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THE OVERLAP OF TWO ALLYL RADICALS OR A FOUR-CENTERED TRANSITION STATE IN THE COPE REARRANGEMENT[1]

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Abstract—From the fact that *meso*-3,4-dimethylhexa-1,5-diene rearranges to *cis*, *trans*-octa-2,6-diene and that *rac*-3,4-dimethylhexa-1,5-diene rearranges to a mixture of *trans*, *trans*-octa-2,6-diene (90%) and *cis*, *cis*-octa-2,6-diene (9%), it is concluded that the four-centered, chair-like transition state is favored in the Cope rearrangement over the six-centered, boat-like structure.

"No-mechanism" is the designation given, half in jest, half in desperation, to "thermo-reorganization" reactions like the Diels-Alder and the Claisen and Cope rearrangements in which modern, mechanistic scrutiny discloses insensitivity to catalysis, little response to changes in medium and no involvement of common intermediates, such as carbanions, free radicals, carbonium ions and carbenes. Theoretical study of such thermally induced, usually cyclic reorganization reactions is concerned with transition states and their energies. The meaningful questions relate to the existence and structure of unstable intermediates, to the description of transition states (the favored one as well as real or reasonable alternatives), and to factors affecting the free energies of the relevant transition states. Although estimation and calculation of the free energies of activation is the most important aim of every mechanistic study, nowhere does this ultimate problem confront one more sharply than in the "thermo-reorganization" reactions.

One of the more general questions concerns the geometry, the electronic nature and the strength of the interaction of two allyl radicals. The question arises in the Claisen and Cope rearrangements, both of which are cyclic, intramolecular reactions of the purely thermally induced type. In the Claisen rearrangement the question is whether a transition state involving six-atom overlap is more or less favorable than a transition state involving four-atom overlap. In the former arrangement the three-carbon, allylic system lies atom-for-atom above the three-atom system of oxygen and the two ring atoms C_1 and C_2 whereas in the four-atom arrangement only two atoms (1′ and 3′) of the allylic system lie above oxygen and atom 2 of the ring, leaving the central atom (2′) of the allylic system and C_1 of the benzene ring separated.[3] In the Cope rearrangement,

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[1] A preliminary announcement of this work was submitted to Angewandte Chemie on 21 February 1961. We were then informed of the editorial policy that "wir rein theoretische Deutungen von Mechanismen nicht bringen. Wir tun es grundsätzlich nicht."

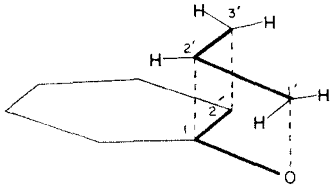
[2] We wish to express our deep appreciation to the Aaron E. Norman Fund, Inc., for the award of the 1960 Hickrill Chemical Research Foundation Postdoctoral Fellowship in Organic Chemistry.

[3] Although the question is not phrased explicitly in reviews of the Claisen rearrangement [(D. S. Tarbell, *Organic Reactions* 2, 1 (1944); C. K. Ingold, *Structure and Mechanism in Organic Chemistry* pp. 598, 619. Cornell Univ., New York (1954); J. Hine, *Physical Organic Chemistry* pp. 455–457. McGraw-Hill, New York (1956)], it has been widely recognized for many years, even though the first published expressions are recent.[4] (B. E. Norcross and W. N. White, *Abstracts of Papers* pp. 15–20. Meeting of Amer. Chem. Soc. Cleveland. 4–10, April (1960); S. J. Rhoads in P. de Mayo (Editor), *Rearrangements in Organic Compounds* Interscience, New York, in press.)

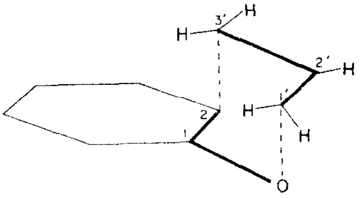
[4] E. N. Marvell and J. L. Stephenson, *J. Org. Chem.* **25**, 676 (1960).

the question is whether the six-atom arrangement of two parallel allylic groups (boat- or roof-like) is of lower or higher free energy than the four-atom arrangement in which only the ends of the allylic system interact (chair-like).

