[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Macro Rings. XVIII. Restricted Rotation and Transannular Electronic Effects in the Paracyclophanes[1]

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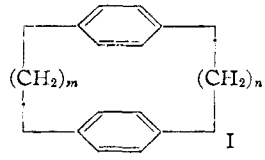
RECEIVED JANUARY 14, 1958

A series of nuclear-substituted derivatives of [3.4]paracyclophane were prepared by either acetylation or nitration reactions. The resulting monoacetyl and mononitro compounds were converted to the carboxylic acid, the acetamido derivative, the amine, the bromide and a number of other substances. The monocarboxylic acid derivative was resolved into its enantiomers, thus demonstrating the presence of restricted rotation of the aromatic rings with respect to one another. Thermal racemization of active acid occurred at 175°. Crude relative rates of acetylation of [2.2]-, [3.4]-, [4.4]- and [6.6]-paracyclophane were determined by competition experiments, and found to differ by the following factors, respectively: >29, 11.2, 1.6 and 1. These results are interpreted in terms of transannular electronic and steric effects.

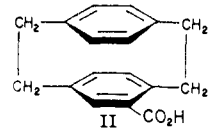
An earlier paper of this series[3] established that while the ultraviolet absorption spectrum of [4.4]-paracylcophane (I, $m = n = 4$) was comparable to that of open chain models, the spectrum of [3.4]paracyclophane (I, $m = 3$, $n = 4$) was abnormal. As the values of m and n were further decreased, the bands associated with the aromatic nuclei moved progressively to longer and longer wave lengths. Thus a point of discontinuity in spectral properties was observed when the shortest distance between the benzene rings passed from 2.84 to 3.73 Å.

Regarding the steric properties of the paracyclophanes, the interesting question arises with respect to the ability of the aromatic nuclei of I to turn over with respect to one another as the values of m and n are varied. Earlier investigations es-

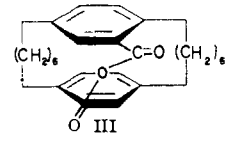


I

tablished that when $m = n = 2$, the rings were prohibited from rotating as shown by the resolvability and optical stability of acid II.[4] Anhydride III, although obtained in an optically active state, gave optically inactive acid when hydrolyzed.[5] As molecular models suggest, the benzene rings in [6.6]paracyclophane appear able to rotate with respect to each other. At some intermediate ring size, some monosubstituted paracyclophane should



II



O III

be resolvable at room temperature or lower, and racemizable at higher temperatures.

The purpose of the present investigation was two-fold: (1) to study transannular electronic effects in electrophilic substitution of the paracyclophanes (I); (2) to study transannular steric effects in the monosubstituted paracyclophanes. The effect of the values of m and n of I on the relative rates of acetylation of I have been employed as a measure of the importance of transannular electronic effects. The resolvability of monosubstituted paracyclophanes was used as a measure of the importance of transannular steric effects.

Synthesis.—Utilizing refined procedures, [3.4]-paracyclophane (IV) was prepared by the method previously reported.[6] Acetylation of this substance gave a 77% yield of monoacetylated and 11% of diacetylated product, both of which appeared to be mixtures of isomers. The monoacetylated cycle was oxidized to the corresponding acid which was resolved through its brucine and strychnine salts, both enantiomers being obtained in an essentially optically pure state. Sharp melting racemic acid was obtained only by mixing these two enantiomers together in equal proportions and crystallizing the mixture. The acid used for the resolution melted over a four degree range, and was probably largely one of the two possible [3.4]-paracyclophanecarboxylic acids contaminated with small amounts of the other. The yield pattern suggests that in the acetylation, one isomer clearly dominated over the other. Although the question of whether the carboxyl group of the resolved acid occupies position 6 or 7 was never settled, structure VI is perhaps the more reasonable of the two (see Discussion). That the optical activity of (−)-VI was associated with molecular asymmetry was demonstrated by decarboxylating VI to give optically inactive IV. This experiment also demonstrates that the [3.4]paracyclophane ring system maintained its integrity during the Friedel-Crafts reaction.

A melting point composition diagram of (+)- and (−)-VI was constructed, and was found to be of the type in which racemic VI formed a molecular compound of higher melting point (185°) than either enantiomer (155°). The diagram possessed eutectics which melted at 151°, and consisted of about 95% of either enantiomer and 5% of racemate.

Hydrocarbon IV was also nitrated to give a mixture of mononitro compound VII and condensation product of a ketone derived from the cycle by oxidation of one of the methylene groups. The position occupied by the nitro group was demonstrated by the reactions formulated to be the

(1) This research was supported in part by a grant from the National Science Foundation, and in part by a grant from the Upjohn Company.

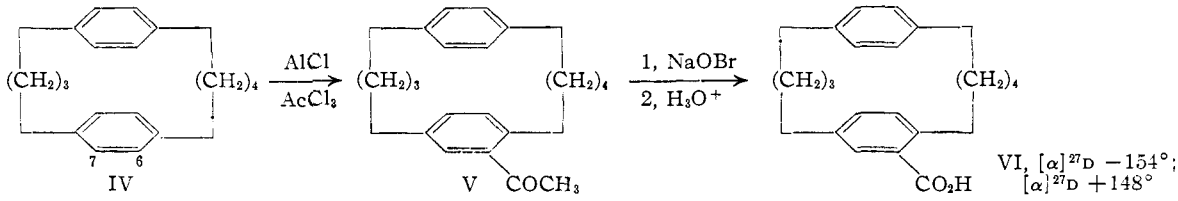
(2) United States Rubber Co. Predoctoral Fellow at U.C.L.A., 1956-1957.

(3) D. J. Cram, N. L. Allinger and H. Steinberg, THIS JOURNAL, **76**, 6132 (1952).

