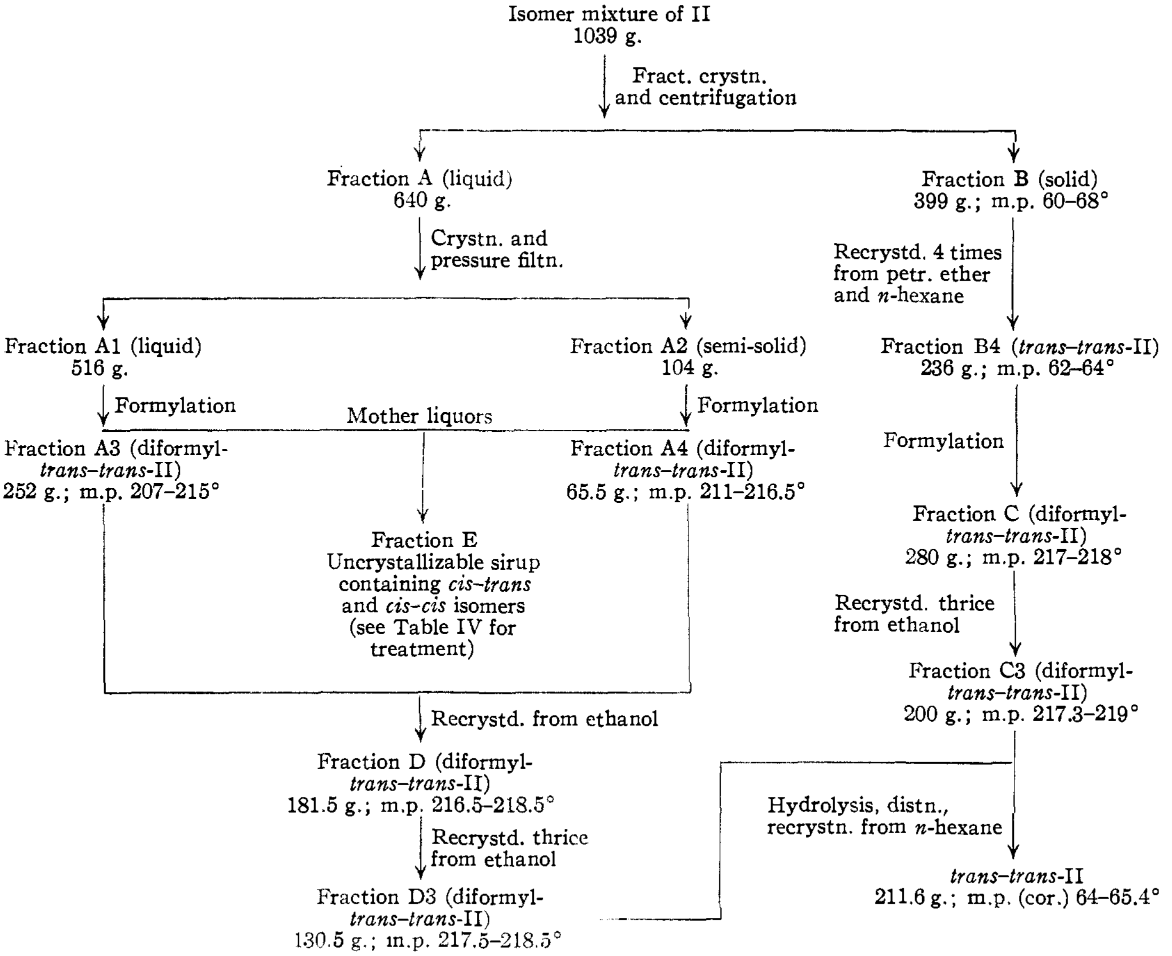
[1] O.P.B. Report, PB-742 (1941), "4,4′-Diaminodicyclohexylmethane."

[2] B.I.O.S. Final Report No. 1472, Item No. 22, "Some Aspects of Textile Research in Germany," p. 6.

[3] Ref. 2, which became available after completion of our work, states that the German workers obtained two of the three isomers of II, melting at 60–63° and 31–33°, respectively.

Table III

Scheme for Isolation of the *trans–trans* Isomer(III) of Bis-(4-aminocyclohexyl)-methane(II)



and rings[4] permits the assignment of the geometric configuration of these isomers with some degree of certainty, *i.e.*, by comparison with systems characterized by the presence of two suitably substituted double bonds. Thus, in the general case represented by VIa, the four geometrically

$R_1HC{=}CH{-}CH{=}CHR_2$ VIa, $R_1$ and $R_2$ unlike
VI VIb, $R_1$ and $R_2$ alike

isomeric forms (*trans–trans*, *trans–cis*, *cis–trans* and *cis–cis*) may exist since there are two sites of restricted rotation due to the presence of double bonds (or rings). This general case is exemplified by 5-(3′,4′-methylenedioxyphenyl)-2,4-pentadienoic acid (piperic acid and its three geometric isomers),[5] of which all four isomers are known, cinnamalacetic acid,[6] of which three isomers are known, and diethyl α-bromomuconate,[7] for which three of the four possible isomers are known.