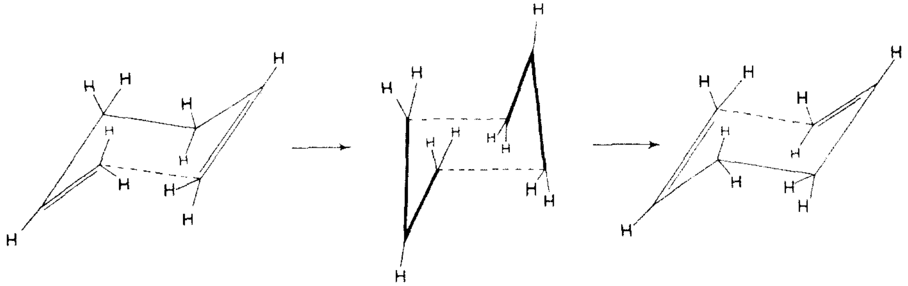
Six-center overlap



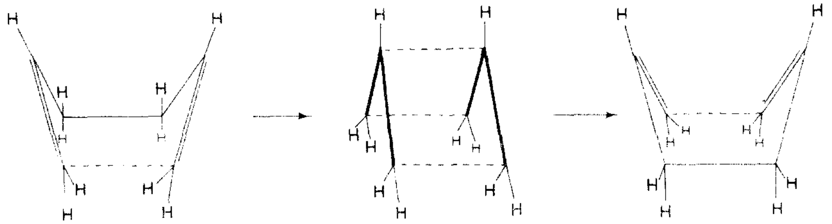
Four-center overlap



Four-center overlap ; chair-like



Six-center overlap ; roof-like



The question cannot be resolved easily in the Claisen rearrangement. Alexander and Kliuber[5] had attempted in vain to solve it by observing the fate of optical activity in the rearrangement of methyl propenyl carbinyl phenyl ether. Later it was hoped to extract a more positive conclusion by examining the fate of geometrical isomerism in the same example. But as pointed out so clearly by Marvell and Stephenson,[4] configuration about the asymmetric carbon atoms and geometrical isomerism are not independent variables provided the reaction is truly intramolecular. The problem is therefore not solvable in the completed Claisen rearrangement; that is, when the phenol is