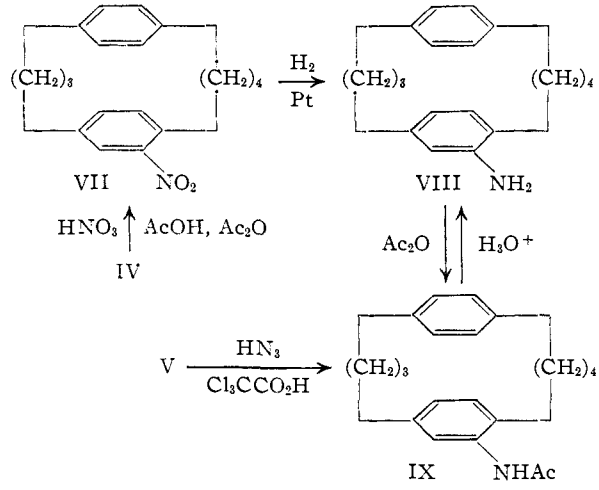
(4) D. J. Cram and N. L. Allinger, *ibid.*, **77**, 6289 (1955).

(5) D. J. Cram and J. Abell, *ibid.*, **77**, 1179 (1955).

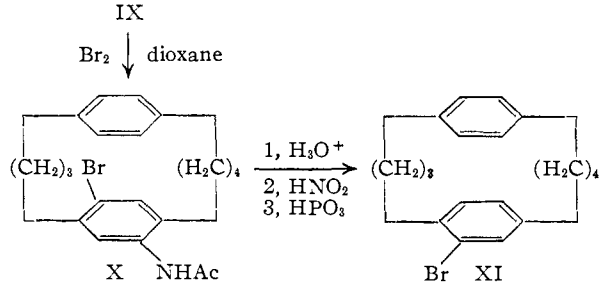
(6) N. L. Allinger and D. J. Cram, *ibid.*, **76**, 2362 (1954).



same as that found in the dominant monoacetyl compound V. Attempts to resolve amine VIII



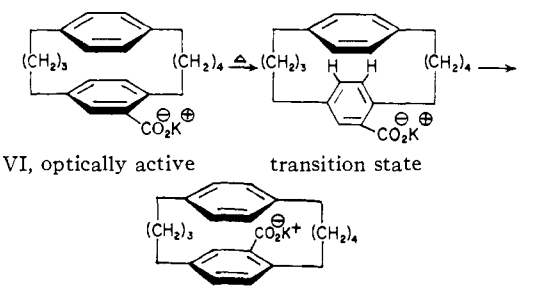
failed due to the non-crystalline character of the salts of this amine with the usual optically active acids. Amide IX was brominated, probably in the 9-position, and the resulting compound X was hydrolyzed and deaminated to give 7-bromo. [3.4]paracyclophane (XI). This structural assignment is of course dependent on that assumed for VI.



Discussion

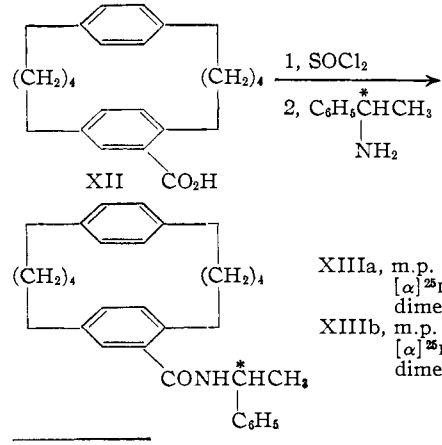
Racemization of Optically Active [3.4]Paracyclophanecarboxylic Acid (VI).—When heated above its melting point (154°), optically active acid VI was found to undergo racemization. A crude estimate of the activation energy for this process was obtained by partially racemizing the acid in a *M* potassium hydroxide solution at 160°, recovering the acid, and measuring the degree of racemization. The racemization rate constant was calculated from one point, and amounted to $k \sim 1.4 \times 10^{-4}$ sec.$^{-1}$, which indicates that $\Delta F \sim -50$ kcal./mole.

This racemization must occur by the benzene ring carrying the carboxyl group turning past the other ring, presumably in that direction which brings the unsubstituted side of the turning benzene through the middle of the cycle. The



geometry of the transition state for this thermal racemization probably involves one of the two benzene rings being perpendicular to the other, as formulated. Some impression of the amount of strain in this transition state can be gained by assuming normal bond lengths and bond angles for this transition state, and calculating the distance of penetration of the normal van der Waals volume of the non-turning benzene by the two hydrogens on the turning benzene. These values turn out to be 1.4 Å. for the hydrogen nearer the 4-membered methylene bridge, and 1.8 Å. for the hydrogen nearer the 3-membered bridge.[7] Similar calculations for the [4.4]paracyclophane provide a value of 1.0 Å. for each hydrogen.

The Question of Whether [4.4]Paracyclophane Carboxylic Acid Is an Asymmetric Molecule.—Since [4.4]paracyclophane is the next higher homolog of the [3.4]-cycle, the interesting question arises as to whether the rotation of the benzene rings is sufficiently restricted in the former (as in the latter) compound as to allow a monosubstituted derivative to exhibit molecular asymmetry. Attempts to resolve acid XII[8] through the crystalline strychnine, cinchonine and cin-



XIIIa, m.p. 119–120°, $[\alpha]^{25}D$ −1.33° (*c* 9 in dimethylformamide)
XIIIb, m.p. 119–120°, $[\alpha]^{25}D$ −1.66° (*c* 5 in dimethylformamide)

(7) In these calculations, the van der Waals thickness of a benzene was assumed to be 3.4 Å., and the van der Waals radius of a hydrogen atom, 0.9 Å.

(8) D. J. Cram and R. W. Kierstead, THIS JOURNAL, **77**, 1186 (1955).

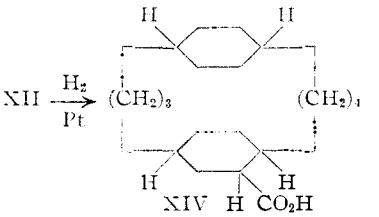
chonidine salts failed to provide optically active acid XII, although the salts after recrystallization appeared to be well defined and homogeneous.