In the particular case illustrated by VIb, where $R_1$ and $R_2$ are alike, three geometric isomers (*trans–trans*, *cis–trans* and *cis–cis*) may theoretically exist. This situation obtains for the molecule II as well as for 1,4-diphenyl-1,3-butadiene,[8] diethyl α,α′-dibromomuconate[9] and benzildioxime,[10] all of which have been isolated in the three possible isomeric forms.

On comparison of the melting points and assigned structures of the foregoing compounds (see Table II), it is apparent that a definite trend between melting point and assigned configuration exists in those cases where all the possible isomers are known, *viz.*, that for any given compound, the *trans–trans* isomer has the highest melting point, followed by the *cis–cis* isomer, with the *cis–trans* (and *trans–cis* isomer) having the lowest melting point(s). The configurations assigned to II are in accord with this generalization.

It should be noted that in no case has the stereochemical configuration of compounds such as VIa and VIb been established by an absolute method, although in a number of cases good evidence exists in support of the assigned structures. In the case of molecules of the type VIb, alteration of one R group (or both R groups by different reagents) should result in two new compounds in the case of

---

(4) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, Vol. I, p. 367.

(5) Lohaus and Gall, *Ann.*, **517**, 278 (1935); Lohaus, *J. prakt. Chem.*, [2] **119**, 235 (1928); Ott and Eichler, *Ber.*, **55**, 2653 (1922).

(6) Perkin, *J. Chem. Soc.*, **31**, 403 (1877); Liebermann, *Ber.*, **28**, 1438 (1895); Lohaus, *Ann.*, **513**, 228 (1934).

(7) Farmer and Duffin, *J. Chem. Soc.*, 402) 1927).

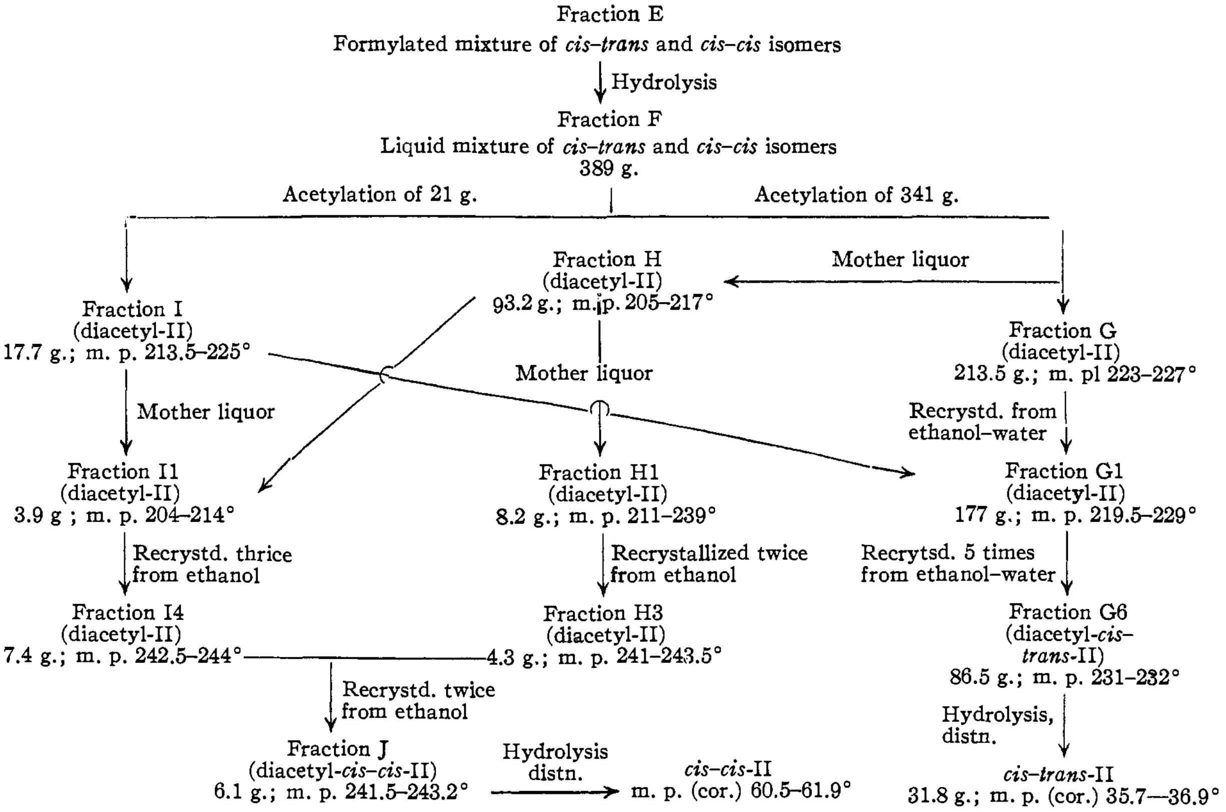
(8) Straus, *Ann.*, **342**, 190 (1905).

