

**Instruments.**—Infrared spectra were run on Perkin-Elmer Model 337 and Model 21 spectrophotometers, ultraviolet spectra on a Cary Model 14 spectrophotometer, and optical rotatory dispersion curves on a Cary Model 60 recording spectropolarimeter.<sup>24</sup> Ultraviolet spectra were determined by Miss Saima Karp,

**Acknowledgment.**—The authors wish to thank Dr. G. G. Lyle for some helpful discussions.

(24) Reference to a company or product does not imply approval or recommendation of the product by the U. S. Department of Agricultural to the exclusion of others that may be suitable.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASSACHUSETTS]

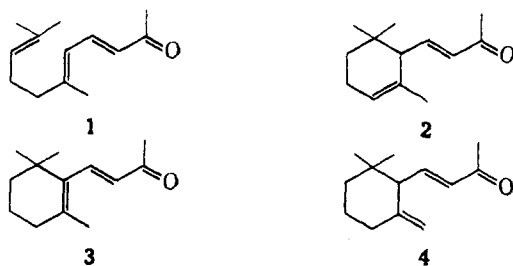
## Bicycloionones and Tricycloionones

BY G. BÜCHI, E. KOLLER, AND C. W. PERRY<sup>1</sup>

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Treatment of *cis*-pseudoionone with titanium tetrachloride in benzene solution yielded an ill-defined mixture of chlorine-containing ketones. After dehydrohalogenation with collidine, bicycloionone and epibicycloionone were isolable in 32 and 3% yields, respectively. The structures of the two bicycloionones were established and their formation is discussed in terms of a speculative scheme. The mineral-acid-catalyzed cyclization of pseudoionone was known to yield minor amounts of tricycloionone. Mechanistic considerations led to a hypothetical structure for this ketone which was fully supported by chemical and spectroscopic arguments.

The strikingly simple synthesis of  $\alpha$ -ionone (2) and  $\beta$ -ionone (3) from pseudoionone (1) was discovered at the end of the last century.<sup>2</sup> This acid-catalyzed cyclization has received a great deal of attention ever since because the ionones are bulk perfumes and starting materials for the syntheses of vitamin A and of the carotenes. More recent investigations<sup>3-5</sup> have shown that minor quantities of  $\gamma$ -ionone (4) are formed also in the cyclization. In the course of efforts to improve yields and to vary the ratio of cyclic products formed the catalytic action of many acidic reagents was studied,<sup>6-8</sup>



Titanium tetrachloride was among the catalysts investigated and reported<sup>7</sup> to yield a product with the composition  $C_{13}H_{19}Cl$ . According to Schinz and Vogt,<sup>9</sup> treatment of pseudoionone (1) with titanium tetrachloride produced varying amounts of  $\beta$ -ionone (3) in addition to a mixture of halogen-containing substances. Dehydrochlorination with hot collidine furnished a halogen-free product,  $C_{13}H_{20}O$ , which we shall call bicycloionone. Because it did not combine with Girard reagent and did not form other carbonyl derivatives, the investigators believed it to be an oxide. Catalytic hydrogenation furnished a saturated dihydro

derivative and oxidation with potassium permanganate gave both a ketodicarboxylic acid ( $C_{13}H_{20}O_5$ ) and a yellow triketone ( $C_{13}H_{18}O_3$ ). These transformations suggested the presence of a disubstituted cyclic double bond in the molecule and, although the evidence available did not reveal the structure of bicycloionone, the problem was not pursued further.

When *cis*-pseudoionone (5)<sup>10</sup> was added to excess titanium tetrachloride in an inert solvent, a mixture of unstable, chlorine-containing compounds was produced. From this a halogen-free mixture consisting of  $\alpha$ -ionone (2, 7%),  $\beta$ -ionone (3, 2%), bicycloionone (32%), and a fourth isomer (3%) was procured by exposure to hot collidine. Similar treatment of *trans*-pseudoionone (1)<sup>10</sup> resulted in a multitude of products, but neither bicycloionone nor the fourth isomer was detected. Bicycloionone was purified carefully and obtained as a low melting solid. Its infrared spectrum possessed absorptions attributable to a carbonyl group and a *cis*-disubstituted double bond. An n.m.r. spectrum<sup>11</sup> revealed four methyl groups all attached to carbon atoms bearing no hydrogen atoms, and one of these methyl substituents apparently was part of an acetyl function (7.98  $\tau$ ). A singlet corresponding in intensity to one proton at 7.60  $\tau$  suggested an additional hydrogen atom adjacent to this carbonyl group. Furthermore, the spectrum confirmed the presence of a disubstituted double bond and the splitting pattern observed required at least one allylic hydrogen atom. In agreement with the earlier report,<sup>9</sup> catalytic hydrogenation of bicycloionone gave the saturated dihydrobicycloionone. Treatment of this ketone with sodium ethoxide in deuterioethanol at room temperature produced a trideuterioketone, but at elevated temperature a fourth deuterium atom was introduced. Examination of the mass spectra of these deuterated compounds showed that they were indeed methyl ketones. These observations completed the characterization of the functional groups and the transformations to be described now revealed the skeletal structure.

