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Many-Membered Carbon Rings. XXIII. Restricted Rotation in a Simple Paracyclophane[1-3]

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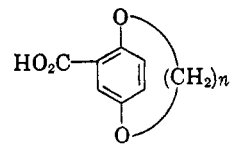
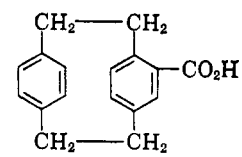
The objective of this investigation was to demonstrate hindered rotation about single bonds in certain simple paracyclophanes. This purpose was achieved by the resolution of a suitable *o*-substituted paracyclophane which had ten carbon atoms in its *para*-bridge, as exemplified by the compound [10]paracyclophane-12-carboxylic acid. This acid was synthesized in three steps from [10]paracyclophane: [10]paracyclophane → 12-chloromethyl[10]paracyclophane (73%) → [10]paracyclophane-12-carboxaldehyde (84%) → [10]paracyclophane-12-carboxylic acid (45%). Resolution of the racemic acid, m.p. 192–193°, into its pure optical antipodes was accomplished by separation of its cinchonidine salts. The active forms of the acid, m.p.'s *ca.* 160° and $\alpha_D \pm 80°$, racemized slowly at room temperature in the solid, crystalline state. Illustrative of some of the difficulties encountered early in this study was the observation that succinoylation of [10]paracyclophane gave only the rearranged product 12-(ω-carboxypropionyl)[10-*m*]cyclophane, a compound unsuitable for the purpose of this study.

Discovery of optical isomerism in the hindered biphenyls[6,7] was a significant and stimulating advance in stereochemistry.[8] It brought sharp attention to some of the consequences of restricted rotation about single bonds and initiated many of the studies germane to modern stereochemistry.

Interesting and unique opportunities to advance further our understanding of the importance of hindrance to free rotation are provided by examination of certain many-membered ring systems.[9] *para*-Bridged derivatives of benzene comprise one such system; representative of the accomplishments here are the resolutions of acids I and II into optical antipodes, reported by A. Lüttringhaus[10] and D. J. Cram,[11] respectively.



I. (n=8, 9)



II

This optical isomerism must derive from restricted rotation about single bonds.

The simple paracyclophane system III should also possess restriction in rotation about single bonds, provided its polymethylene bridge is a chain of ten or less carbon atoms. To demonstrate

(1) For preceding and closely related papers in this series, see (a) A. T. Blomquist and F. Jaffe, *J. Am. Chem. Soc.*, **80**, 3405 (1958), and (b) A. T. Blomquist and B. H. Smith, *J. Am. Chem. Soc.*, **82**, 2073 (1960).

(2) This study was supported in part by the National Science Foundation, Grant NSF-G 2922.

(3) Abstracted from part of the dissertations presented by R. E. Stahl in September, 1954, and B. H. Smith in June, 1960, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) Allied Chemical and Dye Fellow, Cornell University, 1953–1954.

(5) Procter and Gamble Fellow, Cornell University, 1958–1959.

(6) J. Kenner and W. V. Stubbings, *J. Chem. Soc.*, 593 (1921); G. H. Christie and J. Kenner, *J. Chem. Soc.*, 614 (1922).

(7) C. V. Ferriss and E. E. Turner, *J. Chem. Soc.*, 1140 (1920); R. J. W. leFevre and E. E. Turner, *J. Chem. Soc.*, 2476 (1926); *Chem. & Ind.*, **45**, 831 (1926).

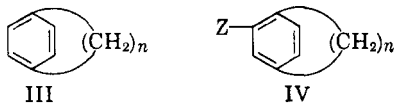
(8) D. H. R. Barton, Chapt. on Stereochemistry in Todd's *Perspectives in Organic Chemistry*, Interscience, New York, 1956.

(9) V. Prelog, Chapt. entitled "Bedeutung der vielgliedrigen Ringverbidungen für die theoretische organische Chemie" in Todd's *Perspectives . . .*, see Ref. 8.