(9) Farmer, *J. Chem. Soc.*, **123**, 2531 (1923).

(10) Meisenheimer and Lamporter, *Ber.*, **57**, 276 (1924).

TABLE IV[a]

SCHEME FOR ISOLATION OF *cis–trans* (IV) AND *cis–cis* (V) ISOMERS OF BIS-(4-AMINOCYCLOHEXYL)-METHANE (II)



[a] Table IV is a continuation of Table III.

the *cis–trans* isomer, thus enabling the identity of this isomer to be established with absolute certainty. This technique has been employed by Kipping[11] in establishing the configuration of one of the geometric isomers of 2,3,5,6-tetramethylpiperazine.

Finally, the relative abundance of the three isomers of II in the mixture obtained by hydrogenation of I with the alkali-promoted cobalt catalyst affords some substantiation of the assigned structures. According to the work of von Auwers[12] and Skita,[13] hydrogenations over platinum lead to *cis* configurations in acid media, while *trans* configurations are favored in neutral or alkaline media. Also, the use of base metal catalysts such as nickel at relatively high temperatures favors the formation of *trans* configurations. This suggests that the *trans–trans* isomer (III) would predominate in the product obtained by hydrogenating I under the conditions of high temperature and high basicity employed, followed by the *cis–trans* isomer (IV), with the *cis–cis* isomer (V) present in least amount. The assigned configurations are in accord with this expectation, the isomer melting at 64–65.4° (*trans–trans*) being predominant, followed by the isomer melting at 35.7–36.9° (*cis–trans*), and the isomer melting at 60.5–61.9° (*cis–cis*) in that order.

## Experimental[14]

### Preparation of Bis-(4-aminocyclohexyl)-methane Isomer Mixture

**Bis-(4-aminophenyl)-methane** (I).—The aromatic diamine (I), purchased from Dow Chemical Company, was recrystallized from 95% ethanol before use.

**Alkali-Promoted Cobalt Catalyst.**—The catalyst, described by Runne,[1] consisted of a mixture of cobaltic oxide, calcium oxide and anhydrous sodium carbonate. Commercial "C.P." grades of cobaltic oxide and anhydrous sodium carbonate were found to be satisfactory, while finely powdered calcium oxide was freshly prepared before use by calcination of a good grade of calcium hydroxide or calcium carbonate.

**Bis-(4-aminocyclohexyl)-methane** (II).—The procedure outlined by Runne[1] was employed for hydrogenation of the aromatic diamine (I) to the mixture of geometric isomers of (II) utilized for the separation of isomers. The following preparation is typical. Molten I (3500 g., 17.65 moles, f.p. (cor.) 92.46°) was charged into a one-gallon autoclave fitted with stirrer and cooling coils, followed by the addition of 350 g. of cobaltic oxide, 525 g. of freshly ignited calcium oxide and 227.5 g. of anhydrous sodium carbonate, the catalyst ingredients being finely powdered. The autoclave was pressured with hydrogen and purged several times to remove oxygen, after which the hydrogenation was carried out with stirring at 210–220° and 2,000–3,200 lb./sq. in. for a period of 5.5 hours. Hydrogen absorption began at 175° but was slow until the temperature reached 210°. The hydrogen absorption was 100 moles as compared with a theoretical value of 106 moles.

---

(11) Kipping, *J. Chem. Soc.*, 1160 (1931).

(12) v. Auwers, *Ann.*, **420**, 84 (1920).

(13) Skita, *Ber.*, **53**, 1792 (1920); Skita and Schneck, *ibid.*, **55**, 144 (1922); Skita, *ibid.*, **56**, 1014 (1923); Skita, Häuber and Schönfelder, *Ann.*, **431** 1 (1923).

(14) All melting points are uncorrected unless otherwise noted. We are indebted to Mr. W. M. D. Bryant of the Polychemicals Department for determination of the corrected melting points on samples which had been sealed in glass under nitrogen. The diamine samples and the thermometer, calibrated by the Bureau of Standards, were totally immersed in a large stirred oil-bath and heated at a rate not exceeding 0.2° per minute. The melting phenomena were observed microscopically with polarized light.