In a second approach to the problem, acid XII was converted to its acid chloride, and in two separate experiments this substance was treated with the two optically pure stereomers of α-phenylethylamine. The total sample of each amide (98% yield) was then recrystallized to give a single sharp-melting compound in each case. That these two amides were enantiomerically and not diastereomerically related was shown by the facts that their melting points were the same, and their optical rotations were of equal magnitude and opposite in sign. When mixed together in equal proportions, the two amides formed a racemic compound with a sharp melting point which was depressed when the substance was mixed with either enantiomer.

This experiment strongly supports the contention that at room temperature, the benzene rings of XII can rotate with respect to one another. Should rotation be restricted, XII would be a racemate, and the amide produced in the two experiments would be mixtures of diastereomers, rather than a single enantiomer. That the two amides were single and enantiomerically related stereomers is indicated by their formation of a racemic compound when mixed. Further support for the above contention is found in work reported previously.[9]

The ability of the benzene rings of XII to rotate at room temperature indicates that the activation energy for racemization of an optically active monosubstituted [4.4]paracyclophane must be not more than 20 kcal. Thus the difference in racemization rates in the [3.4]- and [4.4]-systems must be at least 30 kcal. It is interesting to note that according to the calculation made in the previous section, the difference between the two cycles in distance of penetration of the normal van der Waals volume of the non-turning benzene by the hydrogens of the turning benzene amounts to from 0.4 to 0.8 Å. Thus, should all of the strain of the transition state be concentrated in this type of compression, the cost in activation energy for penetration of about 1.0 Å. is less than 20 kcal., whereas the cost for an additional 0.4 to 0.8 Å. penetration would amount to more than 30 kcal. The actual distance of penetration of van der Waals volumes in the transition state for the racemization of VI must be much lower than the above values. The two benzene rings can become further away from one another by expanding the bond angles between the methylenes of the bridge, by decreasing the bond angles between the aromatic rings and the methylenes, and by bending the non-turning benzene into a shallow tub. All of these means of distributing strain energy are probably utilized.

The Simultaneous and Stereospecific Introduction of Five Asymmetric Centers into an Asymmetric Molecule without Asymmetric Centers.—Optically pure (−)-acid VI when catalytically reduced with hydrogen and platinum gave a fully saturated crystalline acid (84% yield) carrying



five asymmetric centers (XIV). It is highly probable that XIV possesses a structure in which the hydrogens at the points of attachment of the bridges to the cyclohexane rings are *cis* to one another, as well as to the hydrogen attached to the carbon carrying the carboxyl group.[10] The steric situation in XII makes it highly improbable that hydrogen can be added to the inside faces of the benzene rings. The interesting question of whether the cyclohexane rings of XIV can turn over with respect to one another was not settled.

Variation in Rates of Acetylation of the Paracyclophanes as the Distance between the Benzene Rings is Changed.—In a series of competition experiments, the relative rates of monoacetylation of various pairs of paracyclophanes were determined by measuring the relative amounts of each member of the pair that was consumed by a given amount of acetyl chloride–aluminum chloride. The ratio of rates for acetylation of the two hydrocarbons was calculated utilizing equation 1, in which (A_0) and (B_0) are the initial weights of A and

$$\begin{aligned} &A + C \xrightarrow{k_a} \text{products} \\ &B + C \xrightarrow{k_b} \text{products} \end{aligned} \qquad \frac{k_b}{k_a} = \frac{\ln (B_0)/(B)}{\ln (A_0)/(A)} \qquad (1)$$

B while (A) and (B) are the weights of A and B at time t.[11] For optimum accuracy the reactions were interrupted at such a time that (B) was still sufficiently large for accurate measurement. Table I records the results of these experiments along with the estimated error.[12] The reactions

(10) O. Miller, *Bull. soc. chim. Belg.*, **44**, 513 (1935).

(11) T. S. Lee, "Techniques in Organic Chemistry," Vol. VII, Interscience Publishers, Inc., New York, N. Y., 1953, Chapter III.

(12) The authors are indebted to Professor W. G. McMillan for the following derivation of an equation which permits an estimate of these errors in k_b/k_a to be made. In equation 1, w_b, w_{b_0}, w_a and w_{a_0} (weights of hydrocarbons) can be substituted for B, B_0, A and A_0, respectively, to give (2). In a particular competition experiment, there

$$k_b/k_a = \frac{\ln (w_b/w_{b_0})}{\ln (w_a/w_{a_0})} \qquad (2)$$

are two independent variables, w, the total weight of recovered mixture of hydrocarbons and w_a. The third quantity, w_b, is determined by difference, thus

$$w_a = w - w_a \text{ and} \qquad (3)$$

$$k_b/k_a = \frac{\ln [(w - w_a)/w_{b_0}]}{\ln (w_a/w_{a_0})} \qquad (4)$$

The error in k_b/k_a due to w_a is

$$\delta(k_b/k_a)_a = \frac{\delta(k_b/k_a)}{\delta w_a}$$

$$\delta w_a = \frac{-\delta w_a}{\ln_a(w_a/w_{a_0})}\left[\frac{1}{w - w_a} - \frac{-(k_b/k_a)}{w_a}\right] \qquad (5)$$

and the error in k_b/k_a due to w is

$$\delta w_a = \frac{\delta w}{\ln (w_a/w_{a_0})}\left[\frac{1}{w - w_a}\right] \qquad (6)$$

Employing the theorem, if $f(x,y,z)$, then $(\delta f)^2 = (\delta f x)^2 + (\delta f y)^2$

$$[\delta(k_b/k_a)]^2 = \frac{1}{(\ln w_a/w_{a_0})^2}\left[\left(\frac{\delta w}{w - w_a}\right)^2 + (\delta w_a)^2\left(\frac{1}{w - w_a}\right) + \frac{(k_b/k_a)}{w_a}\right]^2$$

(9) D. J. Cram and R. A. Reeves, THIS JOURNAL, **80**, 3094 (1958).

were carried out under non-reversible conditions.

