

Experiments Directed toward the Total Synthesis of Terpenes. III. The Use of *trans*- Δ^6 -Octalone-1 in the Preparation of Dicyclic Intermediates

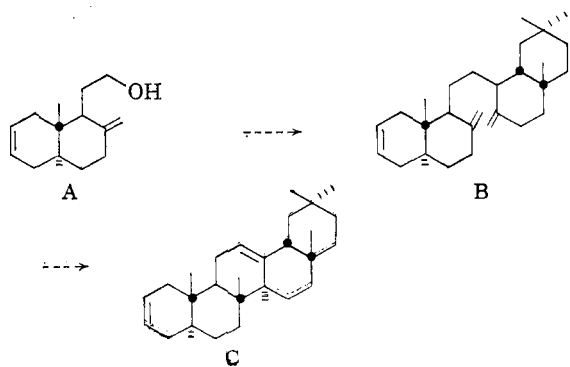
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The synthesis of *trans*- Δ^6 -octalone-1 in 52% yield from benzoquinone is described. Through the agency of the *n*-butylthiomethylene group, this ketone was converted to its 9-methyl derivative and thence to 9-methyl-*trans*-decal-1,6-dione. A method for the introduction of a two carbon residue at C-1 of the methylated octalone is outlined.

The demonstration by Johnson and co-workers² that an angular methyl group could be stereoselectively introduced into 2-furfurylidene-*trans*- Δ^6 -octalone-1 prompted us to consider the possibility of using a similar sequence as the starting point for the synthesis of polycyclic natural products. There is a close similarity between 9-methyl-*trans*- Δ^6 -octalone-1 (6) and the A-B ring system of the triterpenes. The carbonyl at C-1 represents an excellent point of departure for the construction of the rudiments of the C ring. It was felt that by utilization of the *n*-butylthiomethylene blocking group³ in lieu of the furfurylidene group, the stage could be set for the introduction of a two carbon side chain at C-1 *via* the Claisen rearrangement. An example of such a transformation was already available as a result of our synthetic⁴ work in the α -onocerin series. Also, the relative chemical inertness of the double bond in the ketone (6) was considered to be a particular advantage. It could be expected to survive many of the transformations necessary to construct the remainder of the polycyclic ring system, but was always available as a handle for the introduction of the desired substituents at some later stage. In this vein it was considered attractive to prepare *trans*- Δ^6 -octalone-1 (4) and investigate its conversion through the 2-*n*-butylthiomethylene derivative (8) to the alcohol (A). The latter could be coupled with another appropriately substituted dicyclic moiety, and the resulting tetracyclic species (B) cyclized by known methods⁵ to the pentacyclic structure (C).



The first obstacle to be overcome in this program was to obtain a satisfactory method for preparing adequate supplies of *trans*- Δ^6 -octalone-1 (4). Although this ketone was used in model studies by Johnson and co-workers, the only definitive reports of its preparation⁶ left much to be desired. In order to embark on any multistage synthetic scheme, it would be necessary to elaborate a more successful and convenient route to this ketone. A logical starting point for this synthesis appeared to be Δ^6 -octal-1,4-dione (2) readily available through the condensation of butadiene and *p*-benzoquinone.⁷ Since this phase of the work was completed, several reports⁸⁻¹⁰ have appeared which have been concerned with the same Diels-Alder condensation, and we record here only the observations that differ from those reported previously.

The condensation between butadiene and benzoquinone was carried out in acetic acid,¹¹ and the product reduced directly with zinc dust.¹² Isolation of the pure *cis* adduct (1), m.p. 102–104°, was accomplished, essentially as previously described.⁹ Preparatively, however, rather than to isolate this pure *cis* adduct (1), it was found more convenient to purify the reduction product by filtration through alumina. The dione (2) obtained by this procedure in 93% yield was, however, not stereochemically homogeneous, but a mixture of the *cis*- and the *trans*-dione melting between 78° and 85°. From this mixture the pure *trans*-

(1) Public Health Service Research Fellow of the National Heart Institute, 1958–1960.

(2) W. S. Johnson and D. S. Allen, Jr., *J. Am. Chem. Soc.*, **79**, 1261 (1957).

(3) R. E. Ireland and J. A. Marshall, *ibid.*, **81**, 6336 (1959).

(4) R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, 34 (1961).

(5) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, **81**, 1739 (1959).

(6) (a) P. D. Bartlett and G. F. Woods, *ibid.*, **62**, 2933 (1940);

(b) I. N. Nazarov and L. D. Bergel'son, *Zhur. Obshekei Khim.*, **20**, 648 (1950).

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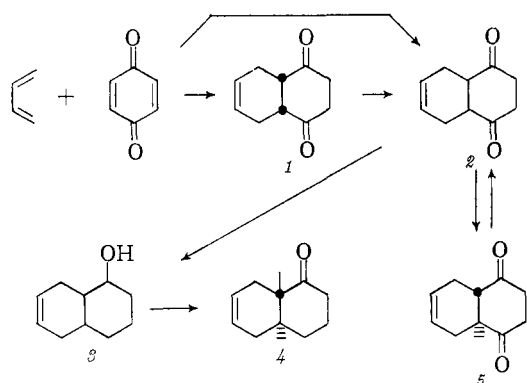
(8) H. B. Henbest, M. Smith, and A. Thomas, *J. Chem. Soc.*, 3293 (1958).

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

(10) E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamn, and P. E. Aldrich, *ibid.*, **80**, 5006 (1958).

(11) L. F. Fieser, *ibid.*, **70**, 3165 (1948).

(12) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).



dione (5), m.p. 95.5–96.5°,¹³ could be obtained in 40% yield by fractional crystallization.

That the dione (2) isolated by chromatography was a *cis-trans* mixture was shown by the formation¹⁴ of a mixture of bisethylenethioketals in 85% yield, melting over the range 131–146°. Repeated recrystallization of this material led to the pure *trans*-bisthioketal melting at 164–165° and identical with that prepared directly from the pure *trans*-dione in 97% yield. When the pure *cis*-dione (1) was similarly converted to the bis-thioether, there was obtained a 98% yield of material melting 110–112°; the mixture melting point of equal portions of these two bis-thioketals was 102–158°.