The sirupy product was discharged from the autoclave while still warm and the autoclave rinsed with methanol. Super-Cel (50 g.) was added to the combined reaction product and washings and the catalyst filtered off by suction through a large Büchner funnel which had been precoated with 15 g. of Darco G-60 and 20 g. of Super-Cel. The filtration, which was very slow, was interrupted after one-half of the solution was filtered, the remaining solution diluted with one l. of methanol and filtration continued at an improved rate through a fresh filter bed. The last traces of catalyst were removed by refiltration through 20 g. of Darco G-60. Diamine occluded by the filter cake was recovered by extraction of the combined filter cakes with two l. of boiling methanol followed by filtration. The recovered catalyst was observed to be pyrophoric, readily igniting when dry.

The combined diamine solutions were concentrated *in vacuo* to remove methanol and the dark-colored liquid residue was then distilled through a two-ft. column packed with glass helices. A liquid foreshot of 55 g. boiling at 94.3–124° (0.6–0.7 mm.) was obtained, followed by 2875 g. (77.4% yield) of II in the form of a colorless sirup which spontaneously set at room temperature to a semisolid crystalline mass; b.p. 126.9° (1.0 mm.) to 124.3° (0.5 mm.); $n^{27.5}D$ 1.5012; neut. equiv. 105.7 (theory 105.2). In addition, there was obtained 483 g. of a colorless solid boiling at 124.3° (0.5 mm.) to 157° (0.7 mm.) which consisted principally of 4-(*p*-aminobenzyl)-cyclohexylamine and 197 g. of non-volatile residue. The alicyclic diamine contained some aromatic amine as impurity, as indicated by an ultraviolet absorption maximum at 2900 Å. and the formation of a red color on diazotization followed by coupling with "H-acid." The diamine possessed a characteristic fatty amine-like odor, rapidly absorbed carbon dioxide and water from the atmosphere and when dropped on the surface of water instantly formed a solid hydrate which markedly lowered the surface tension of water as evidenced by its camphor-like movement on the surface.

Before separation of the geometric isomers, the alicyclic diamine was redistilled *in vacuo* through a packed column to remove small quantities of low-boiling impurities and aromatic amines.

### Separation of Geometric Isomers

The general procedure followed in the isolation of the three isomers of II is outlined in Tables III and IV. The procedures employed are given in detail in the following sections.

A. *trans–trans* II.—A solid isomer mixture of II (1039 g.) prepared as described above was separated into liquid and solid fractions as follows:

The sample was melted and poured into 6-oz. wide-mouth bottles so that the bottles were approximately half full, the bottles capped and allowed to stand undisturbed at room temperature (*ca.* 27–29°) so that only a portion of the diamine crystallized, forming a lattice of large needles with the interstices filled with liquid diamine. The liquid and solid fractions were then separated by centrifuging the bottles in inverted position in a bucket centrifuge at a low speed, the liquid fractions being forced from the solid fractions which adhered to the bottom of the bottles. From this material the following fractions were obtained: Fraction A (liquid), 639.7 g.; Fraction B (solid), 399.5 g.; capillary m.p. 60–68° (melt not clear at 72.5°, indicating presence of carbonate or hydrate or both).

Fraction B (387 g.) was dissolved in 2125 ml. of petroleum ether (b.p. 30–75°) at the boiling point under an atmosphere of dry nitrogen, the cloudy diamine solution filtered hot by gravity into a nitrogen-filled flask, the filter funnel being covered with a larger inverted funnel through which nitrogen was passed, to prevent absorption of water and carbon dioxide by the amine during filtration. The clear, colorless diamine solution was concentrated under nitrogen on the steam-bath to a volume of 850 ml., allowed to crystallize at room temperature and finally in ice, the crystal cake broken up and rapidly filtered while being partially protected by a blanket of nitrogen and the diamine dried *in vacuo* at 50°. This general procedure was utilized for the further recrystallizations of the diamine, which are summarized in the following table, except that filtration of the recrystallized diamine was carried out in a nitrogen-filled dry-box.

RECRYSTALLIZATION OF *trans–trans* II

| Re-crystn. | Solvent | Wt. of prod., g. | Recovery, % | Cap. m.p., °C. |
|---|---|---|---|---|
| 1 | Pet. ether (b.p. 30–75°) | 320 | 82.7 | 60–62.5° cloudy |
| 2 | *n*-Hexane | 284 | 88.8 | 65–66.2° clear |
| 3 | *n*-Hexane | 264 | 93 | 64.4–65.7° clear |
| 4 | *n*-Hexane | 236 (Fraction B4) | 89.7 | 61–65.5° clear |

The diamine absorbs water and carbon dioxide with avidity and it is essential to work in an inert atmosphere, otherwise contamination of product, which is apparent by the formation of a cloudy melt and high melting impurities, ensues. Therefore, all manipulations on the recrystallized diamine, including filling of capillary melting point tubes, were carried out in a nitrogen-filled dry-box. Also, purified petroleum ether or *n*-hexane (95 mole % purity, Phillips) is essential to avoid a colored product. The use of commercial grade *n*-hexane resulted in a yellow product.