(10) A. Lüttringhaus and H. Gralheer, *Ann.*, **557**, 108, 112 (1947). A. Lüttringhaus and G. Eyring, *Angew. Chem.*, **69**, 139 (1957); *Ann.*, **604**, 111 (1957).

(11) D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **77**, 6289 (1958); D. J. Cram, R. J. Wechter, and R. W. Kierstead, *J. Am. Chem. Soc.*, **80**, 3126 (1955).

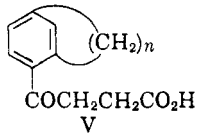
this one need but to resolve suitable derivatives IV of the hydrocarbons III. With the above in mind, work began several years ago in the Cornell



III IV

$n = 8, 9, 10$

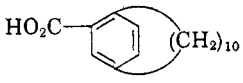
Laboratories on the synthesis of paracyclophanes III and their simple derivatives IV which would be suitable for resolution studies.[12,13] As reported recently,[1a] realization of this objective was delayed by the lack of initial success in obtaining substituted paracyclophanes such as IV by direct substitution of the hydrocarbons III. For example, succinoylation of [9]-and [10]paracyclophane gave only keto acid derivatives of [9-*m*]-and [10-*m*]cyclophane (V),



V

$n = 9, 10$

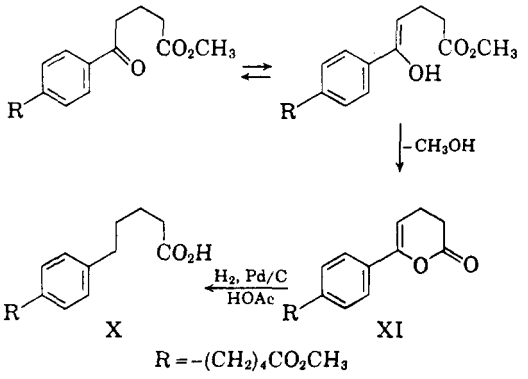
respectively. No restricted rotation is to be expected in such *meta*-bridged compounds and hence their resolution failed.[12,13] A successful route to compounds IV has now been found and a preliminary brief account of the resolution of one of these, [10]paracyclophane-12-carboxylic acid (VI), was recently described.[1b] This article presents in more detail the synthesis and resolution of the paracyclophane carboxylic acid VI.



VI

[10]Paracyclophane (VII), required for the synthesis of the acid VI, was prepared independently by one of us *via* an eight-step reaction sequence from benzene. As the synthesis happened to be basically very similar to the one used by Cram and Daeniker,[14] detailed comment will be made here only on those individual transformations which differed significantly.

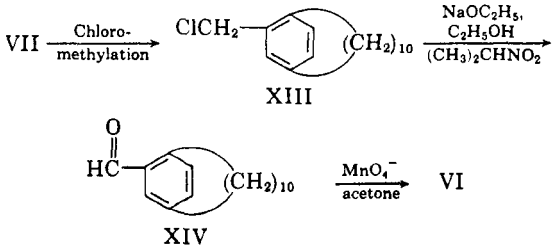
The intermediate δ-phenylvaleric acid (VIII) was obtained smoothly (90%) by catalytic reduction of γ-benzoylbutyric acid. Friedel-Crafts acylation of the methyl ester of VIII with γ-carbomethoxybutyryl chloride gave solid, crystalline methyl γ - [*p*(ω - carbomethoxybutyl)benzoyl] butyrate (IX), m.p. 48–50°, in 90% yield. In our hands, acylation with the ester–acid chloride was much superior to acylation with glutaric anhydride.[13,14] *para* Orientation of the side-chains in the keto diester IX was shown by its oxidative degradation to terephthalic acid. Catalytic reduction of the keto diester IX produced the ester acid methyl δ-[*p*-(ω-carboxybutyl)pentyl] valerate (X), m.p. 68.5–69.5°, in quantitative yield. Formation of the ester acid X probably occurs *via* reduction of the intermediate unsaturated δ-lactone XI as outlined below. Earlier a similar δ-lactone formation had been