It is interesting to note that while the thioether formation apparently did not involve isomerization of the octalin fusion, the bisketalization of the *cis-trans*-dione (2) with ethylene glycol afforded only a single bisketal in 68% yield. This was shown to be the *trans*-fused bisketal by catalytic hydrogenation to the decalin bisketal and direct comparison by mixture melting point with an authentic sample.¹⁵ The formation of only the *trans*-bisketal seems to substantiate the view that the stereochemical instability of the dione is due to the presence of four trigonal carbon atoms. This also indicates that ketal formation proceeds in a stepwise manner, and that any initially formed *cis*-monoketal suffers acid-catalyzed isomerization to the more reactive *trans*-monoketal before completion of the diketalization. Consequently, it was not surprising to find that the same *trans*-diketal was also the sole product when the pure *cis*-dione was used as a starting material.

Contrary to the oxygen analog, thioether formation does not result in isomerization of the octalin system. This result is in accord with the findings of Sondheimer and Rosenthal¹⁶ in the 10-

methyl-1-decalone series where the equilibrium mixture of the *cis* and *trans* isomers also formed a mixture of thioketals.

On the premise that removal of one of the four trigonal carbons in the *cis-trans*-dione (2) would restore stereochemical homogeneity, the dione (2) was reduced with one equivalent of lithium aluminum hydride in a dilute solution. That the desired reduction of only one carbonyl group had occurred was shown by Wolff-Kishner¹⁷ reduction of the resulting product and the isolation of a 5–25% yield of Δ^6 -octalol-1 (3). However, this disappointingly low yield led us to consider the hydride reduction more closely. Operating on the premise that it was impossible to reduce the local concentration of reducing hydride in lithium aluminum hydride, the mono reduction of the dione (2) with lithium tri-*t*-butoxyaluminumhydride¹⁸ was investigated. This latter reagent, having only one active hydride, should be capable of effecting the reduction of only one carbonyl of the dione (2) provided the reaction mixture was sufficiently dilute. Indeed, this proved to be the solution to the problem, for by using lithium tri-*t*-butoxyaluminumhydride in dilute tetrahydrofuran solutions, followed directly by the Wolff-Kishner reduction,¹⁷ it was possible to realize a 64% yield of Δ^6 -octalol-1 (3). When this alcohol was oxidized, using the pyridine–chromic anhydride complex,¹⁹ the desired Δ^6 -octalone-1 (4) was obtained in an 89% yield. Thus, this new procedure allows the preparation of this useful ketone in a 52% over-all yield based on benzoquinone and entails only three product isolations during the five-step reaction sequence. With the ready availability of Δ^6 -octalone-1 (4) now assured, attention could be turned to other aspects of the synthetic scheme.

The next problem to be faced was the introduction of the C-10 angular methyl grouping. Since this problem is similar to that of the methylation of decalone-1, we had the benefit of the vast store of experience gained by others,²⁰ in this area—*i.e.*, the α -methylene grouping must be blocked before we could expect to effect methylation at C-10. However, the requirements to be met by the blocking group were highly restricted. It had to be one that did not deactivate the carbonyl so as to make methylation difficult and yet it must also serve to introduce the Δ^1 -2-hydroxymethyl grouping necessary for the Claisen rearrangement sequence. The latter requirement restricted our interest to blocking groups of the isopropoxymethylene type²¹ which are readily transformed into α,β -unsaturated aldehydes by reduction and then acid-catalyzed rearrangement.⁴ However, the moisture-sensitive

(17) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(18) H. C. Brown and R. F. McFarlin, *ibid.*, **80**, 5372 (1958).

(19) G. I. Poos, G. E. Arth, R. E. Beyle, and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(20) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944); W. S. Johnson, *J. Am. Chem. Soc.*, **65**, 1317 (1943).

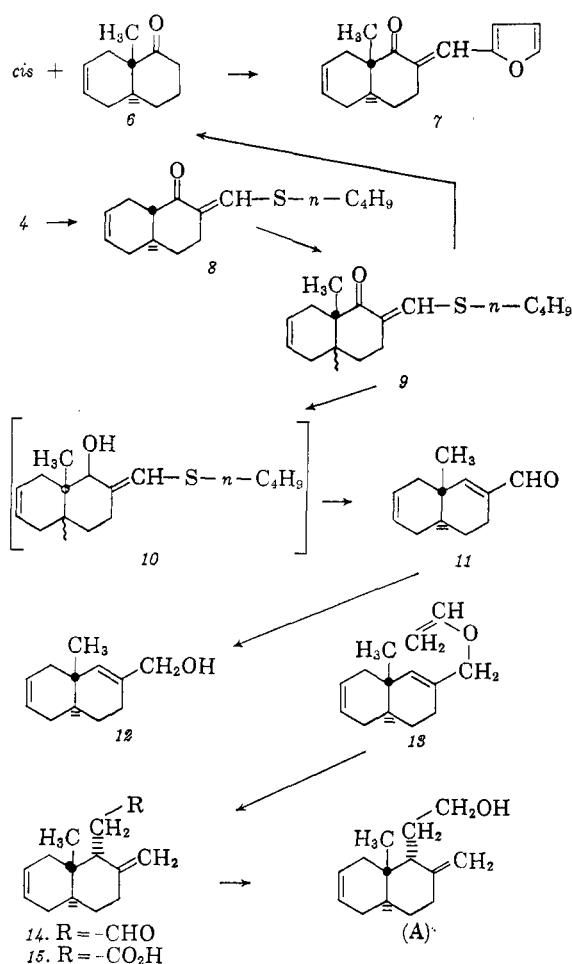
(21) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).

(13) The *trans*- Δ^6 -octal-1,4-dione, m.p. 95.5–96.5°, recorded here does not agree in melting point with that prepared by Henbest and co-workers,⁸ who found m.p. 157–160°. That recorded here may be a lower melting crystalline modification.

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(15) R. Hinderstinn, Ph.D. thesis, University of Wisconsin (1955). The authors are grateful to Prof. W. S. Johnson for providing a sample of this material.

(16) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958).



nature of the isopropoxymethylene group and its deactivating effect on the carbonyl group made a modification of this grouping necessary. As the result of a search for such a blocking group, we found that the *n*-butylthiomethylene grouping³ admirably satisfied these requirements and applied it to the case in hand.