The rather wide melting ranges of the recrystallized samples of the *trans–trans*-isomer, suggesting that an impurity was being carried along through the recrystallizations, led to further purification of the isomer by means of the nicely crystalline, stable diformyl derivative.

**Diformyl Derivative.**—To a solution of 231 g. (1.1 moles) of II (recrystallized four times, m.p. 61–65.5°) in 250 ml. of 95% ethanol was added 334 g. (5.6 moles) of redistilled methyl formate with stirring over a period of 1.5 hours. After addition of methyl formate had progressed for one-half hour, the diformyl derivative began to precipitate from the warm solution as a white, microcrystalline solid. The resulting thick slurry was diluted with 200 ml. of 95% ethanol, heated under reflux for 3 hours, stored at 6° overnight, cooled in ice and the diformyl derivative filtered off by suction, washed with 100 ml. of 95% ethanol and dried *in vacuo;* Fraction C, 280 g. (95.6% yield), m.p. 217–218° (sintering at 215°). Three recrystallizations from boiling ethanol yielded 200 g. of pure diformyl *trans–trans* II (Fraction C3) in the form of colorless, slender prisms, m.p. 217.3–219°. The analytical sample was recrystallized once more from boiling 95% ethanol and dried *in vacuo* at 65° for 1 hour. Analytical data on diformyl *trans–trans* II and other derivatives are reported in Table V.

**Hydrolysis of Diformyl Derivative.**—To 320.9 g. (1.2 moles) of pure diformyl *trans–trans* II was added a mixture of 290 ml. (3.48 moles) of concentrated hydrochloric acid and 350 ml. of distilled water and the mixture heated under reflux for 3 hours, the amide dissolving as the boiling point was reached. On standing overnight the reaction mixture deposited massive, colorless prisms of the dihydrochloride which were redissolved by warming after the addition of 500 ml. of water. The solution was cooled and the free base liberated by the addition of a solution of 240 g. (6 moles) of sodium hydroxide in 500 ml. of water. The partly amorphous, partly microcrystalline precipitate which formed was extracted with 850 ml. of *n*-butyl alcohol in four portions, and the alcohol extract concentrated *in vacuo* to remove alcohol and water. The residue, which contained solid material even when hot, appeared to be only partly hydrolyzed and it was therefore rehydrolyzed by refluxing with a mixture of 500 ml. of concentrated hydrochloric acid and 300 ml. of water for 5 hours. The cooled solution was diluted with 800 ml. of water, warmed to dissolve the precipitated diamine dihydrochloride and the free base liberated as a white, amorphous hydrate by the addition of a solution of 288 g. (7.2 moles) of sodium hydroxide in 600 ml. of water. The diamine hydrate was extracted with 850 ml. of *n*-butyl alcohol in four portions, the alcohol extract washed with 100 ml. of water, and the solvent removed by distillation *in vacuo*. The diamine residue was dissolved in 600 ml. of anhydrous ether while warm, the ether solution filtered to remove a small quantity of inorganic salts, the filtrate concentrated and the residue distilled *in vacuo* under an atmosphere of nitrogen through a two-ft. packed column to obtain 224.1 g. (88.8% yield) of a white, crystalline solid boiling at 130–131° (0.8 mm.). The anhydrous diamine was dissolved in 560 ml. of *n*-hexane by heating, the hot solution filtered by gravity, the filtrate con-

TABLE V

DERIVATIVES OF THE GEOMETRIC ISOMERS OF BIS-(4-AMINOCYCLOHEXYL)-METHANE

| Derivative | Recrystn. solvent | M. p., °C. | Carbon, % Calcd. | Carbon, % Found av. | Hydrogen, % Calcd. | Hydrogen, % Found av. | Nitrogen, % Calcd. | Nitrogen, % Found av. |
|---|---|---|---|---|---|---|---|---|
| | | | *trans–trans*-Isomer | | | | | |
| Picrate | Ethanol | 263 dec. | | | | | 16.91 | 16.85 |
| Diformyl | Ethanol | 217–219 | 67.62 | 67.70 | 9.83 | 9.83 | 10.51 | 10.37 |
| Diacetyl | Ethanol | 271–273 | 69.34 | 69.78 | 10.27 | 10.33 | 9.51 | 9.94 |
| Dibenzoyl | Ethanol | 288–289 | 77.47 | 77.35 | 8.19 | 8.48 | 6.69 | 7.33 |
| | | | *cis–trans*-Isomer | | | | | |
| Picrate | Ethanol | 226 dec. | | | | | 16.91 | 17.23 |
| Diformyl | EtOH–$H_2O$ | 132.5–133.4 | 67.62 | 67.46 | 9.83 | 9.80 | 10.51 | 10.71 |
| Diacetyl | EtOH–$H_2O$ | 231–232 | 69.34 | 69.30 | 10.27 | 10.19 | 9.51 | 9.28 |
| Dibenzoyl | Ethanol | 240–242 | | | | | 6.69 | 6.59 |
| | | | *cis–cis*-Isomer | | | | | |
| Picrate | Ethanol | 218.5–219.5 | | | | | 16.91 | 17.67 |
| Diacetyl | Ethanol | 241.5–243 | 69.34 | 69.58 | 10.27 | 10.37 | 9.51 | 9.52 |
| Dibenzoyl | Ethanol | 259–260 | 77.47 | 77.13 | 8.19 | 8.02 | 6.69 | 6.57 |