If the rate of acetylation of [6.6]paracyclophane is put equal to unity, the relative rates of the [4.4]-, [3.4]- and [2.2]paracyclophanes become 1.6, 11 and 29, respectively. Clearly as the aromatic rings move closer together, the rates of acetylation increase markedly. A field effect cannot be responsible for these rate differences since it would be expected to operate in the direction opposite to what has been observed. Thus the general "electron-withdrawing" character of the benzene not being substituted might be expected to inhibit the creation of positive charge in the benzene being substituted. As the benzenes were pressed together, this inhibition of rate should become much more pronounced, if only field effects were operating.

TABLE I

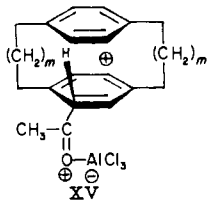
RELATIVE RATES OF ACETYLATION OF THE PARACYCLOPHANES

Competitors (paracyclophanes) B	A	Rate ratio k_b/k_a	Estimated error
[4.4]	*vs.* [6.6]	1.6	±0.37[a]
[3.4]	*vs.* [4.4]	7.0	± .76
[2.2][b]	*vs.* [3.4]	2.6[b]	± .39
[2.2][b]	*vs.* [4.4]	30.0[b]	....[c]

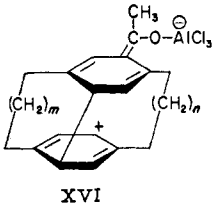
[a] See ref. 11. [b] Since [2.2]paracyclophane is insoluble in the reaction mixture whereas the other cycles were soluble, these values vary somewhat from run to run, and are minimum values since rate of solution might have been limiting. [c] In this experiment the [4.4]paracyclophane was recovered almost quantitatively, and the error could not be estimated. Details of the procedure are found in the Experimental.

If only steric effects controlled the rate pattern, the order would also be expected to be in a direction opposite to that observed. As the two benzene rings are drawn in on one another, in passing to an intermediate such as XV, steric strain should increase, thereby decreasing the rate of substitution.

Earlier papers of this series reported that, unlike the larger paracyclophane (*e.g.*, the [6.6]-cycle), the smaller cycles underwent monoacetylation, but that the rate for introduction of a second acetyl group into the unsubstituted ring occurred at a much lower rate. In other words, an electron-withdrawing substituent in one ring deactivated both rings toward further electrophilic substitution.

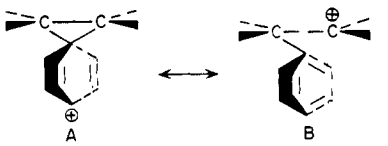


XV



XVI

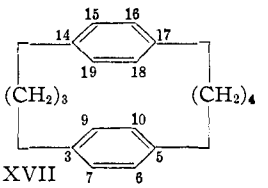
This deactivating effect was explained as being due to transannular resonance in which positive charge of an aluminum chloride-complexed carbonyl group was distributed in both benzene rings of a paracyclophane. This effect should enhance the rate of introduction of the first acetyl group because the greater the delocalization of positive charge, the more stabilized the transition state leading to substituted product. As the two benzene rings are thrust closer together, structures such as XVI might be expected to make greater contributions to the resonance hybrid, and the reaction rate should increase, as has been observed. Some precedent for this type of resonance is found in the phenonium ion,[13] in which structures such as A and B contribute to the resonance hybrid. In a formal sense, in passing from B to A, a π-bond has been converted to a σ-bond. The difference between the phenonium ion and the hybrid of which XVI is a contributor lies in the fact that the π-



A B

orbitals of each benzene ring in XVI ($m = n$) share a common axis of symmetry, whereas in the phenonium ion, the π-orbital of the benzene ring and that of the carbonium ion are almost perpendicular to one another.

The Structure of the Monoacetylated and Mononitrated [3.4]Paracyclophane (Compounds V and VII, Respectively).—In both the acetylation and nitration of [3.4]paracyclophane, one of the two possible position isomers dominated the product. No simple degradative or synthetic scheme which differentiates between the isomers appears to be available. The structures have been assigned as being the 6-derivative on two grounds. (1) The end of the molecule carrying the 4-membered methylene bridge should be less hindered than the end carrying the 3-membered bridge. (2) If structures such as XVI stabilize the transition state for substitution by distributing positive charge in both rings, then the shorter the partial bonds between the two rings, the more stabilized the transition state and the faster the reaction rate. Substitution in the 6-position provides partial bond



XVII

character between the 7–19, the 9–15 and the 5–17 carbons of XVII. Substitution in the 7-position provides partial bond character between the 6–18, 10–16 and 8–14 positions. Of these contributors to the hybrid, those should be the more important which involve shorter bond distances, namely, those in the 8–14, 7–19 and 9–15 positions. Some strain would be involved in the development of a bond in the 8–14 position because of the readjustment of the methylene–benzene bond angles. Thus the hybrid involving partial bond development in the 7–19 and 9–15 positions might be expected to be the more stable, and 6-substituted paracyclophane might dominate the product.

Experimental

[3.4]Paracyclophane (IV).—This compound was prepared as previously reported,[6] with some refinements in the procedure. Acyloin ring closure of 1,3-bis(4-carbomethoxy-

(13) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949).

methylcyclohexyl)-propane was carried out 17 times with an average yield of 15% of crude, distilled acyloin. This material was converted to IV in 10 batches, to give an average yield of 33%, m.p. 116–118°.