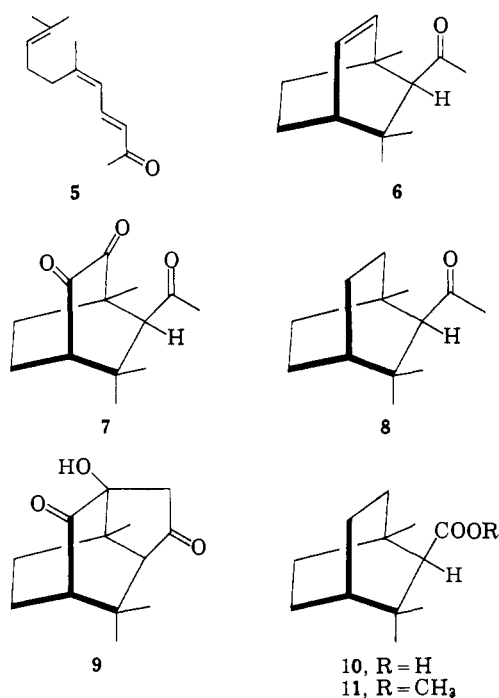
The  $\alpha$ -diketone 7,<sup>9</sup> available from bicycloionone (6)

(10) Y.-R. Naves and A. Odermatt, *Bull. soc. chim. France*, 377 (1958), and other references cited.

(11) Chemical shifts are recorded in  $\tau$ -values: G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

- (1) National Science Foundation Predoctoral Fellow 1960-1962.  
 (2) F. Tiemann and P. Krüger, *Ber.*, **26**, 2675 (1893); **28**, 1757 (1895); **31**, 809 (1898); **33**, 3703 (1900).  
 (3) E. T. Theimer, W. T. Somerville, B. Mitzner, and S. Lemberg, *J. Org. Chem.*, **27**, 635 (1962).  
 (4) G. Ohloff and S. Mignat, *Ann.*, **652**, 115 (1962).  
 (5) D. Felix, G. Ohloff, and E. Kovats, *ibid.*, **652**, 126 (1962).  
 (6) E. Royals, *Ind. Eng. Chem.*, **38**, 546 (1946).  
 (7) Y.-R. Naves, R. Wahl, P. Ardizio, and C. Favre, *Bull. soc. chim. France*, **20**, 873 (1953).  
 (8) Y.-R. Naves, *Compt. rend.*, **236**, 1573 (1953).  
 (9) H. R. Vogt, Ph.D. Thesis, Eidgenössische Technische Hochschule, Zürich (1954).

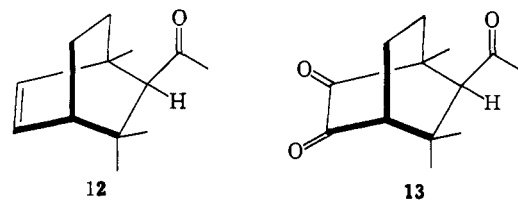
by oxidation with potassium permanganate, gave a negative ferric chloride color test although, to satisfy the n.m.r. evidence just mentioned, at least one hydrogen atom must be located on the carbon atoms adjacent to the  $\alpha$ -diketone grouping. That we were indeed dealing with a nonenolizable  $\alpha$ -diketone was confirmed by the ultraviolet absorption spectrum of the triketone **7** which was identical in both neutral and basic solution. Both ultraviolet and infrared spectra of  $\alpha$ -diketones are influenced strongly by the dihedral angle between the two carbonyl groups.<sup>12</sup> In the case at hand ( $\lambda_{\max}^{\text{EtOH}}$  434  $\mu$ ,  $\nu_{\max}^{\text{Nujol}}$  1720  $\text{cm}^{-1}$ ) the carbonyl functions subtend an angle of 0 to  $\sim 35^\circ$ , midway between camphorquinone (0–10 $^\circ$ ,  $\lambda_{\max}^{\text{EtOH}}$  466  $\mu$ ,  $\nu_{\max}^{\text{Nujol}}$  1753  $\text{cm}^{-1}$ ) and 3,3,6,6-tetramethylcyclohexane-1,2-dione (0–60 $^\circ$ ,  $\lambda_{\max}^{\text{EtOH}}$  380  $\mu$ ,  $\nu_{\max}^{\text{Nujol}}$  1709  $\text{cm}^{-1}$ ). These facts necessitate the placement of the  $\alpha$ -diketone grouping in a bridged framework containing eight carbon atoms. Bicycloionone itself should be a substituted bicyclo[2.2.2]octene and the presence of this structural feature was established as follows.