$R = -(CH_2)_4CO_2CH_3$

observed in a closely related study.[1a] Acyloin cyclization of the dimethyl ester derived from X was effected in good yield (75%) to give 5-oxo-6-hydroxy[10]paracyclophane (XII); and a Clemmensen-type reduction of the latter produced the hydrocarbon VII (80–90%). Both preparations were similar to those described by Cram.[14]

Synthesis of the carboxylic acid VI from the paracyclophane VII required three steps as shown below. Chloromethylation of the hydrocarbon VII a standard procedure[15] was straightforward. It



produced 12 - chloromethyl[10]paracyclophane (XIII), m.p. 75–76°, in *ca.* 70% yield. The benzyl-type halide XIII was best converted to [10]-paracyclophane - 12 - carboxaldehyde (XIV) by the general procedure developed by Hass and Bender,[16] *i.e.*, by reaction of XIII with sodium 2-nitropropanenitronate in ethanol. The aldehyde XIV was thus obtained in 85% yield whereas only about a 20% yield was realized in application of a standard procedure based on Sommelet method.[17]

(12) R. E. Stahl, Ph.D. thesis, Cornell University, Ithaca, N. Y., 1954.

(13) K. L. Lockwood, Ph.D. thesis, Cornell University, Ithaca, N. Y., 1955.

(14) D. J. Cram and H. U. Daeniker, *J. Am. Chem. Soc.*, **76**, 2743 (1954).

(15) O. Grummitt and A. Buck, *Org. Syntheses*, **Coll. Vol. III**, 195 (1955).

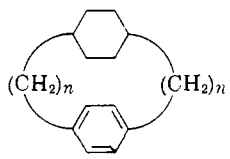
(16) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949).

In the latter there may be steric hindrance to the approach of reactants. Finally, the desired acid VI, m.p. 192–193°, was obtained, with some difficulty and only in fair yield (45%), by permanganate oxidation of the aldehyde XIV. Chemical evidence in support of the structure of acid VI was obtained by two degradations: direct dichromic acid oxidation of VI gave trimellitic acid and decarboxylation of compound VI gave [10]paracyclophane (VII). Terephthalic acid was obtained by the oxidation of this sample of hydrocarbon VII.

Prior to the successful synthesis of the simple acid VI, several aromatic substitution reactions were examined in an effort to obtain derivatives of the paracyclophane VII suitable for resolution studies. Only one of these, the succinoylation of the paracyclophane VII, will be described here.

A standard succinoylation of hydrocarbon VII gave a keto acid, m.p. 132.5–133°, which proved to be 12-(ω-carboxypropionyl)[10-*m*]cyclophane (XV). Alkaline permanganate oxidation of this acid XV gave trimellitic acid. However, hypohalite oxidation of XV gave a new monocarboxylic acid which, after decarboxylation by the quinoline-copper carbonate method,[18] produced liquid [10-*m*]-cyclophane (XVI); infrared absorption bands at 3.31, 6.22, 6.29, and 6.72 μ. Dichromic acid oxidation of the hydrocarbon XVI gave isophthalic acid.

This rearrangement of the *para* bridge in VII to a *meta* position upon succinoylation is not without precedence. Thus, Baddeley has observed a similar migration of *para* side-chain alkyl groups in the acetylation of *p*-diisopropylbenzene.[19] Also, Cram has found that acetylation of paracyclophanes of the type XVII even under mild conditions produces a mixture of isomers.[20]



XVII
$n = 4, 6$

The racemic acid VI, m.p. 192–193°, was resolved easily into its optical antipodes by use of the base cinchonidine. The less soluble salt, in acetone, proved to comprise (+) acid (−) base, m.p. 154–155°, $[\alpha]_D^{27}$ + 22 ± 2°. From this (+) VI was isolated; m.p. 160–161°, $[\alpha]_D^{24}$ +80 ± 2°. Crystallization filtrates enriched in the more soluble (−) acid (−) base salt gave (−) VI; m.p. 159–160°, $[\alpha]_D^{28}$ − 82 ± 2°.