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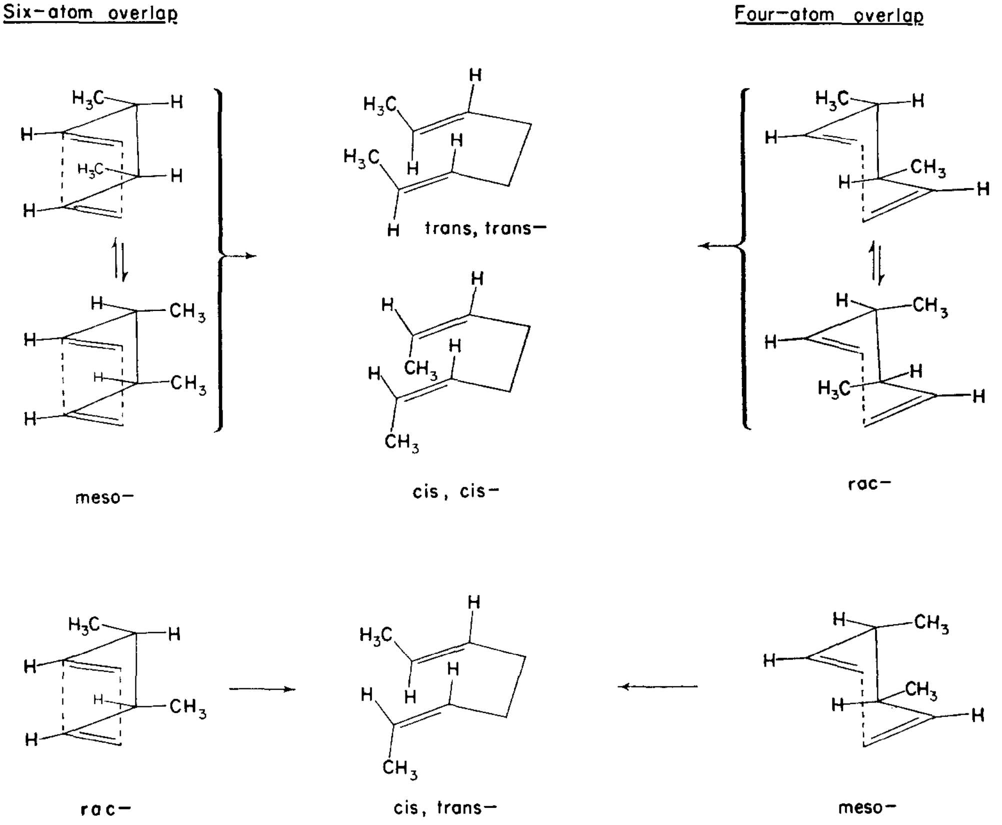
[5] E. R. Alexander and R. W. Kliuber, *J. Amer. Chem. Soc.* 73, 4304 (1951).

the product under scrutiny. It is theoretically interesting that the temporary asymmetric center generated at the ortho position of the phenyl ring in the dienone intermediate provides the additional independent piece of information needed to solve the problem. However, the establishment of the configurational relationship of the original center in the allyl group and the new center in the dienone (knowing the geometrical configuration of the double bond as well) by purely chemical means seems preposterously difficult. By contrast, solution through the application of X-ray crystallography is easily conceivable.

A specific answer to the general question may be obtained by examination of the behavior of *meso*- and *rac*-3,4-dimethylhexa-1,5-diene in the Cope rearrangement. If a transition state of six overlapping atoms is involved, the *meso*-isomer will give *trans*, *trans*-octa-2,6-diene and/or *cis*, *cis*-octa-2,6-diene and the *rac*-isomer will give *cis*, *trans*-octa-2,6-diene. If the overlap of four atoms is preferred in the transition state, the outcome will be the reverse. The *rac*-isomer will give a mixture of *trans*, *trans*- and *cis*, *cis*-, while the *meso*-isomer will give *cis*, *trans*-octa-2,6-diene.



The starting materials: meso- *and* rac-3,4-*dimethylhexa*-1,5-*dienes*

A mixture of the stereoisomeric 3,4-dimethylhexa-1,5-dienes is obtained as a minor product of treating crotyl or methyl vinyl carbinyl halides with magnesium or preformed Grignard reagent.[6,7,8] Following the procedure of Lespieau and Heitzmann,[6] a crude product is obtained which is found on gas-liquid-partition-chromatographic (g.l.p.c.) analysis to consist of 5–6 per cent of 3,4-dimethylhexa-1,5-dienes, 75 per cent 3-methylhepta-1,5-dienes and 20 per cent octa-2,6-dienes. A fraction enriched to 60–70 per cent of 3,4-dimethylhexa-1,5-dienes by two fractional distillations affords pure material when separated by g.l.p.c. on a silicone column (about 1 ml from 100 g of crotyl bromide).

Although the mixture of *meso-* and *rac*-3,4-dimethylhexa-1,5-diene appears as a single peak on the silicone column, g.l.p.c. on a silver nitrate-glycerin column effects separation of the previously unreported isomers. The *meso*-isomer has the shorter retention time and accounts for 70 per cent of the mixture.