6-Acetyl[3.4]paracyclophane (V).—Paracyclophane IV (5.35 g. or 0.0211 mole) was treated with a solution of aluminum chloride (3.65 g. or 0.0274 mole) and acetyl chloride (2.49 g. or 0.0317 mole) in 80 ml. of tetrachloroethylene at room temperature for 1.7 hours with vigorous agitation. The reaction mixture was poured over an ice–hydrochloric acid mixture. The organic phase was removed by steam distillation, and the residue was extracted with ether. The other layer was washed with water, sodium bicarbonate solution, water and then was dried. Evaporation of the solvent under reduced pressure gave a red-brown residue, weighing 5.6 g. This material was chromatographed on 600 g. of activity I (Brockmann) alumina in pentane. The pentane and benzene–ether (49 to 1) eluates contained 0.17 g. (3%) of hydrocarbon; the benzene–ether (1 to 1) contained 4.86 g. (77%) of crude monoacylated cycle; pure ether eluted 0.73 g. (11%) of what is presumed to be mainly bis-acetylated material. A small sample of V was distilled in a molecular still at 150° and at 0.009 mm. for analysis.

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.30; H, 8.27. Found: C, 85.12; H, 8.27.

A small sample of the above ketone was converted by the usual method[14] to its 2,4-dinitrophenylhydrazone derivative, m.p. 199–200°.

Anal. Calcd. for $C_{27}H_{28}N_4O_4$: C, 68.63; H, 5.97. Found: C, 68.37; H, 6.26.

6-Carboxy[3.4]paracyclophane (VI).—To a solution of acetyl compound V (0.22 g. or 0.68 mmole) in 5 ml. of C.P. dioxane was added a solution of 0.63 g. (40 mmoles) of bromine and 0.38 g. (95 mmoles) of sodium hydroxide in 5 ml. of water, both solutions being at 0°. The reaction mixture was shaken vigorously at room temperature for 1.5 hours. Solid sodium bisulfite was then added until the solution became colorless. The solution was then diluted with water, acidified and extracted with chloroform. The extract was dried, the solvent was evaporated under reduced pressure, and the residue was crystallized from acetic acid–ethanol to give material, m.p. 174–181°. This material was sublimed at 170° and 10^{-4} mm. to give sublimate of unchanged melting point. The infrared spectrum exhibited a typical carboxyl absorption at 1688 cm.$^{-1}$, and other absorption bands characteristic of an undimerized aromatic carboxylic acid.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.61; H, 7.54. Found: C, 81.32; H, 7.65.

Resolution of 6-Carboxy[3.4]paracyclophane (V).—A mixture of 1.58 g. (5.36 mmoles) of acid V, 1.09 g. of brucine (2.8 mmoles) and 25 ml. of acetone was heated until solution was complete. The salt that separated at 0° was recrystallized six times from acetone until its melting point no longer changed (m.p. 159–161°). This material (0.26 g.) was shaken with ether and dilute hydrochloric acid, the ether layer was washed with water, dried, and the solvent was evaporated. The residual oil crystallized from ethanol and water to give 0.093 mg. (6%) of long thin needles, m.p. 154–154.9°, $[\alpha]^{27}D$ −154° (*c* 1.3, chloroform).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.61; H, 7.54. Found: C, 81.70; H, 7.46.

The mother liquor from the initial crystallization of the brucine salt was shaken with a mixture of ether and dilute hydrochloric acid, and acid V was recovered and crystallized from an ethanol–acetic acid–water mixture. This material (0.78 g. or 2.61 mmoles) was mixed with 0.502 g. (150 mmoles) of strychnine and heated with a minimum amount of acetone containing 7 ml. of ethanol to effect solution. The salt that separated at 0° was recrystallized four times from ethanol–acetone to constant rotation, $[\alpha]^{27}D$ −2.20° (*c* 0.77, chloroform). The acid was recovered in the usual way, and was crystallized from ethanol–water as long thin needles, m.p. 153.5–154.4°, wt. 0.050 g. (3%), $[\alpha]^{27}D$ +148° (*c* 1.6, chloroform).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.61; H, 7.54. Found: C, 81.73; H, 7.56.

(14) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

A sharp-melting sample of racemic V was prepared by dissolving 6 mg. of each of the above enantiomers in a small amount of ethanol and water. The material that separated possessed a melting point of 183–185°.

Thermal Racemization of 6-Carboxy[3.4]paracyclophane (V).—A sample of 12 mg. of optically active V with $[\alpha]^{27}D$ −154° (*c* 1.3, chloroform) was heated to 175° for one hour, and the product recovered and recrystallized from ethanol–water to give 40% racemized material, $[\alpha]^{25}D$ −91° (*c* 0.17, chloroform). In a second experiment, 31.6 mg. of V with $[\alpha]^{26}D$ −150 (*c* 1.1, chloroform) was heated in 3 ml. of *M* potassium hydroxide solution to 160 ± 1° in a glass ampoule for 4 hours. The recovered crystallized acid gave $[\alpha]^{30}D$ −145° (*c* 1.1, chloroform), or was 4% racemized. The first-order rate constant for the racemization was estimated from this data to be $k \sim 1.4 \times 10^{-4}$ sec.$^{-1}$, and $\Delta F^{\ddagger} \sim 50$ kcal./mole at 433°K.

Decarboxylation of Optically Active 6-Carboxy[3.4]paracyclophane (V).—A mixture of 0.098 g. of 6-carboxy[3.4]-paracyclophane, $[\alpha]^{25}D$ −146° (*c* 1.3, chloroform), 0.10 g. of copper powder and 2 ml. of C.P. quinoline was heated to 215° for 1.5 hours. The mixture was cooled, diluted with 10 ml. of pentane, and the mixture was filtered. The filtrate was extracted with a dilute solution of sodium hydroxide, water and was dried. This solution was adsorbed on a column of 20 g. of basic alumina. Elution of the column with pentane gave 20 mg. (24%) of [3.4]paracyclophane, m.p. 116–117.5°, undepressed by admixture with authentic material, $[\alpha]^{25}D$ 0.00° (*c* 1, chloroform).

