cis- and *trans*-1,5-Diphenylcyclooctane

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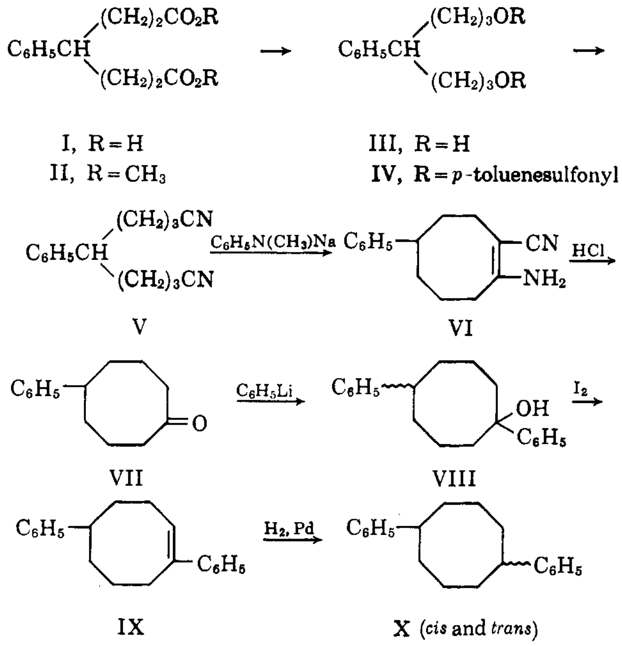
The synthesis of *cis*- and *trans*-1,5-diphenylcyclooctane, used in assigning structures to 1,5-diphenylcyclooctatetraene, is reported. The *cis* and *trans* isomers were separated but configurations were not assigned to them.

cis- and *trans*-1,2-[2] and -1,3-diphenylcyclooctanes[3,4] have been reported. This paper describes the synthesis of the 1,5-isomers (*cis* and *trans*), needed for comparison with the reduction products of the diphenylcyclooctatetraenes in order to assign structures to the four isomeric forms (1,2-, 1,3-, 1,4-, and 1,5-).[5] The reaction sequence shown in Scheme I was used.

SCHEME I



4-Phenylpimelic acid (I) was prepared in an over-all yield of 67% from the Michael condensation product[6-8] of diethyl malonate and ethyl cinnamate *via* 3-phenylglutaric acid,[8] dimethyl 3-phenylglutarate,[9] 3-phenyl-1,5-pentanediol,[10,11] 3-phenyl-1,5-pentanediol di-*p*-toluenesulfonate, and 4-phenylpimelonitrile.[12] Although the syntheses of 3-phenyl-1,5-pentanediol[10,11] and 4-phenylpimelonitrile[12] have been reported, different synthetic methods were used in this investigation. Dimethyl 3-phenylglutarate was converted to 3-phenyl-1,5-pentanediol in 95% yield by reduction with lithium aluminum hydride. The di-*p*-toluenesulfonate of this glycol, prepared in nearly quantitative yield with *p*-toluenesulfonyl chloride in pyridine, was converted to 4-phenylpimelonitrile in 96% yield by refluxing a solution of the ditosylate and potassium cyanide in 80% ethanol. Although the melting point (45.2–46.2°) of this material was lower than that reported in the literature[12] (50–51°), the elemental analysis and infrared spectrum were consistent with the assigned structure. In addition, hydrolysis with concentrated hydrochloric acid proceeded smoothly to give 4-phenylpimelic acid (I) in 82% yield. Dimethyl 4-phenylpimelate (II), prepared in 85% yield by esterification of the acid with methanol and sulfuric acid, was reduced with lithium aluminum hydride yielding 97% of the theoretical amount of 4-phenyl-1,7-heptanediol (III). Conversion of the glycol to the di-*p*-toluenesulfonate (IV), which was not purified, followed by treatment with potassium cyanide in 80% ethanol led to 5-phenylazelanitrile (V) in 54% yield. The yield of the dinitrile may have been lowered because its melting point (34.0–34.6°) made isolation of the product difficult.