Proof of the structure of the two stereoisomers is effected by ozonization and oxidation to the known 2,3-dimethylsuccinic acids.[9] The isomer with the longer retention time affords the lower melting, *rac*-dimethylsuccinic acid which has been resolved by Werner and Basyrin.[10] The predominating *meso*-isomer gives the higher melting, *meso*-dimethylsuccinic acid.

The products: cis, cis-, cis, trans, *and* trans, trans-*octa*-2,6-*dienes*

Although octa-2,6-diene is described as the second, minor product of the coupling of butenylhalides with magnesium,[6,7] the individual geometrical isomers are not reported. Fractional distillation and g.l.p.c. separation on a silicone column of the previously described reaction mixture affords the octa-2,6-dienes uncontaminated by structural isomers. G.l.p.c. on the silver nitrate-glycerin column separates three fractions, the first and second being about equally large, the third considerably smaller. The first substance has a strong band in the infrared at 10·40 μ and no absorption at 6·1 or 13–14 μ consistent with its being the *trans, trans*-isomer. The second has bands at 10·39, 6·02 and 14·3 μ consistent with the presence of one *trans* and one *cis* double bond. The third isomer (still slightly contaminated with *cis, trans*-isomer) shows negligible absorption at 10·40 μ, moderate absorption at 6·04 μ and strong absorption at 14·2 μ and, accordingly, has the *cis, cis*-structure. Ozonolysis of all three isomers gives succinic acid.

After being heated at 230° for 24 hours, all three isomers are recovered unchanged; that is, have suffered less than 1 per cent of isomerization.

Cope rearrangement of meso- *and* rac-3,4-*dimethylhexa*-1,5-*diene*

The *meso*-isomer is partially rearranged when heated at 225° for 6 hours to a mixture of octa-2,6-dienes consisting of 99·7 per cent *cis, trans-* and 0·3 per cent *trans, trans*-isomer.[11] Although the identity of the latter isomer rests on retention time only, that of the former is established by isolation and examination of its infrared spectrum. The *rac*-isomer rearranges essentially completely (97 per cent) in 18 hours at 180° with a comparatively high degree of stereoselectivity to a mixture of 90 per cent *trans, trans-*, 10 per cent *cis, cis-* and less than 1 per cent *cis, trans*-octa-2,6-diene.

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[6] R. Lespieau and R. Heitzmann, *Bull. Soc. Chim.* [5], **3**, 273 (1936).

[7] A. L. Henne, H. Chanan and A. Turk, *J. Amer. Chem. Soc.* **63**, 3474 (1941).

[8] W. G. Young, J. D. Roberts and H. Wax, *J. Amer. Chem. Soc.* **67**, 841 (1945).

[9] L. Schotte and A. Rosenberg, *Arkiv för Kemi* **7**, 479 (1955).

[10] A. Werner and M. Basyrin, *Ber. Dtsch. Chem. Ges.* **46**, 3230 (1913).

[11] At the moment one cannot guarantee a purity of more than 99·5% to the *meso*-isomer.

The conclusion is simple and unequivocal: in these examples of the Cope rearrangement where a free choice of the geometry of the transition state is possible, the four-center, chair-like arrangement is kinetically favored over the six-center, boat- or roof-like form by a factor of more than 300 to 1 or by a difference in free energy of activation of at least 5·7 kcal/mole ($-RT \ln k_6/k_4$ where $T = 498°K$ and $k_6/k_4 = 99{\cdot}7/0{\cdot}3$).