Qualitative observations on the optical stability of the enantiomorphs of the acid VI indicate that the active forms racemize at an appreciable rate in the solid state at room temperature. A quantitative study of the racemization under various conditions is being made. The results of this investigation will be published in due course.

EXPERIMENTAL[21]

δ-Phenylvaleric acid (VIII). A mixture of 60 g. (0.31 mole) of γ-benzoylbutyric acid, m.p. 125–127°,[14] 2.5 g. of 10% palladium on charcoal, and 200 ml. of glacial acetic acid was hydrogenated at 65° in a Parr, low-pressure apparatus.[22] The cooled, filtered, hydrogenated mixture was poured into 750 ml. of cold water with vigorous stirring. The solid product VIII, which crystallized overnight, was collected and dried *in vacuo* at room temperature to give 53 g. (94%) of VIII; m.p. 58–59° (lit.[23] m.p. 57°).

Fischer esterification of 368 g. of the acid VIII gave 385 g. (97%) of methyl δ-phenylvalerate; n_D^{24} 1.4960, b.p. 110° (2.0 mm.).

Methyl γ-[p-(ω-carbomethoxybutyl)benzoyl]butyrate (IX). To a solution of 102 g. (0.53 mole) of the methyl ester of VIII and 87 g. (0.53 mole) of γ-carbomethoxybutyryl chloride[24] in 400 ml. of freshly distilled *s*-tetrachloroethane, cooled to 0°, 220 g. (1.65 moles) of anhydrous aluminum chloride was added with stirring over a 2-hr. period. After addition had been completed, the mixture was stirred at room temperature overnight, cooled again to 0°, and 200 ml. of ether added. With the temperature of the mixture maintained at 0–5°, 800 ml. of 20% aqueous hydrochloric acid was added. The aqueous and organic layers were separated and the aqueous layer extracted with three 200-ml. portions of ether. The combined organic solutions were washed free of acid with saturated aqueous sodium bicarbonate solution, then washed with water, and dried over magnesium sulfate. Distillation of the dried organic solution gave 134.5 g. (79%) of reasonably pure di-ester IX as a yellow solid; m.p. 48–50°, b.p. 215° (0.2 mm.). Pure ester IX, m.p. 49–51°, was obtained as colorless needles after two recrystallizations from 90–100° petroleum ether.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.30; H, 7.51.

The *2,4-dinitrophenylhydrazone derivative* of the keto ester IX was prepared in the usual way[25] and was obtained as red plates after several recrystallizations from aqueous ethanol; m.p. 123.3–124°.

Anal. Calcd. for $C_{24}H_{28}N_4O_8$: C, 57.59; H, 5.64; N, 11.20; mol. wt., 500.5. Found: C, 57.69; H, 5.72; N, 11.37; mol. wt., 497.

A small amount of the keto ester IX was hydrolyzed with 15% methanolic sodium hydroxide to give the known keto-dicarboxylic acid, γ-[p-(ω-carboxybutyl)benzoyl]butyric acid, m.p. 177–178° after recrystallization from 95% ethanol (lit.[14] m.p. 177–178.5°).

(17) S. J. Angyal, J. R. Tetaz, and J. G. Wilson, *Org. Syntheses*, **30**, 67 (1950).

(18) E. B. Herschberg and L. F. Fieser, *J. Am. Chem. Soc.*, **63**, 2561 (1941).

(19) G. Baddeley, *Quart. Rev.*, **8**, 368 (1954); G. Baddeley, G. Holt and W. Pickles, *J. Chem. Soc.*, 4163 (1952).

(20) D. J. Cram and J. Abell, *J. Am. Chem. Soc.*, **77**, 1179 (1955); D. J. Cram and R. W. Kierstad, *J. Am. Chem. Soc.*, **77**, 1186 (1955).

(21) All melting and boiling points are uncorrected. Infrared spectra were determined with Perkin-Elmer Double Beam Spectrophotometers, Models 21 and 137.