Cyclization of 5-phenylazelanitrile with sodium methylanilide[13,14] using the conditions of Ziegler[15,16] led to a 54% yield of 2-cyano-5-phenylcycloocten-1-ylamine (VI) when V was added to the reaction mixture through a simple dilution apparatus.[17] A 33% yield was realized when the dilution apparatus was not used.[13] The product was characterized by analysis and its infrared spectrum, which was similar except for bands due to the phenyl group to the spectrum of 2-cyanocycloocten-1-ylamine, obtained by a similar cyclization of azelanitrile. Hydrolysis of VI with concentrated hydrochloric acid yielded 80% of 5-phenylcyclooctanone (VII). Hydrolysis of VI with sulfuric acid under conditions that have been used successfully in similar cases[13,14] resulted in resinification and no ketone could be isolated. The 5-phenylcycloooctanone was characterized by its infrared spectrum, analysis, analysis of a crystalline semicarbazone, and by conversion in 68% yield to phenylcyclooctane by the modified Wolff–Kishner method of Huang-Minlon.[18] The phenylcyclooctane was identified by its melting point, mixture melting point with an authentic sample,[19] and comparison of its infrared spectrum with that of an authentic sample.

Reaction of 5-phenylcyclooctanone with an ethereal solution of phenyllithium proceeded smoothly yielding 72% of *cis*- and *trans*-1,5-diphenylcyclooctanol (VIII). Recrystallization gave an analytically pure mixture of isomers melting at 149.8–154.2°. Attempted short-

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path distillation of VIII at 200° (0.5 mm.) resulted in partial dehydration to give a mixture of VIII and 1,5-diphenylcyclooctene (IX). The dehydration was completed by heating the mixture with iodine in benzene solution. The ultraviolet spectrum of IX [$\lambda_{\max}$ 248–249 mμ (log ϵ 4.13)] when compared with the ultraviolet spectra of a mixture of 1,3- and 2,4-diphenylcyclooctenes[5] [$\lambda_{\max}$ 248 mμ (log ϵ 4.13)] and 1-phenylcyclooctene[19] [$\lambda_{\max}$ 248 mμ (log ϵ 4.07)] supports the assigned structure.

Catalytic reduction of IX at room temperature and atmospheric pressure over 10% palladium on Norit yielded a crystalline solid that proved to be a mixture of the *cis* and *trans* isomers of 1,5-diphenylcyclooctane (X). The mixture, after sublimation, melted over a 9° range but gave the proper analysis for $C_{20}H_{24}$. A partial separation of the isomers was accomplished by chromatography on alumina. The higher melting isomer, m.p. 80–81°, was eluted in the first few fractions and the lower melting isomer, m.p. 62.0–62.5°, was found in the last fractions. The infrared spectra and analyses of these isomers were consistent with the assigned structures.

Experimental[20]

3-Phenyl-1,5-pentanediol.—A solution of 98 g. of dimethyl 3-phenylglutarate in 400 ml. of dry tetrahydrofuran was added dropwise to a stirred solution of 20 g. of lithium aluminum hydride in 500 ml. of dry tetrahydrofuran at a rate that maintained gentle reflux. After the addition was completed, the reaction mixture was refluxed for 1 hr. and excess lithium aluminum hydride was decomposed by the cautious addition of 30 ml. of water, followed by 500 ml. of 10% hydrochloric acid. The aqueous layer was separated and extracted with two 200-ml. portions of ether. The combined ether extracts and tetrahydrofuran solution were dried over sodium sulfate, solvent was removed, and the residue was distilled through a semimicrocolumn under reduced pressure, yielding 70.8 g. (95%) of 3-phenyl-1,5-pentanediol, b.p. 145–146° (0.3 mm.). The bisphenylurethan, after one recrystallization from benzene, melted at 110.2–111.6° (lit.[10] m.p. 112–113°).

3-Phenyl-1,5-pentanediol Di-*p*-toluenesulfonate.—To an ice-cold solution of 25 g. of 3-phenyl-1,5-pentanediol in 200 ml. of dry pyridine, 58 g. of *p*-toluenesulfonyl chloride was added with stirring. The reaction mixture was cooled in an ice bath for 2 hr. with occasional stirring, treated with 270 ml. of water, and extracted with ether. The ethereal solution was washed successively with 10% hydrochloric acid, water, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. The ether was removed yielding 66.7 g. (98%) of the ditosylate which solidified on standing. After two recrystallizations from dry ether it melted at 92.0–92.6°.