6-Acetamido[3.4]paracyclophane (IX) from 6-Acetyl[3.4]-paracyclophane (V).—To 14 g. of trichloroacetic acid containing 1.4 g. of sulfuric acid at 60° was added 1.5 g. (5.1 mmoles) of 6-acetyl[3.4]paracyclophane. The solution became brown immediately. Over a period of 30 minutes, 0.503 g. (8.2 mmoles) of sodium azide was added. The mixture was heated for an additional 1.5 hours, during which time a green color developed. The reaction mixture was then cooled, diluted with water and extracted with ether. The extract was washed with water, saturated sodium bicarbonate solution, water and was then dried. The solvent was evaporated under reduced pressure, and the residue crystallized from methyl ethyl ketone, wt. 0.68 g. (44%), m.p. 185–187°. Recrystallization of the substance from the same solvent gave white bars, m.p. 189.5–190.8°.

Anal. Calcd. for $C_{21}H_{25}ON$: C, 82.01; H, 8.19. Found: C, 82.00; H, 8.30.

6-Amino[3.4]paracyclophane (VIII) from 6-Acetamido-[3.4]paracyclophane (IX).—A solution of 0.30 g. of amide VIII in 10 ml. of concentrated hydrochloric acid and 10 ml. of 95% ethanol was heated at reflux for 8 hours. The alcohol was evaporated, and the resulting solution was neutralized with sodium carbonate. The organic material was extracted into ether, and the extract was washed with water, sodium bicarbonate solution, water, and was dried. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to give 0.22 g. of a pink powder, m.p. 104–110°. This amine (VIII) was recrystallized (charcoal treatment) from ethanol to give pink plates, m.p. 110.5–111.5°. Attempts to resolve this amine with *d*-camphor-10-sulfonic acid failed.

Anal. Calcd. for $C_{19}H_{23}N$: C, 85.99; H, 8.73. Found: C, 86.00; H, 8.71.

6-Nitro[3.4]paracyclophane (VII).—To a stirred, cold (0°) suspension of 1.0 g. (4.0 mmoles) of [3.4]paracyclophane in a mixture of 25 ml. of glacial acetic acid and 20 ml. of acetic anhydride was added dropwise 0.2 ml. (10 mmoles) of C.P. 100% nitric acid (density 1.52) in 5 ml. of acetic anhydride. The mixture was stirred for three hours after which time it became homogeneous. The excess anhydride was decomposed with ice and water, and the resulting mixture was extracted with ether, and the ether extract was washed with water, with dilute sodium carbonate solution, and again with water. The solution was dried, evaporated, and the residue was dissolved in 20 ml. of 10% ether–pentane. This solution was chromatographed on a column of neutral activity II alumina (60 g.) made up in pentane. Pentane was used to wash a few mg. of starting material from the column. The nitro compound VII was eluted with 5% ether–pentane. Crystallization of this material from methanol–water gave 0.35 g. (30%) of light yellow crystals, m.p. 76.5–79.5°.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17. Found: C, 77.41; H, 7.36.

6-Amino[3.4]paracyclophane (VIII) from 6-Nitro[3.4]-paracyclophane (XII).—A mixture of 10 mg. of prereduced platinum oxide, 10 ml. of 95% ethanol and 23 mg. (0.077 mmole) of nitro compound VII was stirred under an atmosphere of hydrogen until 11 ml. was absorbed. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the resulting solid was recrystallized from ethanol–water to give 9 mg. of product, m.p. 114–117°, undepressed by admixture with amine VIII prepared from amide IX. This amine was acetylated with acetic anhydride and pyridine in the usual way to give acetamido compound IX, m.p. 188–192°, undepressed by admixture with an authentic sample.

6-Acetamido-9-bromo[3.4]paracyclophane (X).—Amide IX (0.210 g. or 0.72 mmole) was suspended in 20 ml. of purified dioxane at room temperature, and to this stirred mixture was added bromine until the solution became distinctly orange. After 10 minutes, water was added, and the precipitate that separated was collected and washed with water, dilute sodium hydroxide and with water. This material was recrystallized from ethanol–water to give stubby colorless needles, wt. 0.135 g. (47%), m.p. 226–230° dec. The infrared spectrum exhibited strong bands at 857 and 877 $cm.^{-1}$, which are characteristic of two adjacent and one isolated hydrogen on a benzene ring.

Anal. Calcd. for $C_{21}H_{24}NOBr$: C, 65.29; H, 6.41. Found: C, 65.36; H, 6.23.

7-Bromo[3.4]paracyclophane (XI).—A mixture of 0.13 g. (0.337 mmole) of bromoamide XI, 10 ml. of ethanol and 2 ml. of 6 *N* hydrochloric acid was heated at reflux for 4 hours. The ethanol was evaporated, 5 ml. of water was added and the mixture was cooled to 0°. A solution of 24 mg. of sodium nitrite in 1 ml. of water was added followed by 5 ml. of glacial acetic acid. The mixture was shaken for 10 minutes at 0°, and 2 ml. of 50% hypophosphorous acid was added keeping the mixture at 0°. The resulting mixture was stirred at 0° for 72 hours, filtered, and the crude product was recrystallized from ethanol (charcoal treatment) to give large shiny plates (45 mg.), m.p. 155.8–156.8°.

Anal. Calcd. for $C_{19}H_{21}Br$: C, 69.30; H, 6.43. Found: C, 69.15; H, 6.68.