(22) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **71**, 1036 (1949).

(23) H. Staudinger and F. Müller, *Ber.*, **56**, 711 (1923).

(24) P. W. Clutterbuck and H. S. Raper, *Biochem. J.*, **19**, 385 (1925).

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., Wiley, New York, 1956, p. 219.

Oxidative degradation of the keto ester IX by the usual sodium dichromate–sulfuric acid method[26] gave terephthalic acid, sublm. at *ca.* 300°, which was converted to its dimethyl ester with diazomethane.[27] This ester had m.p. 136–138° and was identical with authentic dimethyl terephthalate.

Methyl δ-[p-(ω-carboxybutyl)phenyl]valerate (X). This acid ester X was obtained by the catalytic reduction method of Horning and Reisner used in the preparation of the acid VIII.[22] In a typical experiment, hydrogenation of 50 g. of (0.16 mole) of IX in 150 ml. of glacial acetic acid with 2.5 g. of palladium on charcoal catalyst gave 45.6 g. (100%) of the acid ester X which, after recrystallization from petroleum ether (b.p. 90–100°), was obtained as white plates; m.p. 68.5–69.5°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.28; mol. wt., 292. Found: C, 69.81; H, 8.29; mol. wt., 316.

Hydrolysis of the ester acid X with 15% methanolic sodium hydroxide gave the expected dicarboxylic acid, 1,4-bis(ω-carboxybutyl)benzene which, after two recrystallizations from 95% ethanol, had m.p. 181–182° (lit. m.p. 179–182°[14]).

1,4-Bis(ω-carbomethoxybutyl)benzene. This compound was prepared by a Fischer esterification of the acid ester X. From 210 g. of compound X there was obtained 190 g. (86%) of the diester: n_D^{20} 1.4968, b.p. 177–180° (0.13 mm.) [lit.[14] b.p. 182–184° (0.4 mm.)].

5-Oxo-6-hydroxy[10]paracyclophane (XII). The cyclic acyloin was prepared by the method of Cram.[14] In preparations done with *ca.* 0.1 mole of the diester derived from X the yield of acyloin was 72–75%. The distilled acyloin product, b.p. 145–151° (0.15 mm.) and n_D^{21} 1.5466, always contained some of the related α-diketone.

[10]Paracyclophane (VII). This hydrocarbon was prepared by the method of Cram.[14] The crude paracyclophane, after one distillation through a short-pass column, was chromatographed on neutral alumina. A clean separation of hydrocarbon product from the cyclic ketone impurity, 5-oxo[10]paracyclophane, was realized with petroleum ether (b.p. 30–60°) used as an eluant. The chromatographed hydrocarbon, containing some olefinic material, was hydrogenated in ethanol over Adams catalyst. The usual workup then gave pure hydrocarbon; n_D^{27} 1.5332, b.p. 115–117° (1.0 mm.) [lit. values,[14] n_D^{25} 1.5331, b.p. 168° (16 mm.)]. The hydrocarbon was obtained in 80–90% yield in preparations which used 30–35 g. of the acyloin-diketone mixture described in the preceding section.

12-Chloromethyl[10]paracyclophane (XIII). The method used was based on the preparation of 1-chloromethylnaphthalene given in Organic Syntheses. In a typical experiment, a mixture of 16.07 g. (0.074 mole) of hydrocarbon VII, 4.1 g. (0.14 mole of formaldehyde) of paraformaldehyde, 15.7 ml. of glacial acetic acid, 9.7 ml. of 85% phosphoric acid, and 26.6 ml. of concd. hydrochloric acid was refluxed at a bath temperature of 135° with stirring for 6 hr. The cooled mixture was poured into 400 ml. of cold water and extracted with three 200-ml. portions of ether. The ethereal solution was washed with 100 ml. of cold water, three 150-ml. portions of saturated sodium bicarbonate solution, and dried with magnesium sulfate. Distillation of the filtered, dried ether solution gave 10.4 g. (73% based on VII consumed) of the chloromethyl compound XIII; n_D^{20} 1.5775, b.p. 150–152° (0.7 mm.). This liquid product solidified on standing and showed m.p. 62–64°. Recrystallization of this solid from petroleum ether (b.p. 30–60°) at −70° gave compound XIII as white clusters, m.p. 75–76°. This product gave rapidly a positive test for active halogen with silver nitrate reagent.