The *n*-butylthiomethylene grouping was introduced on the α -methylene of the octalone (4) in 85% yield by first hydroxymethylation²¹ and then etherification with *n*-butanethiol.³ The resulting blocked octalone (8), which was quite stable to storage over long periods of time, was readily methylated in 89% yield with potassium *t*-butoxide and methyl iodide. While the methylated derivative (9) was a sharp boiling liquid [b.p. 155–157° (0.4 mm)], it could not be induced to crystallize, and thus no satisfactory criterion of stereochemical homogeneity was readily available. Inasmuch as Johnson and co-workers² report only that the *trans*-9-methyl derivative is the predominant product of methylation, it was felt that it was necessary to investigate the proportion of *cis* and *trans* isomers formed in this case.

To the en¹ advantage was taken of the ready removal of the *n*-butylthiomethylene grouping by

treatment with 12.5% aqueous diethylene glycolic potassium hydroxide solution. Steam distillation from this reaction mixture afforded an 88% yield of the parent methylated octalone. This octalone boiled sharply at 106–107° (7 mm.), and while only a single, sharp peak was observed on gas-liquid chromatography of this material on a silicone gum rubber or Apiezon L columns, the derived 9-methyldecalone, obtained in quantitative yield by catalytic hydrogenation, was shown to consist of two components in the ratio 3:1 by gas-liquid chromatography on a silicone gum rubber column. The wide melting range of the semicarbazone of the 9-methyloctalone, m.p. 195–205°, also bore out the mixed character of the methylated material. An attempt to isolate the pure semicarbazone of the *trans*-ketone by fractional crystallization of this mixture was unsuccessful. That the major component present in the octalone mixture was indeed the desired 9-methyl-*trans*- Δ^6 -octalone (6) was demonstrated on condensation of the material with furfural whereupon a 70% yield of the known furfurylidene derivative² of the *trans* isomer was obtained. The melting point of this sample was not depressed when mixed with an authentic specimen.²²

These results suggest that while the methylation of the 2-*n*-butylthiomethylene- Δ^6 -octalone-1 (8) was not stereospecific, it is more stereoselective²³ than that reported by Johnson and co-workers² using the corresponding 2-furfurylidene derivative. Thus the steric course of the angular methylation reaction would seem to be a function not only of the C-6:7 double bond but also of the kind of blocking group used. The steric results reported here are reminiscent of those observed earlier by Johnson and Posvic²¹ in the α -decalone series where the isopropoxymethylene grouping appeared to enhance the *trans* to *cis* ratio.

The problem of how to treat this *cis-trans*-octalone mixture with regard to further synthetic efforts now presented itself. Inasmuch as the desired *trans* isomer represented at least 70% of this octalone mixture, it was felt that further synthetic transformations were worthwhile. It also appeared reasonable to expect that by further modification of the octalone system that products related to the *trans*-octalone could be separated from the mixture by virtue of its preponderance. Such was shown (*vide supra*) to be the case in the formation of the furfurylidene derivative (7) from the octalone mixture. To this end then we turned our attention to the synthetic problems inherent in the introduction of the side chain at C-1.

As suggested above, advantage was taken of the experience gained in our synthetic work⁴ in the

(22) The authors are grateful to Professor W. S. Johnson for providing us with this sample.

(23) The term *stereospecific* is taken to mean that a single diastereoisomeric racemate is formed to the exclusion of all others, while *stereoselective* implies only that one predominates over the others.

α -onocerin series, and it was planned to use the Claisen rearrangement²⁴ to introduce the two carbon residue at C-1. In order to set the stage for this reaction the blocked methylated octalone (9) was reduced with sodium borohydride and the resulting alcohol (10) rearranged without purification with aqueous mineral acid. Recent work both in these laboratories²⁵ and those of Stiles and co-workers²⁶ substantiates the view that the aldehyde (11), isolated in 63% yield, is generated by hydrolysis of the hemi-thioacetal formed by allylic rearrangement of the alcohol (10).

While this aldehyde (11) was a liquid, a sharp melting semicarbazone (m.p. 216–218°) was obtained in 87% yield. This observation, taken with the fact that the aldehyde (11) was isolated in a yield such that it could not be related to the minor *cis* constituent of the octalone mixture, indicated that it was indeed the desired *trans* system. Further confirmation of this view was obtained by examination of the alcohol (12) obtained in 88% yield from the aldehyde (11) by reduction with sodium borohydride. Gas-liquid chromatography of this alcohol on a diethylene glycol succinate polyester column indicate the presence of only one component, and a crystalline *p*-nitrobenzoate (m.p. 108–110°) of the alcohol was obtained in 88% yield.

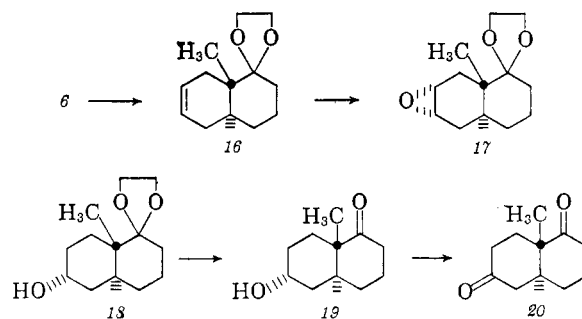
Since the above results strongly indicated that modification of the octalone system along the desired synthetic pathway was successful in removing the undesired *cis* isomer, further efforts could be undertaken with less trepidation. Thus equilibration²⁷ of the allylic alcohol (12) with ethyl vinyl ether, followed by careful chromatography led to an 80% yield of the vinyl ether (13). In our experience this equilibration reaction is quite satisfactory with primary allylic alcohols, such as (12), while the secondary allylic alcohols²⁸ behave somewhat more erratically.

When the vinyl ether (13) was heated in a sealed tube under a nitrogen atmosphere, the aldehyde (14) was generated in 90% yield. Since this aldehyde showed only one peak on gas-liquid chromatography on the polyester column and was oxidized in 87% yield to the corresponding acid (15) by silver oxide,²⁸ we consider the pyrolytic rearrangement to be highly stereoselective in generating only one of the two possible C-1 epimers. By analogy to the results obtained in the α -onocerin work⁴ the α (axial) configuration is assigned to the acetaldehyde residue at C-1. If a bicyclic intermediate with this stereochemistry were carried undisturbed to a triterpene nucleus,

the unnatural C-9:C-10 *syn* configuration would result. However, in view of the fact that the proposed final stage of this synthesis would be analogous to that employed by Corey⁶—*i.e.*, acid-catalyzed carbonium ion cyclization—the asymmetry at C-9 will be destroyed and can be re-established in the desired natural configuration. Thus the α (axial) character of the two carbon C-1 residue was not considered a drawback to the synthetic scheme. To the contrary the axial C-1 group has extended the scope of this work in that it offers the only satisfactory presently known route to such diterpenoid acids as eperuic acid²⁹ and perhydrophenanthrenes with the *trans-syn-cis* backbone.³⁰ The results of work along these lines will be the subject of another communication.