We prefer not to offer hypothetical explanations for the lower energy of the four-center orientation beyond mentioning briefly the possible effect of differences in conformation and orbital overlap. The extreme versions of the four- and six-centered states are suggestive of the chair and boat conformations of cyclohexane, which differ in energy by 5–6 kcal/mole.[12] By virtue of similar non-bonded interactions the four- and six-centered states may partake of a similar difference in energy. In allowing overlap of orbitals in the vicinity of the middle carbon atoms of the formal, allyl radicals, the two arrangements differ markedly. The four-centered allows none; whereas the six-centered allows more or less interaction depending on the angle between the two planes of the allyl radicals. R. S. Berry[13] points out that the pair of electrons in the lowest π_1-orbital of the allyl radical will repel the approach of another molecule about equally at all three carbon atoms. The odd electron in the π_2-orbital may form an attractive bond with the identically situated electron of a second allyl radical, but since this orbital has a node at the central carbon atom, effective bonding will occur only at the ends of the two allyl radicals. The repulsive effect of the electrons in the π_1-orbitals is obviously lower in the four-center arrangement than in the six, while the attractive, bonding force is the same in both.

The *rac*-isomer has the choice between two four-center transition states, one leading to *trans*, *trans*-, the other to *cis*, *cis*-octa-2,6-diene. The former is favored by a difference in the free energy of activation of about 2·0 kcal/mole ($-RT \ln k_{t,t}/k_{c,c}$ where $T = 435°K$ and $k_{t,t}/k_{c,c} = 90/10$). Here it should be said that the transition state leading to the thermodynamically less favored *cis*-double bond of necessity involves (in the terminology of cyclohexane conformation) an axially oriented methyl group whereas the formation of a *trans*-double bond is synonymous with an equatorially oriented methyl. Stated somewhat differently, an axially oriented methyl group must lead to a *cis*-double bond in the four-centered transition state and to a *trans*-double bond in the six-centered state. That these two factors should add up to about 1 kcal/mole for each *cis*-double bond formed does not seem out of line and can be used as a calibrating quantity.

Rearrangements of such molecules as *cis*-1,2-divinyl-cyclopropane and cyclobutane,[14] the 1-hydroxydicyclopentadienes,[15] and methacrolein dimer[16] occur smoothly even though the transition states are far removed from the favored four-center arrangement and are obliged to assume a geometry more like that of the six-center state. Perhaps it is reasonable to assume that rearrangements to which the four-center transition state is barred will proceed by a transition state whose geometry keeps the two central atoms of the rearranging triads as far from each other as other constraints

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[12] W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H Dreger and W. N. Hubbard, *J. Amer. Chem. Soc* **83**, 606 (1961).

[13] R. S. Berry, Department of Chemistry, Yale University, private communication.

[14] E. Vogel, *Angew. Chem.* **72**, 21 (1960).

[15] R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959).

[16] R. P. Lutz and J. D. Roberts, *J. Amer. Chem. Soc.* **83**, 2198 (1961).

within the molecule will allow. How much faster rearrangements of this type might go if a pure four-center arrangement were available remains to be determined.[17]

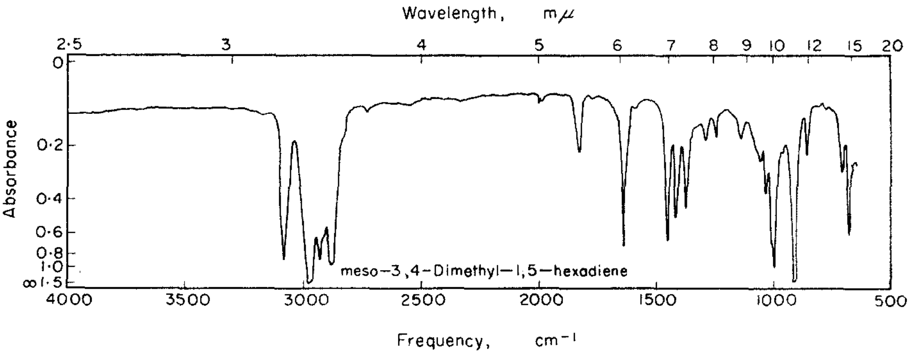
EXPERIMENTAL[18]