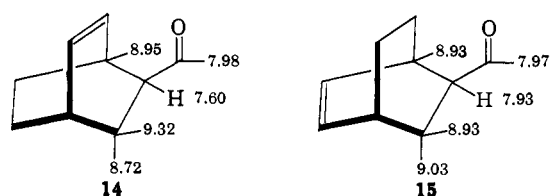
Oxidation of dihydrobicycloionone (**8**) with nitric acid gave a C<sub>12</sub>-carboxylic acid (**10**). To exclude skeletal rearrangement in the course of this brutal oxidation, the acid was reconverted to the original ketone **8** by condensing its acid chloride with methylmagnesium iodide. The acid **10** was readily resolved using quinine, and the (–)-methyl ester **11** prepared from the (–)-acid was racemized on prolonged treatment with sodium methoxide in hot tetrahydrofuran solution. Epimerization has thus resulted in racemization, demonstrating that the hypothetical hydrocarbon formally available by replacement of the carbomethoxy group by a hydrogen atom has a plane of symmetry. This can be rationalized if a bridged structure is present; since one bridge is already known to contain a chain of two methylene groups, the second bridge must have an identical part structure. Only two carbon

atoms are available for the construction of the third bridge, and the saturated ester **11** consequently has to be a substituted bicyclo[2.2.2]octane. All atoms of the bicycloionone molecule are now accounted for. To arrive at its structure it was only necessary to differentiate between two remaining possibilities; namely, **6** and its isomer with the methyl group placed on the other bridgehead carbon atom. The latter structure is ruled out by the n.m.r. spectrum of bicycloionone in which the methine proton adjacent to the carbonyl group appeared as a singlet. Further evidence in favor of **6** was provided by the mass spectrum (see below).

Before discussing the stereochemistry of bicycloionone (**6**) it might be useful to consider the structure of the fourth isomer produced in the cyclization of *cis*-pseudoionone (**5**). This substance again did not combine with carbonyl reagents, but the infrared spectrum exhibits absorption associated with a carbonyl group. Additional peaks suggested that the new isomer also contains a *cis*-disubstituted double bond. The n.m.r. spectrum was very similar to that of bicycloionone (**6**) and the presence of one allylic proton was revealed by the quadruplet signal for one of the olefinic protons. These spectral properties led us to believe that the fourth isomer was epibicycloionone (**12**) and in confirmation of this hypothesis base-catalyzed epimerization yielded an equilibrium mixture containing bicycloionone (**6**) and epibicycloionone (**12**) in a ratio of three to one. Catalytic hydrogenation of the epimer **12** furnished the previously mentioned dihydroketone **8**.



The configuration of the acetyl group in the two epimers **6** and **12** rests on several observations. Bicycloionone (**6**) but not its epimer **12** displays two absorption maxima in the carbonyl region of the infrared spectrum and two maxima in the ultraviolet spectrum. This is best explained by assuming interactions between the carbonyl group and the proximate double bond. The same conclusion concerning the geometry of the two isomers can be reached from an examination of the two n.m.r. spectra. Owing to the shielding effects of the double bond and the carbonyl group, the methyl substituent in bicycloionone (**6**) with *endo* relationship to the double bond appears at very high field. The difference in chemical shift of the methine protons adjacent to the carbonyl groups in the two isomers can be attributed to the same effect (see **14** and **15**).