centrated on a steam-bath to a volume of 390 ml. and the diamine obtained by crystallization at room temperature. The cake of white needles was broken up, filtered, washed with 100 ml. of *n*-hexane and dried *in vacuo* for one hour at 50° to yield 211.6 g. of colorless, anhydrous diamine; m.p. (cor.) 64–65.4°; freezing point (cor.) 65.39°. All manipulations on the anhydrous diamine were carried out in a nitrogen atmosphere.

*Anal.* Calcd. for $C_{13}H_{26}N_2$: C, 74.22; H, 12.46; N, 13.32; neut. equiv., 105.2. Found: C, 73.62, 73.44; H, 12.44, 12.32; N, 12.95, 13.18; neut. equiv., 105.4, 105.1.

This highly purified sample of *trans–trans* II also exhibited a wide melting range (60–64.7°) unless sufficient precautions were taken,[14] and it was therefore considered that recrystallization of the diamine itself yielded a product free from the other two isomers. This is presumed to be the isomer, m.p. 60–63°, reported by the German workers.[3]

B. *cis–trans* II.—The mother liquor (Fraction E, Tables III and IV) remaining after removal of diformyl-*trans–trans* II consisted essentially of a mixture of the diformyl derivatives of the *cis–trans* and *cis–cis* isomers. Upon concentration of Fraction E under water-pump vacuum at a bath temperature no greater than 80°, a clear, light yellow, very viscous sirup resulted which resisted all efforts at crystallization, including molecular distillation and precipitation with various solvents at low temperatures. Therefore, the sirup was hydrolyzed to the diamine by heating on the steam-bath with one l. of 6 *N* HCl until solution resulted, the clear yellow-red solution refluxed for 3 hours, cooled, and a solution of 480 g. (12 moles) of sodium hydroxide in one l. of water was added with cooling whereupon the diamine separated as a white gelatinous hydrate which was extracted from the aqueous solution with 5 portions of *n*-butyl alcohol with a total volume of 1000 ml. The *n*-butyl alcohol extract was washed with two 200-ml. portions of water and the solution concentrated *in vacuo* until essentially all the water and alcohol were removed. The residual liquid diamine was freed from inorganic salts by filtration, the salts washed with ether and the combined filtrate and washings distilled *in vacuo* through a packed column to yield 389 g. of liquid diamine (Fraction F); b.p. 131–139° (0.8–0.55 mm.); $n^{25}D$ 1.5050.

In view of its high solubility, low melting point, and tendency to absorb carbon dioxide and water from the air, it was decided to convert the diamine mixture to a stable crystalline derivative which on fractional crystallization might yield the remaining two isomers. For this purpose the acetyl derivative proved suitable.

**Acetyl Derivative.**—To a solution of 341 g. (1.62 moles) of Fraction F in a mixture of 400 ml. of glacial acetic acid and 400 ml. of water was added 497 g. (4.8 moles) of acetic anhydride with stirring at a temperature of 50° over a period of 55 minutes, the reaction mixture being cooled with ice as needed to maintain the desired temperature. The clear, colorless reaction mixture was then maintained at 50° with stirring for one-half hour, slowly diluted with 800 ml. of water with stirring and crystallization allowed to proceed slowly at room temperature and finally in ice. The white sandy crystalline precipitate was filtered off, washed with 325 ml. of 25% acetic acid and 1600 ml. of water and air-dried; Fraction G (wt. 213.5 g.; m.p. 223–227° sintering at 216.5°). The combined washings were added to the mother liquor, the mixture diluted with six liters of water and stored overnight at 6°. The precipitated crystalline material was filtered off, washed with one l. of water and dried; Fraction H (wt. 93.2 g.; m.p. 205–217°). The combined mother liquor and washings were concentrated under water-pump vacuum, the small quantities of crystalline material which separated being filtered off and combined; Fraction H1 (wt. 8.2 g., m.p. 211–239°). Further concentration of the mother liquor yielded 228 g. of a clear, yellow, viscous, water-soluble sirup, probably partially acetylated diamine, which was not investigated further. A second portion (wt. 21 g.) of Fraction F was acetylated essentially by the foregoing procedure and the products subjected to fractional crystallization together with those from the larger run as shown in Table IV.