It was a simple matter to attain the desired objective of this phase of the work—namely, the alcohol (A)—by sodium borohydride reduction of the aldehyde (14). A 90% yield of this alcohol resulted and established the feasibility of this reaction sequence for the construction of a triterpene precursor, the over-all yield of the alcohol (A) from *trans*- Δ^6 -octalone-1 (4) being 28%.

Before proceeding further with the synthesis, we deemed it advisable to investigate the conversion of the double bond of the octalone system to an oxygen function. This is a step that would, in the general synthetic scheme, be left to the last, but before investing more effort in this route a method for this transformation was sought. Further, the successful conversion of the methylated *cis-trans*-octalone mixture to the known *trans*-dione



(20)³¹ would reinforce the hypothesis that this mixture could be used in synthetic sequences where the *trans* isomer was desired.

The best model for this phase of the work seemed to be the 9-methyloctalone mixture itself, and on the grounds that the C-1 keto group would not be present in the final pentacyclic structure, this function was blocked by formation of the ketal (16) in 96% yield. Treatment of this ketal with perbenzoic acid generated an oxide in 86% yield to which we have assigned the α -configura-

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(25) R. F. Church, Ph.D. thesis, University of Michigan, 1961.

(26) M. Stiles and A. Longroy, *Tetrahedron Letters*, 337 (1961).

(27) W. H. Watenabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(28) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(29) F. E. King and G. Jones, *J. Chem. Soc.*, 658 (1955); C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957).

(30) R. F. Church and R. E. Ireland, *Tetrahedron Letters*, 493 (1961).

(31) V. Prelog and D. Zisch, *Helv. Chim. Acta*, **42**, 1862 (1959).

tion (17) for the *trans*-fused isomer by analogy to similar steroidal oxides.³² On reduction with lithium aluminum hydride the oxide (17) was cleaved to a ketal alcohol. If the α -oxide assignment for the *trans*-fused isomer is correct, this ketal alcohol should have the structure (18) and thus the hydroxy group will be in the desired 6 α (axial) position. In order to prove this assignment of the newly introduced oxygen atom, the crude hydroxy ketal (18) was cleaved by aqueous mineral acid. This hydroxy ketone (19) was isolated as a crystalline solid (m.p. 112–114°) in 46% yield from the oxide (18) and in an over-all 38% yield from the methyloctalone mixture. The high over-all yield of this process again indicates that this material represents the *trans*-fused system. Final confirmatory evidence of both the placement of the new oxygen function at C-6 and the *trans*-fused nature of the system was found when the hydroxy ketone (19) was oxidized with Jones reagent³³ to the dione (20). The dione (20) prepared by this route melted at 56–57° alone or on admixture with an authentic sample prepared from 10-methyl- $\Delta^{1(9)}$ -octal-2,5-dione by the procedure of Birch and co-workers.³⁴ This reaction sequence should be equally as applicable to the pentacyclic stage of our synthesis and also can be adapted to allow the introduction of the C-4 *gem*-dimethyl grouping.

With the completion of these experiments the first portion of our synthetic task has been achieved, and synthetic efforts aimed at the preparation of the other necessary dicyclic moiety that will represent rings D and E are in progress.

Experimental³⁵

cis-trans- Δ^6 -Octal-1,4-dione (2).—The benzene concentrate obtained from the reduction⁸ of the crude adduct¹⁰ formed by 130 g. (2.4 moles) butadiene and 216 g. (2.0 moles) *p*-benzoquinone was eluted from 2500 g. of alumina with 7 l. of benzene. Removal of the benzene afforded 300 g. (93%) of the *cis-trans*-dione mixture (2), m.p. 78–85°.

trans- Δ^6 -Octal-1,4-dione (5).—A 2.0-g. sample of the mixture of *cis-trans*-dione (2) was dissolved in 100 ml. of refluxing petroleum ether (b.p. 40–60°). The solution was allowed to cool to room temperature and stand for several hours. Filtration afforded 0.8 g. (40%) of the *trans*-dione as fine white needles, m.p. 95.5–96.6°. The melting point did

not change on further careful crystallization from the same solvent.

Anal. Calcd. for C₁₀H₁₂O₂: C, 73.14; H, 7.37. Found: C, 73.20; H, 7.41.

trans- Δ^6 -Octal-1,4-dione Bisethylene Ketal.—A mixture of 16.4 g. (0.10 mole) of *cis-trans*- Δ^6 -octal-1,4-dione, m.p. 78–85°, 13 g. (0.22 mole) of ethylene glycol, and a trace of *p*-toluenesulfonic acid in 200 ml. of benzene was refluxed overnight. After the benzene was removed at reduced pressure, the residue, which amounted to 17 g. (68%) crystallized, m.p. 92–95°. Recrystallization from *n*-hexane gave hard rhombic crystals, m.p. 95.5–96.5°.

Anal. Calcd. for C₁₄H₂₀O₄: C, 66.63; H, 7.98. Found: C, 66.35; H, 7.95.

The *trans*-bisketal could also be prepared from *cis*- Δ^6 -octal-1,4-dione (1) in 60% yield. The material melted at 95–97° after one recrystallization from *n*-hexane. This material on admixture with the *trans*-bisketal prepared above melted at 95–98°.

trans-Decal-1,4-dione Bisethylene Ketal.—A solution of 1.1 g. (0.004 mole) of *trans*- Δ^6 -octal-1,4-dione bisethylene ketal in 20 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure over 50 mg. of 10% palladium-on-carbon. The theoretical amount of hydrogen was absorbed in 20 min., and after removal of the catalyst, the solvent was evaporated in an airjet. The residue crystallized from hexane gave hard white rhombic crystals, m.p. 77–79°, alone or on admixture with an authentic sample.¹⁴

cis- Δ^6 -Octal-1,4-dione Bisethylene Thioketal.—To a solution of 6.6 g. (0.04 mole) of *cis*- Δ^6 -octal-1,4-dione (m.p. 102–104°)⁶ and 10.8 ml. (0.12 mole) of 1,2-ethanedithiol, and 50 ml. of glacial acetic acid was added slowly and with rapid swirling, 10.8 ml. of boron trifluoride etherate. Heat was evolved and almost immediately, the solid white thioketal precipitated from the reaction mixture. Swirling was continued for 10 min., and the mixture was cooled and filtered affording 11.3 g. (98%) of white crystalline bithioketal, m.p. 110–112°. Recrystallization from acetone raised the melting point to 114–115°.