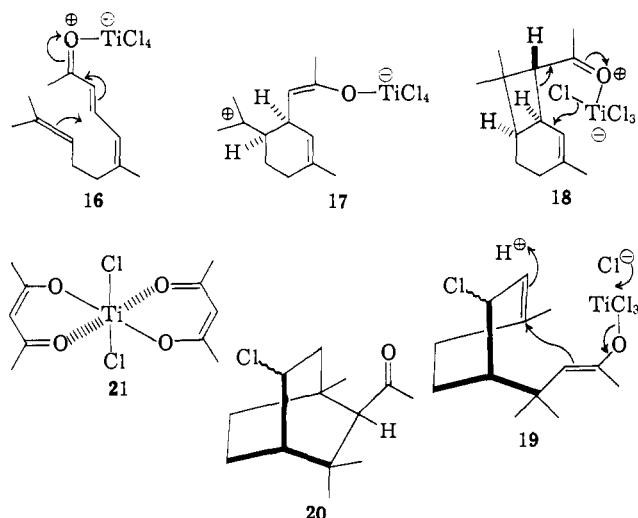


Despite their epimeric nature, the two bicycloionones **6** and **12** give rather different fragmentation patterns in the mass spectrometer. The spectra, which provide

(12) N. J. Leonard and P. M. Nader, *J. Am. Chem. Soc.*, **72**, 5388 (1950); C. Sandris and G. Ourisson, *Bull. soc. chim. France*, 350 (1958).

further evidence in favor of the stereochemistry assigned and for the location of the bridgehead methyl group, have been discussed elsewhere.<sup>13</sup> Finally, on treatment with alkali, the triketone **7** was converted to the aldol **9** whose spectral properties were in full accord with the structure assigned. Identical treatment of the epitriketone **13** available by oxidation of epibicycloionone (**12**) with potassium permanganate afforded neither the triketone **7** nor the aldol **9**. Consequently, epimerization did not occur under these conditions and the cyclization leading to the tricyclic aldol **9** provided chemical evidence for the configuration of bicycloionone (**6**).

Cyclization of *cis*-pseudoionone (**5**) with vanadium tetrachloride followed by treatment with collidine also produced the bicycloionones **6** and **12**, although in inferior yield. In contrast, attempts to prepare these substances from either *cis*- (**5**) or *trans*-pseudoionones (**1**) with the aid of boron trifluoride<sup>14</sup> in either benzene or benzene-acetic acid solutions failed. The mechanism of these cyclizations is not clear as yet, but a few comments seem justified at this time. The possibility that bicycloionone (**6**) is formed initially but subsequently converted to a chloroketone (**20**) seems eliminated for the following reasons. The unsaturated ketone **6** was recovered unchanged after treatment with a large excess of hydrogen chloride in benzene solution. In a similar experiment but with added titanium tetrachloride bicycloionone **6** was transformed to a mixture of three products; after treatment with collidine the original ketone was not detected by gas chromatography. Titanium tetrachloride is known to be a strong electrophile capable of forming complexes with ketones.<sup>15</sup> This suggests that the mechanism of cyclization involves prior complexing of the carbonyl oxygen atom with the Lewis acid to give an intermediate (**16**) which when derived from *cis*-pseudoionone (**5**) can cyclize to the monocyclic complex **17** and thence to the bicyclic structure **18**.



To study the behavior of the hypothetical cyclobutane intermediate **18** an attempt was made to prepare

(13) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 148.

(14) A. Kitchens, U. S. Patent 2,517,576 (1938).

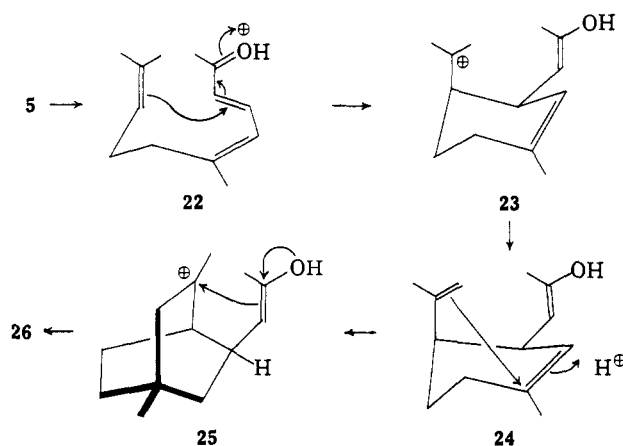
(15) B. P. Susz and A. Lachavanne, *Helv. Chim. Acta*, **41**, 634 (1958); B. P. Susz, *Compt. rend.*, **248**, 2569 (1959); D. Cassimatis and B. P. Susz, *Helv. Chim. Acta*, **43**, 852 (1960).

its organic moiety by ultraviolet irradiation of pseudoionone.<sup>16</sup> Irradiation of either *trans*- (**1**) or *cis*-pseudoionone (**5**) led to a steady-state mixture of the two starting ketones and a third substance. Repeated fractional distillation yielded a fraction containing 20% *cis*-pseudoionone (**5**), 5% *trans*-pseudoionone (**1**), and 75% of the photoproduct. The spectral properties of this concentrate were very similar to those of the starting ketones indicating that the photoisomer was not the desired cyclobutane but most probably a geometric isomer of pseudoionone containing a *cis*-disubstituted double bond.