Anal. Calcd. for $C_{17}H_{25}Cl$: C, 77.09; H, 9.55; Cl, 13.39; mol. wt., 265. Found: C, 77.26; H, 9.32; Cl, 13.15; mol. wt., 259.

(26) Ref. 25, p. 250.

(27) F. Arndt, *Org. Syntheses*, Coll. Vol II, 165 (1943).

[10]Paracyclophane-12-carboxaldehyde (XIV). The general method of Hass and Bender for the conversion of benzyl halides to aromatic aldehydes[16] was the basis for the preparation of the aldehyde XIV from the chloromethyl compound XIII. 2-Nitropropane (1.99 g., 0.022 mole) was added to a solution of sodium ethoxide in ethanol, prepared by the reaction of 0.370 g. (0.016 g.-atom) of clean sodium with 10 ml. of freshly prepared absolute ethanol. The nitronate salt which precipitated was brought into solution by the addition of 20 ml. of absolute ethanol. To this ethanolic solution 4.0 g. (0.015 mole) of the chloro compound XIII was added and the mixture stirred vigorously for 48 hr. The precipitated sodium chloride, 0.80 g. (90%), was filtered and the filtrate poured into 200 ml. of cold water. The ethanol-water solution was extracted with the 200-ml. portions of ether; the ethereal extract was washed with two 50-ml. portions of cold, 10% sodium hydroxide solution, and dried over magnesium sulfate. The filtered, dried solution was distilled to give 3.1 g. (84%) of the aldehyde XIV; n_D^{20} 1.5803, b.p. 130° (0.15 mm.).

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.76; H, 9.68.

The aldehyde XIV showed a strong carbonyl band at 5.92 μ in the infrared, characteristic of aromatic aldehydes in the condensed phase.[28] The aldehyde gave a negative Beilstein test for chlorine[29] and a positive Tollens test[30] for the aldehyde group. The *2,4-dinitrophenylhydrazone derivative* of the aldehyde XIV was prepared and had m.p. 202–203° after four recrystallizations from ethanol-water.

Anal. Calcd. for $C_{23}H_{28}N_4O_4$: C, 65.07; 6.65; N, 13.20. Found: C, 65.16; H, 6.39; N, 13.47.

An alternate route to the aldehyde XIV based on the procedure given in *Organic Syntheses* for the preparation of naphthalene-1-carboxaldehyde was examined and was found to be inferior to the Hass and Bender method. At best the aldehyde XIV could be obtained in only about 20% yield by the alternate route.

[10]Paracyclophane-12-carboxylic acid (VI). A solution of 2.2 g. (0.0090 mole) of the aldehyde XIV in 25 ml. of acetone (which previously had been refluxed and distilled from potassium permanganate) was treated with 0.25 g. (0.0016 mole) of powdered potassium permanganate. This mixture was stirred at 35° until the purple permanganate color had disappeared. The mixture was filtered and the acetone filtrate set aside. The manganese dioxide filter cake was stirred with 35 ml. of water and filtered. This aqueous filtrate, basic to litmus, was acidified with concentrated hydrochloric acid and the precipitated white solid filtered. The foregoing treatment of the manganese dioxide was repeated until aqueous filtrates no longer gave a precipitate when acidified; the filter cake was then discarded. The original acetone filtrate was stirred with another 0.25-g. portion of powdered potassium permanganate and the above isolation repeated. Finally, the acetone filtrate was treated with additional 0.25-g. portions of permanganate until the purple color persisted for several hours. The filtrate was then discarded. The several crops of precipitated organic acid were combined, dried *in vacuo* at 50° and recrystallized several times from ethanol-water to give 1.05 g. (45%) of the acid VI; m.p. 192–193°.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.56; H, 9.12.