Anal. Calcd. for $C_{25}H_{28}O_6S_2$: C, 61.45; H, 5.78. Found: C, 61.27; H, 5.97.

4-Phenylpimelonitrile.—A solution of 66.7 g. of crude 3-phenyl-1,5-pentanediol di-*p*-toluenesulfonate, 27.5 g. of potassium cyanide, and 500 ml. of 80% ethanol was refluxed for 7 hr. Most of the ethanol was distilled from the reaction mixture and 300 ml. of water was added to the residue. The aqueous mixture was extracted with ether and the combined ethereal solutions were washed thoroughly with water and dried over magnesium sulfate. Distillation of the ether left 26 g. (96%) of crude 4-phenylpimelonitrile. Upon distillation through a semimicrocolumn the product had b.p. 148° (0.015 mm.), and crystallized on cooling. Analytically pure 4-phenylpimelonitrile was obtained after one recrystallization from anhydrous ether, m.p. 45.2–46.2° (lit.[12] m.p. 50–51°).

Dimethyl 4-Phenylpimelate (II).—A solution of 48.5 g. of crude 4-phenylpimelic acid, 15 ml. of concentrated sulfuric acid, and 350 ml. of anhydrous methanol was refluxed for 5 hr. The reaction mixture was cooled and treated with 400 ml. of water and made basic by addition of sodium bicarbonate. The reaction mixture was extracted with ether, and the ether extracts were washed with water and dried over magnesium sulfate. The ether was distilled and distillation of the residue through a semimicrocolumn yielded 46 g. (85%) of dimethyl 4-phenylpimelate, b.p. 130–135° (0.4 mm.), $n^{25}D$ 1.4968.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.38; H, 7.68.

4-Phenyl-1,7-heptanediol (III).—In an atmosphere of nitrogen a solution of 60 g. of dimethyl 4-phenylpimelate in 350 ml. of dry ether was added dropwise with stirring to a solution of 10.8 g. of lithium aluminum hydride in 750 ml. of dry ether. The reaction mixture was refluxed for 1 hr. and excess lithium aluminum hydride was decomposed by the cautious addition of 25 ml. of water, followed by 750 ml. of 10% hydrochloric acid. The two phases were separated and the aqueous layer was extracted twice with 200-ml. portions of ether. After drying the combined ether layer and ethereal extracts over magnesium sulfate and removal of solvent, there remained 46 g. (97%) of crude 4-phenyl-1,7-heptanediol. Distillation through a semimicrocolumn yielded III as a cloudy viscous oil, b.p. 123–124° (0.011 mm.).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.83; H, 9.83.

4-Phenyl-1,7-heptanediol Di-*p*-toluenesulfonate (IV).—To an ice-cold solution of 16.3 g. of 4-phenyl-1,7-heptanediol in 150 ml. of dry pyridine, 33.1 g. of *p*-toluenesulfonyl chloride was added with stirring. The resulting solution was cooled in an ice bath for 2 hr. with occasional stirring, treated with 210 ml. of water, and extracted with ether. The ethereal solution was washed successively with 10% hydrochloric acid, water, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. Upon removal of the ether there remained 38 g. (94%) of IV as an oil that failed to crystallize.

5-Phenylazelanitrile (V).—A solution of 38 g. of crude 4-phenyl-1,7-heptanediol di-*p*-toluenesulfonate and 15.3 g. of potassium cyanide in 250 ml. of 80% ethanol was refluxed for 11 hr. After distillation of most of the ethanol from the reaction mixture, 200 ml. of water was added and the mixture was extracted with ether. The ethereal solution was thoroughly washed with water and dried over magnesium sulfate. The residue, after removal of the ether, was twice decolorized with activated charcoal in methanol solution. Upon concentration and cooling of the methanol solution 9 g. (54%) of the dinitrile crystallized. Two recrystallizations from dry methanol yielded analytically pure 5-phenylazelanitrile, m.p. 34.0–34.6°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.55; H, 7.98; N, 12.35.