Anal. Calcd. for C₁₄H₂₀S₄: C, 53.20; H, 6.38; S, 40.40. Found: C, 53.31; H, 6.42; S, 40.27.

trans- Δ^6 -Octal-1,4-dione Bisethylene Thioketal.—The reaction run as described above on 0.66 g. (0.004 mole) of *trans*-dione (5) gave 1.22 g. (97%) of crude *trans*-bithioketal, m.p. 163.5–165°. One recrystallization from acetone afforded the bithioketal as hard white rhombic crystals, m.p. 164.5–165.5°. This compound on admixture with the *trans* isomer obtained from fractional crystallization of the mixture of *cis*- and *trans*-thioketals melted at 164–165°.

Anal. Calcd. for C₁₄H₂₀S₄: C, 53.20; H, 6.38; S, 40.40. Found: C, 53.24; H, 6.44; S, 40.54.

Mixture of *cis*- and *trans*- Δ^6 -Octal-1,4-dione Bisethylene Thioketals.—The reaction run as described above on 6.6 g. (0.04 mole) *cis-trans*-dione (2) afforded 10.7 g. (85%) of crude bithioketals, m.p. 131–146°. Repeated recrystallization from acetone resulted in the purification of a less soluble component (the *trans* isomer) of m.p. 164–165°. This compound on admixture with the *cis*-bithioketal melted at 102–158°.

Δ^6 -Octalol-1 (3) A. From Lithium Aluminum Hydride Reduction of *cis-trans*-Dione (2).—To a rapidly stirred solution of 82 g. (0.5 mole) of *cis-trans*- Δ^6 -octal-1,4-dione (2) in 1500 ml. of anhydrous ether was added at a slow dropwise rate, 235 ml. of a 2 *N* ethereal lithium aluminum hydride solution. The thick, white suspension was stirred for 2 hr., and then 8 ml. of 10% aqueous sodium hydroxide and 10 ml. of water was added to decompose the metal complexes. The solid salts were removed by filtration, the filter washed with ether, and a filtrate freed of ether by distillation at reduced pressure.

A solution of the residue in 1 l. of diethylene glycol was treated with 90 g. (1.5 moles) of 85% potassium hydroxide pellets and 58 ml. (1.5 moles) of 95% hydrazine. The mix-

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(33) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(34) A. J. Birch, E. Pridie, and H. Smith, *J. Chem. Soc.* 4688 (1958).

(35) Melting points were taken on a Kofler hot stage and are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137, and ultraviolet spectra were determined on a Cary recording spectrophotometer (Model 11 MS). Temperature programmed gas-liquid chromatograms were obtained on an F and M Scientific Corp. Model 500 instrument; isothermal chromatograms were measured on a Barber-Coleman Model 10 instrument.

ture was stirred at 120° for 2 hr., the temperature was increased to 185°, and a volatile material was collected through a take-off head. When the mixture was cooled 1 l. of water was added, and the aqueous solution was extracted with five 300-ml. portions of ether. The combined ethereal extracts were washed with 300 ml. of water, 300 ml. of saturated salt solution, and dried over anhydrous sodium sulfate. Distillation of the resulting dried solution afforded 10.5 g. of Δ^2 -octalin,^{8,9} b.p. 73–74° (20 mm.) (15.5% yield based on dione) and 13.5 g. of the alcohol (3), b.p. 125–126° (20 mm.) (17.8% yield).

Anal. Calcd. for C₁₀H₁₆O: C, 78.89; H, 10.59. Found: C, 78.72; H, 10.48.

The yield of alcohol in other runs varied between 5 and 25%.

B. From Lithium Tri-*t*-butoxyaluminumhydride.—To a solution of 23.8 g. (0.145 mole) of *cis-trans*- Δ^6 -octal-1,4-dione (2) in 500 ml. of dry tetrahydrofuran was added at a slow dropwise rate 140 ml. of a 1.1 M (0.154 mole) lithium tri-*t*-butoxyaluminumhydride¹⁸ in dry tetrahydrofuran. After 3 hr. 9.2 ml. of 10% aqueous sodium hydroxide and 11.5 ml. of water were added to the clear orange solution to decompose the metal complexes. The solid precipitate was removed by filtration, and the blood-red filtrate was freed of tetrahydrofuran by distillation at reduced pressure. When the residue was subjected to the modified¹⁷ Wolff-Kishner reduction previously described, there was obtained 11.5 g. [52% yield based on dione (2)] of Δ^6 -octalol-1, b.p. 124–125° (17 mm.).

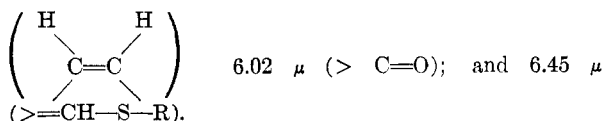
***trans*- Δ^6 -Octalone-1 (4).**—To a solution of 20 g. (0.4 equivalents) of chromium trioxide in 200 ml. of pyridine¹⁹ was added a solution of 20.2 g. (0.4 mole) of Δ^6 -octalol-1 (3) in 200 ml. of pyridine. The reaction mixture was stirred overnight, poured into 800 ml. of water, and extracted with four 300-ml. portions of ether. The combined ethereal extracts were washed with 400 ml. of water, two 400-ml. portions of 2% aqueous sulfuric acid, 400 ml. of water, 200 ml. of saturated salt solution, and dried over anhydrous sodium sulfate. After the ether was removed at reduced pressure, distillation of the residue afforded 17.7 g. (89%) of colorless liquid, b.p. 111–112° (14 mm.). The distillate solidified to a white solid, m.p. 32–34°.

Anal. Calcd. for C₁₀H₁₄O: C, 79.95; H, 9.38. Found: C, 79.72; H, 9.43.