Fraction G, which proved to be largely diacetyl *cis–trans* II, was dissolved in 900 ml. of boiling 95% ethanol, the solution diluted while hot with 750 ml. of water and allowed to crystallize first at room temperature and then in ice. The crystals were filtered off, washed with 200 ml. of 50% ethanol and dried; Fraction G1 (wt. 177 g., m.p. 219.5–229° with sintering at 217°). Fractions G1 and I were combined and recrystallized five times from hot ethanol–water to yield pure diacetyl-*cis–trans* II (Fraction G6) in the form of small needles and clusters of needles melting at 231–232°; weight 86.5 g.

**Hydrolysis of Diacetyl Derivative.**—The pure *cis–trans* isomer was isolated as follows: A mixture of 140 g. (0.475 mole) of pure diacetyl *cis–trans* II, 400 ml. of concentrated hydrochloric acid and 130 ml. of water was heated under reflux for 11 hours. An additional 150 ml. of concentrated hydrochloric acid was then added and the mixture again refluxed for 8 hours, this procedure being repeated three more times, after which hydrolysis appeared to be complete. Upon standing for several days at room temperature, the solution precipitated colorless rectangular prisms, about 20 mm. × 5 mm., which were presumed to be the dihydrochloride. Without redissolving the precipitated salt, a solution of 480 g. (12 moles) of sodium hydroxide in one l. of water was added to the hydrolysate with cooling, whereupon the diamine precipitated in the form of a yellow-white gelatinous mass. The diamine was extracted with 700 ml. of *n*-butyl alcohol in four portions and the combined alcohol extracts washed with two 100-ml. portions of water and concentrated *in vacuo* to a light yellow viscous sirup. The sirup was filtered from a small quantity of inorganic salts which were washed with ether and the combined filtrate and washings distilled *in vacuo* through a 10-inch packed column to yield, after discarding 0.5 g. of foreshot, 97.1 g. (97%) of *cis–trans* II boiling at 120.3° (0.8 mm.). This isomer was collected as a colorless somewhat viscous sirup, $n^{25}D$ 1.5046, $d^{25}_4$ 0.9608 which slowly crystallized at room temperature when the receiver was cooled momentarily with Dry Ice; m.p. (cor.) 35.7–36.9°.[14]

*Anal.* Calcd. for $C_{13}H_{16}N_2$: C, 74.22; H, 12.46; N, 13.32; neut. equiv., 105.2. Found: C, 73.70, 73.58;

H, 12.76, 12.54; N, 13.02, 13.06; neut. equiv., 105.2.

An isomer melting at 31–33° was obtained by the German workers.[2,3] Their sample of the *cis–trans* isomer apparently was impure.

C. *cis–cis* II.—Whereas the first crop of crystalline material obtained on acetylation of Fraction F yielded diacetyl *cis–trans* II, the third isomer was concentrated in the succeeding crops in spite of its lower solubility because of the relatively small amount of this isomer produced under the conditions of hydrogenation. Thus, on working up Fraction H and the mother liquors from Fractions H and I, according to the scheme outlined in Table IV, there were obtained two relatively pure samples of diacetyl *cis–cis* II (Fractions I4 and H3) totaling 11.87 g. After two additional recrystallizations from boiling 95% ethanol, in which it is relatively insoluble, pure diacetyl *cis–cis* II (Fraction J) was obtained as colorless, waxy, butterfly-shaped plates or small plate-like prisms melting at 241.5–243.2°.

Pure *cis–cis* II was isolated as follows: To 106 g. (0.36 mole) of pure diacetyl *cis–cis* II was added 300 ml. (3.6 mole) of concentrated hydrochloric acid and 100 ml. of water and the mixture refluxed for 13.5 hours, the derivative dissolving almost immediately in the hot acid. An additional 100 ml. of concentrated hydrochloric acid was then added and the mixture again refluxed for 8 hours. This procedure was repeated three times using a total of 250 ml. of concentrated hydrochloric acid after which hydrolysis appeared to be complete. On interrupting the hydrolysis overnight, the hydrolysate deposited colorless crystals, presumably of the dihydrochloride, which again dissolved on heating. To the cooled reaction mixture (containing solid hydrochloride) was added with cooling a solution of 290 g. (7.25 moles) of sodium hydroxide in 600 ml. of water, whereupon the diamine precipitated as a white amorphous hydrate. The diamine was extracted with 500 ml. of *n*-butyl alcohol in four portions, the combined alcohol solutions washed with two 50-ml. portions of water and the alcohol removed by distillation *in vacuo*, leaving a clear light yellow sirup which crystallized spontaneously. On distillation *in vacuo* through a 10-inch packed column, there was obtained, after rejecting 0.4 g. of crystalline foreshot, 71.8 g. (94.8% yield) of *cis–cis* II as a colorless liquid which immediately set to a colorless crystalline solid; b.p. 141° (2 mm.). On redistillation there was obtained 68.6 g. of *cis–cis* II boiling at 139.8–139.3° (1.9–1.8 mm.); m.p. (cor.) 60.5–61.9°.[14]

*Anal.* Calcd. for $C_{13}H_{26}N_2$: C, 74.22; H, 12.46; N, 13.32; neut. equiv., 105.2. Found: C, 74.73, 74.64; H, 12.47, 12.55; N, 13.35, 13.27; neut. equiv., 105.0, 105.5.