2-Cyano-5-phenylcycloocten-1-ylamine (VI).—Sodium methylanilide was prepared under an atmosphere of nitrogen by refluxing for 4 hr. with vigorous stirring a mixture of 40.4 g. of naphthalene, 12 g. of sodium wire, 70 g. of redistilled methylaniline, and 785 ml. of anhydrous ether contained in a 3-l. three-necked flask fitted with a mercury-sealed Hershberg stirrer and a simple dilution apparatus.[17] To the well-stirred, boiling solution of sodium methylanilide a solution of 11.8 g. of 5-phenylazelanitrile in 250 ml. of anhydrous ether was added dropwise through the dilution apparatus over a period of 8 hr. The reaction mixture was refluxed for 1 hr., cooled, and cautiously treated with 750 ml. of water with stirring and cooling. The ethereal layer was separated and the aqueous layer was extracted with 250 ml. of ether. The ether was distilled from the combined ethereal solutions and the residue was steam distilled to remove the methylaniline and dihydronaphthalenes. The material remaining after the steam distillation was extracted with ether and the ethereal solution was dried over magnesium sulfate and concentrated. The remaining oil was dissolved in dry ether and ethanol and, upon cooling in a Dry Ice–acetone bath, crystalline 2-cyano-5-phenylcycloocten-1-ylamine was deposited.[21] By successive concentrations and coolings of the mother liquor, a total of 6.4 g. (54%) of material melting at 87.4–96.6° was collected. Recrystallization from absolute ethanol yielded VI as crystals, m.p. 96.8–98.0°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.76; H, 8.19; N, 12.26.

5-Phenylcyclooctanone (VII).—A mixture of 1.3 g. of 2-cyano-5-phenylcycloocten-1-ylamine and 100 ml. of concentrated

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[20] Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

[21] The enamine structure VI (rather than the isomeric iminonitrile structure) was assigned on the basis of its ultraviolet spectrum [$\lambda_{\max}^{CHCl_3}$ 264 mμ (log ϵ 4.02)] and the n.m.r. spectrum (two NH_2 protons at τ 5.45 and four allylic protons centered at 7.67, in addition to the expected aryl and methylene protons). We are indebted to R. B. Kinnel for these data.

hydrochloric acid was refluxed for 7 hr. The reaction mixture was diluted with 50 ml. of water and extracted with 200 ml. of ether. After drying the ethereal solution over magnesium sulfate, the ether was removed and the residue was distilled through a semimicrocolumn, yielding 0.92 g. (80%) of 5-phenylcyclooctanone, b.p. 110–111° (0.3 mm.), n^{25}D 1.5378.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.12; H, 8.95.

The semicarbazone, recrystallized from aqueous ethanol, melted at 188.2–189.4° dec.

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.12. Found: C, 69.30; H, 8.05; N, 16.19.

A solution of 0.18 g. of 5-phenylcyclooctanone, 0.5 g. of potassium hydroxide, and 1.0 ml. of 85% hydrazine hydrate in 10 ml. of diethylene glycol was refluxed for 1 hr. The solution was heated to 200–210° for 3 hr. and approximately 1 ml. of distillate was collected. The distillate was returned to the cooled reaction mixture, which was then treated with 50 ml. of water and extracted with a total of 75 ml. of ether. The ethereal solution was washed with water, dried over magnesium sulfate, and concentrated by slow distillation through a semimicrocolumn. The residue was purified by filtration through 5 g. of alumina with 75 ml. of benzene. After the benzene was removed, short-path distillation of the residue under reduced pressure (0.3 mm.) with a heating block temperature of 100° yielded 0.113 g. (68%) of phenylcyclooctane, n^{25}D 1.5288, m.p. 5.9–9.0°, which did not depress the melting point of an authentic sample.[19]

1,5-Diphenylcyclooctanol (VIII).—A solution of 0.94 g. of 5-phenylcyclooctanone in 10 ml. of anhydrous ether was added dropwise to a solution of phenyllithium prepared from 0.15 g. of lithium wire and 1.31 g. of bromobenzene in 35 ml. of anhydrous ether. The reaction mixture was refluxed for 1 hr. and treated with 25 ml. of water. The resulting two-phase mixture was separated and the aqueous layer was extracted with 100 ml. of ether. The combined ethereal solutions were dried over magnesium sulfate. After distillation of the ether there remained 0.93 g. (72%) of a crystalline residue. Two crystallizations from 95% ethanol followed by sublimation yielded a mixture of *cis*- and *trans*-1,5-diphenylcyclooctanol, m.p. 149.8–154.2°.