The oxime had m.p. 154–156° from ethanol. (Reported²⁶ for the oxime of *trans*- Δ^6 -octal-1-one, m.p. 153–155°.)

2-*n*-Butylthiomethylene-*trans*- Δ^6 -octalone-1 (8).—To an ice-cooled suspension of 43 g. (0.8 mole) of dry sodium methoxide in 300 ml. of dry benzene in a nitrogen atmosphere was added dropwise with stirring 30 g. (0.2 mole) of *trans*- Δ^6 -octalone-1 (4) and 65 ml. (60 g., 0.8 mole) of purified ethyl formate in 100 ml. of dry benzene. After standing overnight at room temperature, 100 ml. of water was added, and the separated benzene layer washed two times with 50-ml. portions of 5% aqueous sodium hydroxide. The combined ice-cold basic solution was made strongly acidic with concd. hydrochloric acid, and the hydroxy-methylene derivative extracted with benzene. The benzene solution was washed with water, dried, and concentrated to approximately 250 ml.

To this dry benzene solution was added 24.4 ml. (19 g., 0.21 mole) of *n*-butyl mercaptan and a trace of *p*-toluenesulfonic acid. After this solution was refluxed in a nitrogen atmosphere for 5 hr. under a water separator, 4 ml. of water was collected. The cooled benzene solution was washed with water, 10% aqueous potassium bicarbonate, water, and dried (Na₂SO₄). Distillation of the residue obtained after removal of the solvent afforded 42 g. (85%) of 2-*n*-butylthiomethylene-*trans*- Δ^6 -octalone-1 (8), b.p. 129–131° (0.1 mm.). This material solidified (m.p. 61–63°) and a portion, crystallized two times in petroleum ether (b.p. 40–60°) for analysis, melted at 64–64.5°. Ultraviolet: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 813 m μ (18,000). Infrared: $\lambda_{\text{max}}^{\text{HCCl}_3}$ 3.29 μ



Anal. Calcd. for C₁₅H₂₂OS: C, 71.95; H, 8.86; S, 12.80. Found: C, 71.75; H, 8.68; S, 12.92.

9-Methyl-2-*n*-butylthiomethylene-*trans*- Δ^6 -octalone-1 (9).—To a solution of 30 g. (1.9 moles) of potassium metal in 800 ml. of *t*-butyl alcohol in a nitrogen atmosphere was added 42 g. (0.17 mole) of the blocked octalone (8) in 150 ml. of dry benzene. After stirring three minutes at room temperature, the reaction mixture was cooled in an ice bath, and 100 ml. of methyl iodide was added all at once. The mixture was warmed to room temperature over 0.5 hr., and then refluxed for 2 hr. Most of the *t*-butyl alcohol was removed at reduced pressure, 100 ml. of water added, and the aqueous mixture extracted two times with 100-ml. portions of ether. The combined ethereal solution was washed with water, saturated salt solution and dried (Na₂SO₄). On distillation of the residue obtained after removal of the solvent there was obtained 40 g. (89%) of the methylated blocked octalone (9) as a yellow liquid, b.p. 155–157° (0.4 mm.). A sample redistilled for analysis was boiled at 127° (0.07 mm.). Ultraviolet: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 310 m μ (16,800).

Anal. Calcd. for C₁₆H₂₄OS: C, 72.67; H, 9.15; S, 12.12. Found: C, 72.41; H, 9.16; S, 12.37.

9-Methyl-*cis-trans*- Δ^6 -octalone-1.—A solution of 40.5 g. (0.154 mole) of 9-methyl-2-*n*-butylthiomethylene-*trans*- Δ^6 -octalone-1 (9) in 300 ml. of diethylene glycol and 300 ml. of 25% aqueous potassium hydroxide was refluxed in a nitrogen atmosphere for 17 hr. Water was added to the warm reaction mixture, and the ketone removed by steam distillation. The steam distillate (1500 ml.) was extracted three times with 200-ml. portions of ether. The combined ethereal extracts were dried and distilled. In this manner there was obtained 22.0 g. (88%) of 9-methyl-*cis-trans*- Δ^6 -octalone-1, b.p. 106–107° (7 mm.). Gas-liquid chromatography of this material on an Apiezon L column at 190° showed only one peak at 9.5 min. On a 10% silicone gum rubber column using temperature programming again one peak was observed at 198°. Redistillation afforded the analytical sample boiling at 126° (21 mm.).

Anal. Calcd. for C₁₁H₁₆O: C, 80.44; H, 9.82. Found: C, 80.26; H, 9.87.

The semicarbazone, prepared in 92% yield according to the procedure of Fieser,²⁶ melted at 195–205°. The melting point was not improved by further crystallization from either alcohol or methanol.

In another experiment 5.2 g. (0.02 mole) of the *n*-butylthiomethylene derivative (9) was cleaved as above, affording 3.2 g. crude octalone (6). When this material was condensed with furfural according to the procedure of Johnson and co-workers,²⁷ there was obtained 4.3 g. (90%) crude crystalline furfurylidene octalone, m.p. 70–75°. After two recrystallizations from ethanol, there was isolated 3.4 g. (70%) of the pure derivative (7), m.p. 76–78° alone or on admixture with an authentic sample.²²

After hydrogenation of 4.00 g. (0.0244 mole) of the *cis-trans*-methyl octalone over 250 mg. of 10% palladium-on-carbon in 30 ml. of ethyl acetate, there resulted 4.0 g. (98%) of *cis-trans*-methyldecalone-1, b.p. 100° (7 mm.) (bath temp.). Temperature programmed gas-liquid chromatography of this material on a silicone gum rubber—Chromosorb P column indicated the presence of two components in the ratio 1:3 eluted at 185° and 191°, respectively.

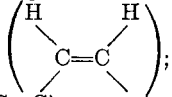
9-Methyl-*trans*- $\Delta^1,6$ -hexalin-2-carboxyaldehyde (11).—A solution of 5.7 g. (0.15 mole) of sodium borohydride in 15 ml. of 0.1 N aqueous sodium hydroxide was added to a

(36) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, p. 85.

(37) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6321 (1956).

solution of 40 g. (0.15 mole) of the *n*-butylthiomethylene ketone (9) in 500 ml. of methanol, and the reaction mixture was stirred at room temperature for 12 hr. Most of the methanol was removed at reduced pressure, and the product was isolated with ether in the usual manner.