By taking into account the actual amounts of the three isomers isolated and the fraction of the initial amount of II accounted for as pure isomers, it is estimated that the three isomers occur in II in the following proportions: 50–60% *trans–trans* II, 30–40% *cis–trans* II and 5–10% *cis–cis* II.

**Preparation of Derivatives.**—The melting points and analytical data for the picrates and the diformyl, diacetyl and dibenzoyl derivatives of the isomers of II are listed in Table V. The general procedure employed for acetylation and formylation has been previously described. Ethanol was used as solvent in the preparation of the picrates. The dibenzoyl derivatives were prepared by reaction of II with benzoyl chloride in pyridine.

## Summary

The isolation and characterization of the three geometric isomers of bis-(4-aminocyclohexyl)-methane are described. Spatial configurations are assigned on the basis of (1) the melting points of the isomers in comparison with analogous systems and (2) the relative abundance of the three isomers under the conditions of formation.

WILMINGTON, DELAWARE RECEIVED JUNE 26, 1950

---

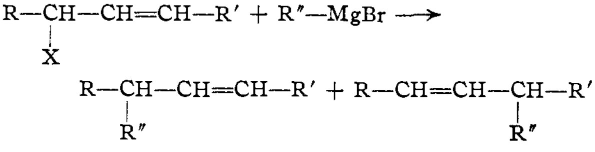
[CONTRIBUTION FROM THE STERLING MEMORIAL LABORATORY, YALE UNIVERSITY]

# Reaction of 3,5-Dibromocyclopentene with Grignard Reagents

BY GEORGE W. BARBER[1] AND J. ENGLISH, JR.

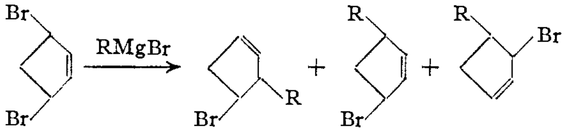
A recent paper by Reid and Yost[2] in which they report unsuccessful attempts to effect reaction of 3,5-dibromocyclopentene with Grignard reagents prompts us to report at this time some preliminary results obtained in this Laboratory in the spring of 1947. Like Reid and Yost we were attracted by the possibility of utilizing the readily available *cis*- and *trans*-3,5-dibromocyclopentenes for the synthesis of 3,5-dialkylcyclopentenes related to the structures proposed for the plant-growth hormones, auxin-a and auxin-b.[3] Although partial success on treating 3,5-dibromocyclopentene with Grignard reagents is reported here, this approach to the auxin ring structure was subsequently abandoned in favor of the more promising synthesis of substituted cyclopentene carboxaldehydes from substituted catechols.[4]

The action of Grignard reagents on unsymmetrically substituted allyl halides has been investigated only slightly, but in a few instances allylic rearrangement during the reaction has been observed to take place to a greater or less extent, mixtures of products invariably having been obtained.[5,6,7,8]



$$\underset{\substack{|\\ X}}{R-CH}-CH=CH-R' + R''-MgBr \longrightarrow \underset{\substack{|\\ R''}}{R-CH}-CH=CH-R' + R-CH=CH-\underset{\substack{|\\ R''}}{CH}-R'$$

In view of these reports, it seemed likely that the reaction of 3,5-dibromocyclopentene with a Grignard reagent would yield a similar but more complicated mixture of products, according to the following scheme.



I II III

---

[1] George S. Cox Medical Research Institute, University of Pennsylvania. Taken from a thesis submitted by George W. Barber to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the Ph.D. degree.

[2] E. B. Reid and J. F. Yost, THIS JOURNAL, **72**, 1807 (1950).

[3] F. Kögl, *Ber.*, **68A**, 16 (1935).

[4] J. English and G. W. Barber, THIS JOURNAL, **71**, 3310 (1949).

[5] C. Prevost and J. Daujat, *Bull. soc. chim.*, [4] **47**, 588 (1930).

[6] W. C. Young, J. D. Roberts and H. Wax, THIS JOURNAL, **67**, 841 (1945).

[7] A. N. Pudovic and B. A. Arbuzov, *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, 246 (1948); *C. A.*, **42**, 4973b (1948).

[8] W. H. Carothers and G. J. Berchet, THIS JOURNAL, **55**, 2807 (1933).