A rearrangement of the cyclobutane complex **18** to the monocyclic intermediate **19** is postulated to account for the introduction of chlorine into the molecule; the displacement of chloride by a carbonyl oxygen atom has precedent in the formation of the complex **21** from titanium tetrachloride and acetylacetone.<sup>17</sup> The final cyclization of the complex **19** to the chloroketone **20** requires hydrogen chloride which is definitely present in the reaction mixture. It has to be reiterated that this scheme is purely speculative and that the structure of the crucial chloroketone **20** was not established because attempts to isolate it in pure form failed.

In the course of extensive studies on the mineral acid-catalyzed cyclization of pseudoionone, Naves and Bachmann<sup>18</sup> isolated a new isomer of ionone. This substance gave a negative iodoform test, did not combine with bisulfite, but reacted smoothly with Girard reagent thus allowing its separation from "nonketonic" products. It was stable to potassium permanganate at ambient temperature and the ultraviolet spectrum<sup>19</sup> of the semicarbazone revealed no conjugated chromophore. On the basis of this evidence it was concluded that the new isomer was tricyclic and, accordingly, it was called tricycloionone.

We have studied the chemistry of tricycloionone in some detail and wish to present evidence in favor of structure **26**. The pure ketone, identical with an au-



thentic sample,<sup>20</sup> was isolable in 2% yield from "ionone forerun" supplied by Maywood Chemical Works, May-

(16) Compare with the photochemical cyclizations of carvone to carvone-camphor (G. Ciamician and P. Silber, *Ber.*, **41**, 1928 (1908); G. Büchi and I. M. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957)) and of citral to photo-citral-B (R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, **19**, 1995 (1963)).

(17) K. C. Pande and R. C. Mehrotra, *Chem. Ind. (London)*, 1198 (1958).

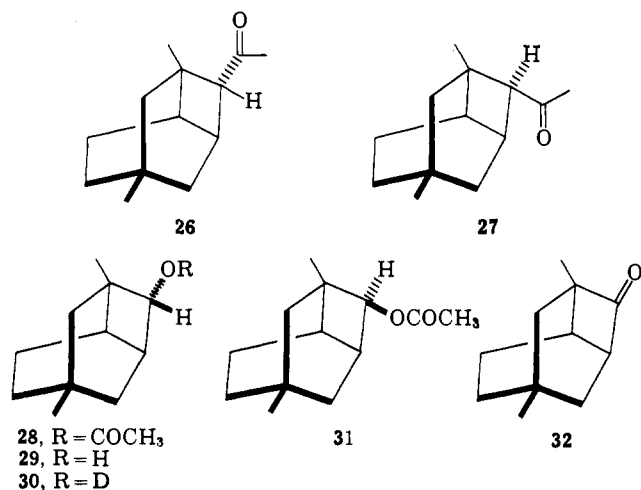
(18) Y.-R. Naves and P. Bachmann, *Helv. Chim. Acta*, **27**, 645 (1944).

(19) Y.-R. Naves and P. Ardizio, *ibid.*, **31**, 1427 (1948).

(20) We wish to thank Dr. Y.-R. Naves, Givaudan and Cie., Geneva, for a sample of tricycloionone semicarbazone.