After a solution of the crude *n*-butylthiomethylene alcohol in 700 ml. of ethanol and 130 ml. of 10% aqueous hydrochloric acid had stirred for 24 hr., most of the solvent was removed at reduced pressure, and the aldehyde isolated by ether extraction. Distillation of the residue obtained after evaporation of the ether afforded 16.7 g. (63%) of the α,β -unsaturated aldehyde, b.p. 62–64° (0.1 mm.). Redistillation afforded the analytical sample boiling at 65° (0.1

mm.). Infrared: $\lambda_{\text{max}}^{\text{film}}$ 3.29 μ ; 3.68 μ , 5.95 μ (—CHO); 6.12 μ (conj. C=C).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.26; H, 8.89.

The semicarbazone, prepared in 87% yield according to the procedure of Fieser,³⁶ melted at 216–218°.

Anal. Calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.90; H, 8.12; N, 17.89.

9-Methyl-*trans*- $\Delta^{1,6}$ -hexylmethanol (12).—To a solution of 880 mg. (5.4 mmoles) of the aldehyde (11) in 25 ml. of methanol was added a solution of 230 mg. (6 mmoles) of sodium borohydride in 10 ml. of 0.1 *N* aqueous sodium hydroxide. The solution was stirred at room temperature for 2 hr., and the product isolated with ether in the usual manner. When the residue, obtained after the evaporation of the ether, was evaporatively distilled at 90° (0.05 mm.) (bath temp.) there was obtained 790 mg. (88%) of the alcohol (12). Redistillation of a sample of this material at 90° (0.05 mm.) (bath temp.) afforded the analytical sample. Gas-liquid chromatography of this material on a 6-ft. column of 15% diethylene glycol succinate polyester on Chromosorb W at 145° showed one symmetrical peak with a retention time of 13.4 min.

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.85; H, 10.18. Found: C, 80.65; H, 10.03.

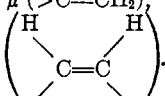
The *p*-nitrobenzoate of this alcohol, obtained from *p*-nitrobenzyl chloride in pyridine, melted at 108–110°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.62; H, 6.52; N, 4.34.

Equilibration of the Alcohol (12) with Ethyl Vinyl Ether.—Following the procedure of Watanabe,³⁷ 620 mg. (3.8 mmoles) of the alcohol (12) in 15 ml. of ethyl vinyl ether containing 150 mg. of mercuric acetate was refluxed for 6 hr. Solid potassium carbonate was added, the excess ethyl vinyl ether removed on the steam bath, and the residue transferred to a column packed with 60 gm. of alumina. Evaporative distillation of the material eluted with 1 l. of petroleum ether (40–60°) at 65° (0.03 mm.) (bath temp.) afforded 612 mg. (80%) of the vinyl ether (13) as a colorless, mobile liquid. The analytical sample was obtained by another evaporative distillation at 65° (0.03 mm.) (bath temp.).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.02; H, 9.66.

Pyrolysis of the Vinyl Ether (13).—Following the procedure of Burgstahler,³⁸ 490 mg. (2.4 mmoles) of the vinyl ether (13) under nitrogen in a sealed tube was heated at 196° for 3 hr. in a refluxing ethylene glycol bath. The contents of the cooled tube were chromatographed on 50 g. of Florisil. Elution with 500 ml. of 1% petroleum ether (b.p. 40–60°) gave 440 mg. (90%) of colorless liquid aldehyde (14). Evaporative distillation of this material at 90° (0.05 mm.) (bath temp.) afforded 400 mg. (82%) of the aldehyde (14). On gas-liquid chromatography of this aldehyde on a 15% diethylene glycol succinate–Chromosorb W column at 145°, there was found a single sharp peak at 12.8 min. Infrared:

$\lambda_{\text{max}}^{\text{film}}$ 3.23 μ , 11.18 μ ($>\text{C}=\text{CH}_2$); 3.68 μ , 5.82 μ (—CHO) and 3.29 μ , 6.10 μ .

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.01; H, 9.95.

9-Methyl-2-methylene-*trans*- Δ^6 -octal-1 α -yl Acetic Acid (15).—The procedure followed is a modification of that of Robinson.²⁸ To a rapidly stirred solution of 250 mg. (1.2 mmoles) of the aldehyde (14) in 7 ml. of ethanol and 2.2 ml. of a solution containing 1.24 g. silver nitrate in 13 ml. of water was added dropwise 8.4 ml. of a solution containing 1.24 g. of sodium hydroxide in 50 ml. of water. The mixture was stirred for 2 hr.; the precipitated silver removed by filtration and the filtrate washed with ether. Acidification of the basic aqueous solution afforded the acid (15), which was isolated with ether in the usual manner. The oily residue (230 mg., 87%), obtained by the evaporation of the ether, crystallized on trituration with petroleum ether (b.p. 40–60°); recrystallization of this material afforded 160 mg. (61%) of the acid (15), m.p. 103–111°. The analytical sample obtained after two further crystallizations from petroleum ether (b.p. 40–60°) melted at 115–117°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15. Found: C, 76.46; H, 9.25.

9-Methyl-2-methylene-*trans*- Δ^6 -octal-1 α -ylethanol (A).—To a solution of 102 mg. (0.5 mmoles) of the aldehyde (14) in 2.5 ml. of methanol was added 23 mg. of sodium borohydride in 1 ml. of 0.1 *N* aqueous sodium hydroxide. After the usual work-up, there was obtained 90 mg. (90%) of the alcohol (A) as a liquid which was evaporatively distilled at 90° (0.05 mm.) (bath temp.).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C, 81.50; H, 10.75. Found: C, 81.12; H, 10.55.

The *p*-nitrobenzoate, obtained from *p*-nitrobenzyl chloride in pyridine, melted at 73–76°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.00; H, 7.20; N, 4.11.

9-Methyl-1,1-ethylenedioxy-*trans*- Δ^6 -octalin (16).—A solution of 2.2 g. (0.013 mole) of the methylated *cis-trans* octalone mixture, 1.2 g. (0.02 mole) of ethylene glycol, and a trace of *p*-toluenesulfonic acid in 40 ml. of benzene was refluxed under a water separator for 12 hr. The mixture was washed with 10% aqueous potassium bicarbonate solution and dried (Na_2SO_4). After the solvent was removed at reduced pressure, the residue afforded 2.6 g. (96%) of the ketal (16), b.p. 173° (30 mm.) (bath temp.).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 74.96; H, 9.68. Found: C, 74.94; H, 9.78.