(−)-Perhydro-6-carboxy[3.4]paracyclophane (XIV).—To a suspension of 30 mg. of prereduced platinum oxide in 10 ml. of glacial acetic acid was added 32 mg. (0.109 mmole) of (−)-6-carboxy[3.4]paracyclophane ($[\alpha]^{27}D$ −146°, *c* 1, chloroform) dissolved in 10 ml. of glacial acetic acid. The mixture was stirred in an atmosphere of hydrogen for 10 hours during which time 6 moles of hydrogen was absorbed. The solution was filtered, and the solvent was evaporated under reduced pressure. The colorless oily residue was dissolved in ethanol and crystallized by the addition of water to give 18 mg. (54%) of long colorless needles, m.p. 144.5–145°, $[\alpha]^{25}D$ −24.0° (*c* 0.14, chloroform). The infrared spectrum carried a carboxyl band at 1693 $cm.^{-1}$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.50; H, 11.33.

(−)-N-α-Phenylethyl-6-formamido[4.4]paracyclophane (XIIIa).—A mixture of 6-carboxy[4.4]paracyclophane (160 mg.) and 5 ml. of thionyl chloride was refluxed for 30 minutes, and the excess thionyl chloride was evaporated under reduced pressure. The brown residue was dissolved in 2 ml. of dry ether, and to this was added dropwise 314 mg. of optically pure (+)-α-phenylethylamine dissolved in ether. The resulting mixture was shaken for one hour, and then shaken with a mixture of ether and dilute hydrochloric acid. The ether layer was washed with dilute sodium hydroxide, with water, and was dried. The ether was evaporated to give 209 mg. (98%) of amide XIIIa, m.p. 115–120°. One crystallization of this material from aqueous methanol gave 172 mg. of needles of XIIIa, m.p. 119–120°, $[\alpha]^{25}D$ −1.33° (*c* 9, dimethylformamide).

Anal. Calcd. for $C_{29}H_{33}ON$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.78; H, 8.17; N, 3.54.

(+)-N-α-Phenylethyl-6-formamido[4.4]paracyclophane (XIIIb).—An identical procedure was used to prepare this isomer. From 160 mg. of acid was obtained 210 mg. (98%) of amide, m.p. 117–120°. One recrystallization of this material from aqueous methanol gave 175 mg. of amide as needles, m.p. 119–220°, $[\alpha]^{25}D$ +1.66° (*c* 5, dimethylformamide). Mixed melting point determinations made on these two amides gave the following results: 90% (+)-amide, 10% (−)-amide, m.p. 117–127°; 50% (+)-amide, 50% (−)-amide, m.p. 152–152.5°; 10% (+)-amide, 90% (−)-amide, m.p. 117–130°.

Anal. Calcd. for $C_{29}H_{30}ON$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.70; H, 8.00; N, 3.60.

Homocompetitive Rates. General Procedure.—A solution of one mole of aluminum chloride and 1.1 moles of acetyl chloride was prepared in the proper solvent in a flask protected by a drying tube, and the mixture was agitated by means of a magnetic stirrer. A mixture of 2 moles (combined) of the hydrocarbons was introduced in the solid state or in a small quantity of solvent. The reactions were carried out under the conditions of time, temperature and solvent required for the synthetic acetylation of the more sensitive of the two paracyclophanes in question. The reaction mixture was poured onto ice and hydrochloric acid, and a second solvent was added (either ether or chloroform). The aqueous layer was thoroughly extracted, and the organic layer was washed with water, sodium carbonate solution, water and was dried. The solvent was evaporated under reduced pressure. The residue was dissolved in either pentane or a minimum amount of chloroform, depending on the solubility of the hydrocarbons in question. This solution was chromatographed on a column of basic alumina, activity II, made up in pentane (the weight of alumina was always greater than 100 times the combined weights of the hydrocarbons originally involved). The unreacted hydrocarbons were totally eluted with pentane, weighed and submitted to the analytical procedure designed for that specific system. The data are summarized in Table II. The high yields of monoacetylated material obtained in these reactions (75–90%) indicate that the rate of disappearance of starting material is roughly the same as the rate of acetylation.

Details Regarding Particular Rate Compositions.—In the run involving the [6.6]- and [4.4]paracyclophanes as starting materials, a control was run on the loss due to the isolation procedure. A mixture of 10.9 mg. of [6.6]- and 11.0 mg. of [4.4]-cycle was dissolved in a minimum amount of pentane and adsorbed on a column of 25 g. of neutral activity I alumina made up in pentane. The column was eluted with pentane in 10-ml. fractions. Only fractions 4–7 contained paracyclophane, wt. 20.5 mg. No fractionation of the two components was evident from the elution pattern.

Analysis of the two component reaction mixture was carried out with infrared technique, making use of the bond at 864 $cm.^{-1}$ for the [6.6]-compound and at 819 $cm.^{-1}$ for the [4.4]-compound. Analyses were made in chloroform as solvent in a sodium chloride cell (0.115 mm. thick). Known mixtures were first run, and the composition of the unknown mixture was determined graphically. In calculating k_b/k_a and $\delta(k_b/k_a)$, an error of 5% was assumed for the total weight of hydrocarbon lost in the reaction work up, as was indicated by the control. A maximum error of 3% was assumed in the infrared analysis.

In the competition experiment involving the [4.4]- and [3.4]-cycles, the analysis of the recovered hydrocarbons was performed utilizing the strong absorption band in the infrared at 855 $cm.^{-1}$ exhibited by [3.4]paracyclophane, and not by [4.4]paracyclophane. The analysis was performed by comparing absorption intensities of known mixtures of hydrocarbons with the unknown, chloroform solutions in a sodium cell 0.115 mm. thick. In calculating rate ratios, again a 5% loss of hydrocarbons during isolation was assumed; a maximum infrared error of 3% was assumed.

In the experiment with [3.4]- and [2.2]paracyclophanes as starting material, the reaction mixture (*ca.* 0.5 g.) was chromatographed on a column of 70 g. of basic alumina (activity I), and the hydrocarbons were eluted with pentane in 400-ml. cuts. Fractions 1 and 2 contained 0.154 g. of [3.4]paracyclophane, m.p. 117°. Fractions 3–8 contained 0.1528 g. of material which was mainly [2.2]paracyclophane. These latter fractions were combined and mixed with 10 ml. of boiling ethanol. Filtration of this mixture gave 0.111 g. of [2.2]paracyclophane, m.p. 284–286°. In calculating k_b/k_a and $\delta(k_b/k_a)$, a 5% error in separation of the two hydrocarbons and a 5% error in obtaining all of the unreacted hydrocarbon was assumed.