Anal. Calcd. for $C_{20}H_{24}O$: C, 85.66; H, 8.63. Found: C, 85.72; H, 8.62.

1,5-Diphenylcyclooctene (IX).—Short-path distillation at 0.5 mm. with a heating block temperature of 200° of the 1,5-diphenylcyclooctanol from 2.29 g. of 5-phenylcyclooctanone yielded 2.52 g. of a mixture of 1,5-diphenylcyclooctanol and 1,5-diphenylcyclooctene. This mixture was dissolved in 110 ml. of dry benzene to which a few crystals of iodine had been added. The solution was refluxed with an attached water trap[22] for 23 hr. The reaction mixture was washed with sodium thiosulfate solution and with two small portions of water. The residue, after distillation of the benzene, was passed over 8.0 g. of silica gel and eluted with 250 ml. of petroleum ether (b.p. 35–60°). After distillation of the petroleum ether, short-path distillation of the residue at 0.4 mm. with a heating block temperature of 180° yielded 2.04 g. (69% from the ketone) of 1,5-diphenylcyclooctene, n^{25}D 1.5937.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.42; H, 8.09.

***cis*- and *trans*-1,5-Diphenylcyclooctane (X).**—Catalytic hydrogenation of 0.282 g. of 1,5-diphenylcyclooctene over 0.239 g. of 10% palladium on Norit in 10 ml. of 1:1 ethyl acetate–methanol required 48 min. and 101% of 1 molar equiv. of hydrogen was absorbed. The catalyst was separated by filtration and washed with methanol. Distillation of the solvent from the filtrate and sublimation of the residue at 100° (0.3 mm.) yielded a mixture of *cis*- and *trans*-1,5-diphenylcyclooctane, m.p. 57.0–66.2°.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 91.15; H, 9.07.

Separation of the *cis* and *trans* isomers was effected by chromatography of a 0.42-g. sample on 127 g. of alumina (Merck, Brockmann grade I)[23] in a 72 × 1.9 cm. column. The hydrocarbons were eluted with *n*-hexane; a total of 380 ml. was passed through the column before any hydrocarbon was found in the effluent. The next three 10-ml. fractions contained a total of 44 mg. of the higher melting isomer, which, after one recrystallization from methanol, melted at 80–81°.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 91.13; H, 9.33.

Fourteen 10-ml. fractions containing a mixture of the isomers, m.p. 52.8–72.4°, were then collected. The next four fractions contained 54 mg. of the lower melting isomer, which was rechromatographed and recrystallized from dry methanol and then melted at 62.0–62.5°.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 90.85; H, 9.19.

The higher melting isomer was also obtained in a fairly pure state by repeated recrystallization of the original mixture from ethanol and methanol.

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Highly Strained Bicyclic Systems. X.[1-3] The Chemistry of 6-Substituted *exo*-5-Chlorobicyclo[2.1.1]hexanes

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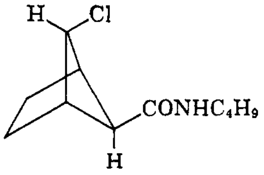
The synthesis of the epimeric *exo*-5-chlorobicyclo[2.1.1]hexane-6-carboxylic acids and related compounds is described. Dehalogenation of the *exo* acid gives the previously unavailable bicyclo[2.1.1]hexane-*exo*-5-carboxylic acid.

exo-5-Chlorobicyclo[2.1.1]hexane-*exo*-6-*t*-butylcarboxamide (1) has recently been shown to be a compound of considerable interest; it has provided the first example of a large, long-range, spin–spin coupling ($^4J_{AB}$ = 7 c.p.s.) between distant protons of known geometry,[4] and it was found to cyclize to give the first known example of a tricyclo[$3.1.0.0^{2,6}$]hexane (2) upon treatment with *n*-butyllithium.[5] In fact, neither of



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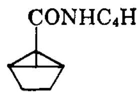

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