Oxidation of the acid VI with sodium dichromate–sulfuric acid[28] gave a tan solid which showed m.p. 215–218° dec. This solid was identical with a sample of authentic trimellitic acid.

(28) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1956, pp. 223–224.

(29) F. Feigl, *Spot Tests in Organic Analysis*, 5th ed., Elsevier Publishing Co., Amsterdam, 1956, p. 80.

(30) Ref. 25, p. 162.

Decarboxylation of the acid VI. The quinoline-cupric carbonate decarboxylation method of Herschberg and Fieser[31] was used successfully in this experiment. A mixture of 15 ml. of redistilled quinoline, 0.0509 of the acid VI, and 0.015 g. of basic cupric carbonate was refluxed at 230–240° for 90 min. The cooled mixture was poured into 75 ml. of 10% hydrochloric acid and the solution extracted with two 100-ml. portions of petroleum ether (b.p. 30–60°). The petroleum ether was washed with 5% hydrochloric acid until the odor of quinoline could no longer be detected. The solution was then dried, evaporated to *ca.* 10 ml., and chromatographed twice on alumina. With petroleum ether (b.p. 30–60°) as an eluant there was obtained *ca.* 40 mg. of a colorless liquid whose infrared spectrum was identical with that of [10]-paracyclophane. Dichromic acid oxidation of this liquid gave a white solid which failed to melt up to 350°. Reaction of this high-melting solid with an ethereal solution of diazomethane[27] gave, after the usual work-up, fine white needles, m.p. 140–141°, identical with authentic dimethyl terephthalate.

Succinoylation of [10]paracyclophane. 12-ω-Carboxypropionyl [10-m]cyclophane (XV). To a mixture of 5 g. (0.023 mole) of [10]-paracyclophane, 2.32 g. (0.023 mole) of succinic anhydride,[32] and 15 ml. of redistilled *s*-tetrachloroethane which had been stirred for 5 min. there was added, with stirring, 6.94 g. (0.052 mole) of anhydrous aluminum chloride over a period of 1–2 hr. Stirring was continued for 12 hr. and the mixture was then allowed to stand for another 12 hr. After the reaction mixture had been quenched with ice and hydrochloric acid, it was steam distilled to remove all *s*-tetrachloroethane. The distilland was extracted with ether and the ether extracts treated with excess 10% aqueous sodium hydroxide. The sodium salt of the acid which precipitated, was washed with ether and water and added to dilute hydrochloric acid. This acid mixture was stirred and heated for 0.5–1 hr. and then filtered to give 5.8 g. of crude keto acid XV which had m.p. 122.5–124.5°. After two recrystallizations from 95% ethanol the pure keto acid XV was obtained, m.p. 132.5–133°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; neut. equiv., 316.4. Found: C, 76.07; H, 8.88; neut. equiv., 316.6.

Aqueous alkaline permanganate oxidation of the keto acid XV (0.5 g.) produced 0.25 g. of trimellitic acid, m.p. 215° dec.

[10-m]Cyclophane (XVI). A solution of sodium hypochlorite was prepared by bubbling 1.54 g. of chlorine into a solution of 2.1 g. of sodium hydroxide in 30 ml. of water cooled with an ice salt bath. The keto acid XV (1 g.) was added to this solution with stirring and the mixture heated to 60° for 10 min. As not all of the acid was in solution, 5 ml. of dioxane was added and the mixture stirred vigorously at 60° for 1.5 hr. Sodium bisulfite solution was added dropwise to the cooled reaction mixture until excess hypohalite was destroyed, as indicated by starch-iodine paper. The usual work-up gave a crude solid acid which had m.p. 105–120° and gave a positive Beilstein test for halogen. This crude acid was treated with acetic acid and zinc dust at reflux temperature for 3 hr. The mixture was cooled, filtered, and extracted with ether. Acidification of the sodium hydroxide extract of the ether solution gave a gummy solid acid which, after one crystallization from ethanol, had m.p. 118–124° and showed a single band in the carbonyl region of the infrared at 5.92 μ. This sample of [10-m]cyclophane-12-carboxylic acid, 0.5 g., was not purified but used directly in the decarboxylation step.