In the experiment with [4.4]- and [2.2]paracyclophane

TABLE II

HOMOCOMPETITIVE RATE DATA

Paracyclophanes	Weight in mg. A_0[a]	A[a]	B_0[a]	B[a]	Solvent	T, °C.	Time, hr.	k_b/k_a[a]	$\delta(k_b/k_a)$[b]
[6.6] and [4.4]	800	392	1320	408	CS_2	25	1.5	1.6	±0.37
[4.4] and [3.4]	161	136	216	69	CS_2	25	1.0	7.0	± .76
[3.4] and [2.2]	242	194	198	111	$C_2H_2Cl_4$	−20	0.5	2.6	± .39
[4.4] and [2.2]	1003	1000	823	212	$C_2H_2Cl_4$	−20	0.5	100	....

[a] Defined in equation 1. [b] Defined in equation 5.

the procedure employed was identical to that employed with the [3.4]- and [2.2]-cycles. The [4.4]-cycle was recovered almost quantitatively. An assumed 5% error in isolation of hydrocarbon and 5% in analysis requires $\delta(k_b/k_a)$ to be larger than k_b/k_a. Therefore this experiment serves only for qualitative purposes.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Seven-membered Heterocyclic Systems. I. The Synthesis of 2,3,6,7-Tetrahydroöxepine

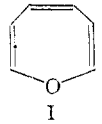
BY JERROLD MEINWALD AND HITOSI NOZAKI[1]

RECEIVED JANUARY 22, 1958

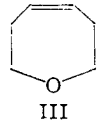
A seven-step synthesis of 2,3,6,7-tetrahydroöxepine (III) starting from 3-butyn-1-ol (IV) is described. The cyclization of *cis*-6-iodo-3-hexen-1-ol (X), brought about by the use of silver oxide in ether, gives III in *ca.* 25% yield, accompanied by some elimination product, *cis*-3,5-hexadien-1-ol (XI). Attempts to prepare oxepine itself by more direct routes are described briefly.

Introduction.—Interest in the chemistry of seven-membered ring compounds has grown apace in recent times. The principal recent advances have been confined largely to the field of carbocyclic compounds related to tropolones or azulenes. The simple heterocyclic compounds, such as oxepine (I), would also be of considerable theoretical interest, however, since they bear the same electronic relationship to cycloöctatetraene as furan and pyrrole do to benzene. This comparison is especially intriguing, since models reveal that the seven-membered heterocycles, in contrast to cycloöctatetraene, can attain planarity with a relatively small amount of steric strain.

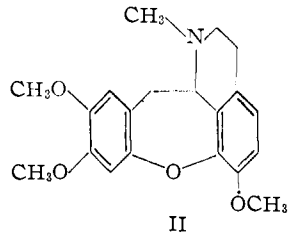
Several groups of workers are actively pursuing the chemistry of the benzo-derivatives of seven-membered heterocycles.[2] This work has been motivated in part by the discovery that the alkaloid cularine (II) has a dibenzdihydroöxepine skeleton.[3] In spite of this activity, the synthesis of oxepine, or of the other parent systems (with nitrogen or sulfur as the heteroatom) has yet to be achieved. It is the purpose of this paper to describe the synthesis of a promising intermediate, 2,3,6,7-tetrahydroöxepine (III), as well as to outline several attempts to prepare oxepine itself *via* more direct routes.[3a]



I

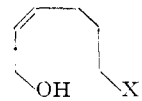


III

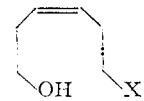


II

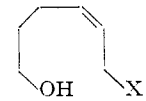
Synthesis of 2,3,6,7-Tetrahydroöxepine (III).—The successful synthesis of III was carried out in a series of seven steps starting from commercially available 3-butyn-1-ol. The over-all scheme is summarized in Chart I. The general idea for this reaction sequence stemmed from the hope that an intramolecular nucleophilic substitution could be encouraged to lead to a seven-membered ring by the inclusion of a *cis*-double bond in a suitable 1,6-disubstituted hexane derivative. This idea led to the consideration of three potential types of intermediate, shown as A, B and C. Of these possibilities, B seemed preferable to the others since in it neither the –OH nor the –X group is allylic. It was therefore decided to utilize a compound of type B as the immediate precursor of the seven-membered heterocyclic system.



A



B



C

3-Butyn-1-ol (IV) was converted into its tetrahydropyranyl ether V and alkylated to give VI, using ethylene oxide and lithium amide in liquid ammonia, as previously described.[4] Partial catalytic

(1) On leave from the Department of Industrial Chemistry, Kyôto University, Kyôto, Japan.

(2) See, for example, J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 4174 (1957); J. D. Louden and L. A. Summers, *ibid.*, 3809 (1957); K. Dimroth and H. Freyschlag, *Chem. Ber.*, **90**, 1628 (1957).

(3) R. H. F. Manske, THIS JOURNAL, **72**, 55 (1950).

(3a) NOTE ADDED IN PROOF.—Since the submission of this manuscript, some valuable, unpublished work of H. J. Dauben, Jr., and S. B. Maerov in the field of seven-membered heterocyclic compounds has come to our attention (S. B. Maerov, Doctoral Thesis, University of Washington, 1954). These authors have prepared a tetrahydroöxepine (or mixture of isomeric tetrahydroöxepines) by the acid-catalyzed dehydration of oxepin-4-ol. However, neither the homogeneity of this product nor the double bond position(s) appear to have been established.

(4) R. A. Raphael and C. M. Roxburgh, *J. Chem. Soc.*, 3875 (1952).