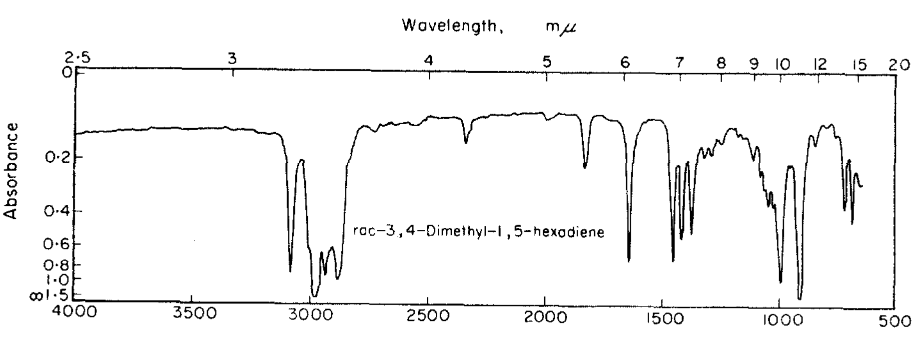
3,4-*Dimethylhexa*-1,5-*diene*

The procedure of Lespieau and Heitzmann[6] has been modified and the distribution of products has been determined by gas-liquid-partition-chromatography (g.l.p.c.).

A solution of 100 g (0·74 mole) crotylbromide in 200 ml absolute ether was added with cooling to a suspension of 13·0 g (0·56 atom) magnesium turnings at a rate sufficient to maintain gentle boiling (1 hr). After an hours' reflux, the cooled solution was treated at 0° with concentrated aqueous ammonium chloride. The aqueous layer was extracted twice with ether. Combined with the original ether layer, these were dried over sodium sulfate and concentrated to a residue which was boiled under reflux with 100 ml dry pyridine for 3 hr, cooled, diluted with 200 ml water and extracted three times with 100 ml portions of ether. The combined ethereal extracts were washed twice with 100 ml portions of 10% aqueous sulfuric acid, twice with 100 ml portions of saturated aqueous sodium bicarbonate and twice with water. Drying over anhydrous sodium sulfate and concentrating by careful distillation gave a crude product consisting of 3,4-dimethylhexa-1,5-diene (5–6%), 3-methylhepta-1,5-diene (74%) and octa-2,6-diene (20%). This mixture could be separated on a 5 ft column of silicone on firebrick (650 plates) at 3 lb helium and 75°. Under these conditions the hexadienes had a retention time of 13 min; the heptadienes, 17 min, and the octadienes, 25 min.

For the success of the following separation all excess crotyl bromide must have been destroyed by treatment with pyridine. The crude product was carefully distilled twice in a 60 cm spinning band column to give 2–3 ml of a mixture consisting of ca. 65% 3,4-dimethylhexa-1,5-diene and 35% 3-methylhepta-1,5-diene. Separation in a 2 m column of firebrick with silicone oil at 60° and 10 lb helium afforded ca. 1 ml pure 3,4-dimethylhexa-1,5-diene.





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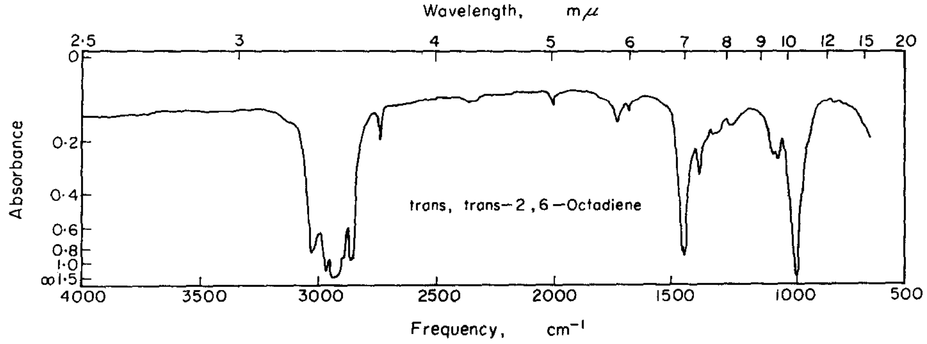
[17] We have in mind a study of such systems as the *meso*- and *rac*-2,2′bis-methylene bicyclohexyl.