Decarboxylation of this impure acid was carried out as described in a preceding section. From 0.48 g. of acid there was obtained, after the usual work-up and final purification by chromatography on silica gel, 0.25 g. of colorless liquid hydrocarbon XVI which showed $n_D^{25.5}$ 1.5287 and infrared absorption at 3.31, 6.22, 6.29, and 6.72 μ.

Anal. Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.80; H, 11.20.

Dichromic acid oxidation of the hydrocarbon XVI gave an acid which showed m.p. 345° dec. Its melting point was undepressed upon admixture with an authentic sample of isophthalic acid.

Resolution of the acid VI. A mixture of 0.2500 g. (0.00096 mole) of the acid VI and 0.2826 g. (0.0096 mole) of cinchonidine (Merck) in 30 ml. of acetone was warmed until solution was complete. The warm solution was filtered and reduced in volume to 15 ml. After standing at room temperature for 84 hr., 0.069 g. of a white solid, m.p. 147–151°, was filtered. The filtrate was reduced in volume to 5 ml. and, after standing at room temperature for 24 hr., 0.080 g. of a solid, m.p. 143–147°, was filtered. The two crops of solids were combined and after three recrystallizations from acetone showed constant m.p. 154–155° and unchanged optical rotation, $[\alpha]_D^{27}$ +22 ± 2° (*c* = 10 in chloroform).

Anal. Calcd. for $C_{36}H_{46}N_2O_3$: C, 77.93; H, 8.36; N, 5.06. Found: C, 78.15; H, 8.20; N, 5.03.

This solid salt was dissolved in 2 ml. of chloroform and 15 ml. of 5% hydrochloric acid added with vigorous shaking. The layers were separated and the chloroform solution dried with magnesium sulfate. The dried solution was evaporated at room temperature under a stream of nitrogen to give a white solid, m.p. 152–165°. After two recrystallizations from ethanol-water this solid gave (+) VI as fine white needles; m.p. 160–161°, $[\alpha]_D^{24}$ + 80.5 ± 2° (*c* = 0.77 in chloroform). Further crystallization did not change either the melting point or the optical rotation. The infrared spectrum of this (+) VI was identical with that of (±) VI.

Anal. Found: C, 78.50; H, 9.25.

The original mother liquor and filtrates from the recrystallization of the (+) acid (−) base salt were combined and evaporated to give a glassy residue. This residue was dissolved in 5 ml. of chloroform and treated with 20 ml. of 5% hydrochloric acid (vigorous shaking). From the separated and dried chloroform solution there was obtained a white solid, m.p. 150–188°, after evaporation of the solvent. This solid was dissolved in warm ethanol, water was added to the cloud point, and the solution then allowed to stand at room temperature until cool. The solid which separated was filtered and dried *in vacuo*. It showed m.p. 192–193° and $[\alpha]_D^{28}$ 0° in chloroform. The filtrate was cooled to 0° for 30 min., the crystalline solid filtered and recrystallized twice from ethanol-water. There was thus obtained (−) VI; m.p. 159–160°, $[\alpha]_D^{28}$ −82.3 ± 2° (*c* = 0.96 in chloroform). Another recrystallization of this (−) VI effected no further change in either the melting point or optical rotation. The infrared spectrum of this (−) VI was identical with that of (±) VI.

Anal. Found: C, 78.39; H, 9.31.

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(31) E. B. Herschberg and L. F. Fieser, *J. Am. Chem. Soc.*, **63**, 2561 (1941).

(32) Purified by the procedure given by R. L. Shriner and H. C. Struck, *Org. Syntheses*, Coll. Vol. II, 561 (1943).