9-Methyl-1,1-ethylenedioxy-6 α ,7 α -oxido-*trans*-decalin (17).—A solution of 6.0 g. (0.029 mole) of the ketal (16) in 200 ml. of benzene was treated with 60 ml. (0.03 mole) of a 0.5 *M* of perbenzoic acid, and the reaction mixture allowed to stand in the dark at room temperature for 10 hr. At the end of this period the solution gave a negative starch-iodide test and was washed with 10% aqueous potassium bicarbonate, dried (Na_2SO_4), and distilled. In this fashion there was obtained 5.6 g. (86%) of the oxide (17) as a colorless liquid, b.p. 98–100° (0.1 mm.). The analytical sample boiled at 100° (0.1 mm.).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 69.61; H, 8.99. Found: C, 69.42; H, 9.02.

9-Methyl-6 α -hydroxy-*trans*-decalone-1 (19).—To a slurry of 3 g. (0.081 mole) of lithium aluminum hydride in 250 ml. of dry ether was added 5.3 g. (0.024 mole) of the oxide (17) in 25 ml. of dry ether. After the reaction mixture was refluxed for 11 hr. in a nitrogen atmosphere, the hydride complex was destroyed with 6 ml. of water and 4.8 ml. of 10% aqueous sodium hydroxide solution. After filtration of the precipitated salts and evaporation of the ether, there remained 4.0 g. (76%) of crude hydroxy ketal (18) as a colorless oil.

The hydroxy ketal (18) in 100 ml. of acetone and 100 ml. of 3 *N* aqueous hydrochloric acid was warmed on the steam bath for 10 min. Most of the acetone was removed at reduced pressure and the resulting oil isolated by ether extraction. On trituration with petroleum ether b.p. (60–75°) this oil crystallized; recrystallization from the same solvent afforded 2.0 g. (61%; 46% over-all) of the hydroxy ketone (19), m.p. 112–114°. After two further crystallizations from petroleum ether (b.p. 60–75°) the analytical sample melted at 113–114°.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.30; H, 9.85.

9-Methyl-*trans*-decal-1,6-dione (20).—An ice-cooled solution of 60 mg. (0.33 mmole) of the hydroxy ketone (19) in 2 ml. of acetone was oxidized with 0.08 ml. of Jones

reagent.³² Chromatography of the resulting oil on 3 g. of alumina afforded 46 mg. (78%) of the dione, m.p. 54–57°, eluted with 200 ml. of 50% benzene petroleum ether (b.p. 40–60°). Recrystallization of this dione from ether-petroleum ether (b.p. 40–60°) afforded 34 mg., m.p. 56.5–57.5° alone or on admixture with the authentic sample.³³

Acknowledgment.—It is a pleasure to acknowledge the financial support of the National Institutes of Health through a research grant RG-9067.

(33) Prepared from 10-methyl- $\Delta^{1(9)}$ -octal-2,5-dione by the method of A. J. Birch, E. Pridie, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

Synthesis of a Macrocycle by Application of the Wittig Reaction

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A model macrocycle 1,2,5,6,9,10,13,14-tetrabenzocyclohexadeca-1,3,5,7,9,11,13,15-octaene (I) has been successfully synthesized by a five-step process employing Wittig reactions for the preparation of intermediates and final ring closure. This sequence appears to be preferable to classical approaches for macrocyclic syntheses. Evidence derived from absorption spectra indicates (I) to exist in an all-*trans* configuration and a nonconjugated conformation.

In recent years, applications of the extremely versatile Wittig reaction¹ have been extended beyond the preparation of acyclic olefins to the synthesis of medium ring compounds. Intermolecular processes have been employed by Wittig and co-workers in the synthesis of 1,2-benzocyclohepta-1,3,6-triene and 1,2-benzocycloocta-1,3,7-triene from phthalaldehyde and the ylides, $Ph_3P=CH(CH_2)_nCH=PPh_3$ ($n = 1,2$)² and by Dimroth in a similar synthesis of 3-benzoxepin.³ Recently, Bieber⁴ has reported the first successful intramolecular Wittig reaction; the ylide derived from (5-oxo-5-phenylpentyl)-triphenylphosphonium bromide readily cyclizes to 1-phenylcyclopentene.

This study was designed to test the feasibility of extending the Wittig olefin formation procedure to macrocyclic compounds. Many of the known methods for the formation of macrocycles involve multistep processes giving low yields and often introducing elements of structural ambiguity. Application of the Wittig reaction in this area might be of more general synthetic utility since the reaction is structurally unequivocal and more direct synthetic routes may be derived. The macrocycle, 1,2,5,6,9,10,13,14-tetrabenzocyclohexadeca-1,3,5,7,9,11,13,15-octaene (I) was chosen as the synthe-

tic objective of this study because it had previously been synthesized in an unambiguous fashion by Bergmann⁵ by a typical multistep process; this material was also of interest as a possible coordinating agent for metal ions.

The general method employed for the synthesis of I is patterned after that of previous workers^{2,3} and is shown in the sequence of reactions 1–4.

The phosphonium salt (V), the precursor of the required diylide, is an *o*-distyrylbenzene structure and is consequently amenable to synthesis by Wittig techniques. Wittig² showed that *o*-divinylbenzene could be synthesized in good yield by reaction of *o*-phthalaldehyde with a methylene ylide and a related synthesis of a 2,2'-divinylbiphenyl derivative has been reported.⁶ More recently, Campbell and McDonald demonstrated convincingly that the Wittig reaction is a superior method for the synthesis of *p*-distyrylbenzenes⁷; the general experimental techniques employed in the Wittig reactions (reactions 1,4) in this study are modifications of established procedures.^{7,8}

In a preliminary study, the synthesis of 1,2-distyrylbenzene (IVa) was carried out as a model for the synthesis of IVb. The *o*-xylylene bisphosphonium salt (II) was prepared in good yield by quaternization of triphenylphosphine with *o*-xylyl-

(1) For recent reviews, see: U. Schöllkopf, *Angew. Chem.*, **71**, 260 (1959); S. Trippett in "Advances in Organic Chemistry: Methods and Results," Vol. I, R. A. Raphael, E. C. Taylor, and H. Wynberg, eds., Interscience Press, New York, 1960, pp. 83–102.

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