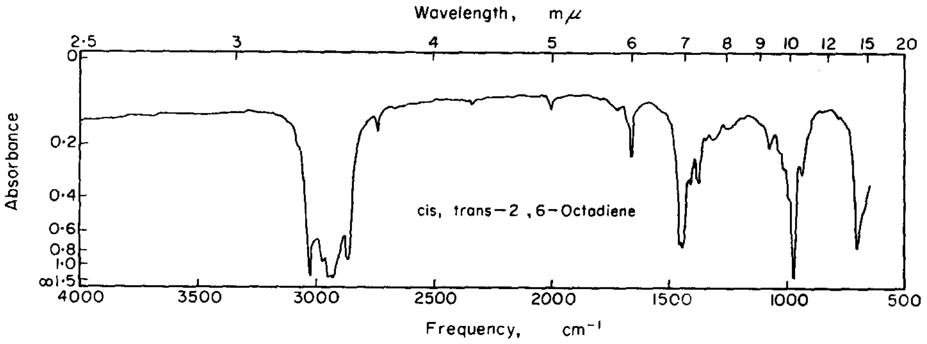
[18] Infrared spectra were taken on a Perkin-Elmer Model 221 at slit program 927, gain 4·8, attenuator speed 11·00, scan time 10 and suppression 5 on neat samples in 0·025 mm NaCl cells.

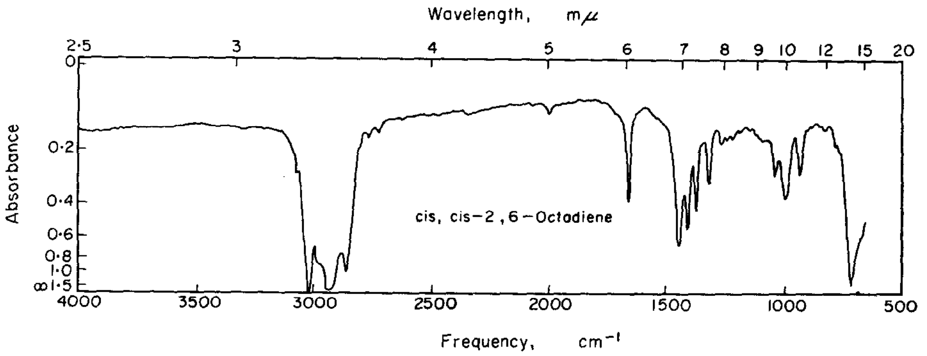
Meso- *and* rac-3,4-*dimethylhexa*-1,5-*diene*

Separation of the two stereoisomers, which have identical retention times on the silicone column, can be effected on a freshly prepared column containing silver nitrate. This packing is prepared by evaporating solvent at 30–35° in a rotating vacuum evaporator from a suspension of 40–60 mesh firebrick in an equal volume of methanol containing 30 wt.-% (based on firebrick) of a 30% solution of silver nitrate in glycerine. The dried material is packed immediately into a column which is then conditioned by heating for 2 hr at 60–65° and 5 lb hydrogen. The separating power of these columns diminished so rapidly that their useful life was no more than two weeks.

In a 4 m column (725 plates) at 49° and with 5 lb helium, tailing was sufficiently bad even with samples of 5–10 μl that two passes were required to give pure samples. The *meso*-isomer has the shorter retention time (34·4 min compared to 45·3 min for the *rac*-isomer) and accounts for 70% of the mixture. Infrared spectra of the two isomers are shown on page 72.







A solution of 100 μl of the *meso*-isomer in 2 ml of ethyl acetate was ozonized at −70°. Concentration *in vacuo* gave a residue which was boiled under reflux for 3 hr with 2 ml of a mixture of acetic acid (6 ml) and 30% hydrogen peroxide (3 ml). The mixture was concentrated *in vacuo* and twice taken up in 1 ml of water and concentrated again. The residue was then crystallized from 0·5 ml water to give *meso*-2,3-dimethylsuccinic acid: m.p. 185–187° (reported[9] m.p. 198° with dec). The infrared spectrum is in good agreement with that reported.[9]

Ozonolysis of the *rac*-isomer (20 μl) in the same manner afforded *rac*-2,3-dimethylsuccinic acid, m.p. 116–117° from benzene (reported[9] m.p. 129°) and having an infrared spectrum identical with that reported.[9]

Isolation of the geometrically isomeric octa-2,6-dienes

Careful fractional distillation of the highest boiling fraction of the product of the reaction of crotyl bromide and magnesium afforded octa-2,6-diene (b.p. 123–125°; reported[7] b.p. 124·5°) from which the last traces of 3-methylhepta-1,5-diene could be removed by g.l.p.c. on a silicone column. G.l.p.c. on the silver nitrate column described above (370 plates in this example, 50°, 10 lb He) afforded three fractions: the first corresponded to the *trans, trans*-isomer (44·6%, retention time 13 min) the second to the *cis, trans*-isomer (49·0%, 19·6 min) and the third to the *cis, cis*-isomer (6·4%, 34·6 min). The infrared spectra of these previously unreported isomers are shown on page 73.

Each of the isomers has been oxidized to succinic acid. Ozonolysis of 100 μl in 2 ml ethyl acetate at −70°, concentration *in vacuo*, oxidation of the residue in 2 ml of a mixture of acetic acid (6 ml) and 30% hydrogen peroxide (3 ml) by boiling for 3 hr, concentration *in vacuo*, dissolution in 1 ml of water and concentration *in vacuo* (repeated twice), and crystallization from water afforded succinic acid, identified in all cases by m.p. (182–183° from *trans, trans*; 181–182° from *cis, trans*; 183–184° from *cis, cis*) and infrared spectra.

Thermal isomerization of the 3,4-dimethylhexa-1,5-dienes

(a) *Meso*-isomer. The product from heating 50 μl of pure *meso*-3,4-dimethylhexa-1,5-diene in a sealed capillary ampoule under hydrogen at 225° for 6 hr was separated from unreacted starting material on a silicone column. G.l.p.c. of the octa-2,6-diene fraction on the silver nitrate column afforded *cis, trans*-octa-2,6-diene (99·7%) and *trans, trans*-octa-2,6-diene (0·3%). The former isomer was collected and identified by comparison of its infrared spectrum with that of the sample prepared above. Identification of the *trans, trans*-isomer rested on retention time alone. After 48 hr at 150°, 48 hr at 200° and 24 hr at 280°, *meso*-3,4-dimethylhexadiene had rearranged to the extent of 5, 86 and 97%, respectively.

(b) *Rac*-isomer. G.l.p.c. analysis on the silicone column of the product of heating 40 μl of pure *rac*-3,4-dimethylhexa-1,5-diene in a sealed capillary ampoule under hydrogen for 18 hr at 180° indicated 97% rearrangement to octa-2,6-dienes. Analysis of this fraction on the silver nitrate column showed it to consist of the *trans, trans*-isomer (90%), the *cis, cis*-isomer (10%) and less than 1% of the *cis, trans*-isomer. (The ratio of *trans, trans* to *cis, cis* is 90 : 10 within experimental error whether the temperature of the rearrangement be 225·4°, 209·3° or 193·5°.) The *trans, trans*-isomer was identified by isolation and comparison of its infrared spectrum with that of the sample prepared above; the other isomers were identified by comparison of their retention times with those of the authentic samples prepared above.

(c) Thermal stability of octa-2,6-dienes. All three isomers, *cis, cis*-. *cis, trans*-, and *trans, trans*-, were unchanged after 24 hr at 230°.