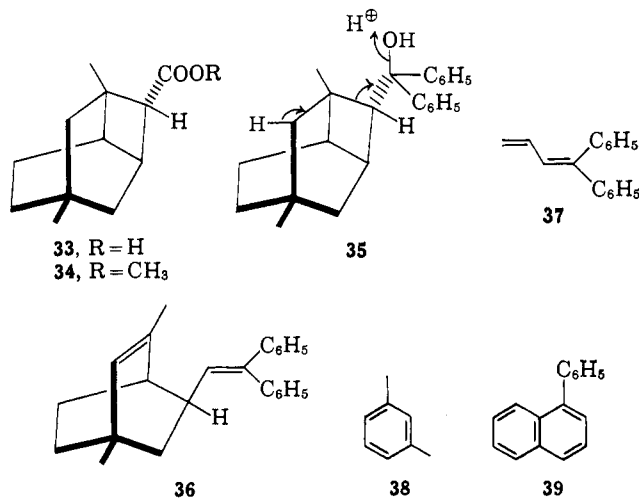
wood, N. J.<sup>21</sup> Since "ionone forerun" seems to represent only a "small" fraction of the total product formed in the cyclization of technical pseudoionone, the actual yield of tricycloionone must be very low. An n.m.r. spectrum of tricycloionone revealed the presence of *only three* methyl groups. One of these is part of an acetyl group, while the two others are bonded to carbon atoms bearing no hydrogen. We assumed that tricycloionone originates from *cis*-pseudoionone (5) and mechanistic considerations presented in the sequence 5 → 22 → 23 → 24 → 25 → 26 led to structure 26 which has been shown to be correct.

Tricycloionone was easily isomerized by strong base to a mixture of epimers 26 and 27. Pure epitricycloionone (27) could be converted to the same equilibrium mixture containing approximately two parts of tricycloionone (26) and one part of its epimer 27. Dreiding molecular models suggest that the *exo* isomer 26 should predominate at equilibrium and further data in support of this will be presented below. Mass spectra of tetradeuteriotricycloionone and its epimer confirmed the presence of the acetyl group and the adjacent hydrogen atom. It was hoped that the infrared spectrum of the ketone 32 might provide evidence for the cyclobutane ring, and this degradation product was acquired as follows. Oxidation of the two ketones 26 and 27 with peracetic acid yielded the epimeric acetates 28 and 31. The n.m.r. spectrum of the acetate 28 had a singlet signal at 5.67  $\tau$  attributable to the proton on the carbon atom bearing the acetoxy group, while the spectrum of the epimer 31 exhibited a doublet for the same proton. An examination of molecular models shows that the dihedral angle between the proton in question and that adjacent to it is approximately 90° in the acetate 28 and, in agreement with theory, no coupling is observed.<sup>22</sup> In the epimeric acetate 31 the dihedral angle between these two protons is much smaller and the appearance of a doublet ( $J = 6$  c.p.s.) is justified. Hydrolysis of the acetate 28 furnished the alcohol 29 whose n.m.r. spectrum was initially disturbing because it revealed coupling of the hydrogen atom bearing the hydroxy group. In the deuterated alcohol 30, however, this same proton appeared again as a singlet. Oxidation of the alcohol 28 gave the cyclobutanone 32,

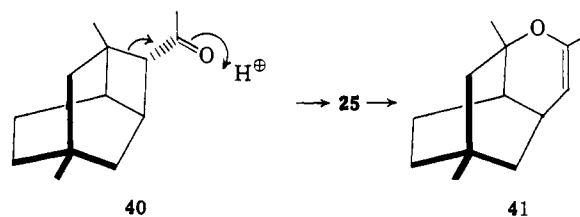


$\nu_{\max}^{\text{C=O}}$  1772 cm.<sup>-1</sup>, whose n.m.r. spectrum indicated the presence of only one proton adjacent to the carbonyl function.

We now wish to discuss another series of transformations which provided further support for the structure of tricycloionone (26), particularly because it led to compounds of established structures. Oxidation of tricycloionone (26) with sodium hypochlorite furnished the carboxylic acid 33 which was transformed to the methyl ester 34, whose n.m.r. spectrum had a one-proton singlet at 7.91  $\tau$  indicating that no epimerization had occurred in the course of these operations. Treatment of the ester 34 with excess phenylmagnesium bromide gave a sensitive alcohol 35 which was not obtained in pure form. When this alcohol was subjected to the action of acetic anhydride, it was smoothly converted to the diphenylethylene 36 whose n.m.r. spectrum was in full accord with the bicyclic structure assigned. Dehydrogenation of the hydrocarbon over a palladium catalyst yielded *m*-xylene (38) and 1-phenylnaphthalene (39). The latter hydrocarbon apparently originated from initially formed 1,1-diphenylbutadiene (37); under identical conditions this diene (37) was indeed transformed to 1-phenylnaphthalene (39).



In conclusion, we would like to describe an experiment which was designed to provide chemical evidence for the acetylcyclobutane moiety in tricycloionone (26). In concentrated sulfuric acid at 0° tricycloionone (26) was rapidly transformed to an isomer with intense infrared absorption at 1680 cm.<sup>-1</sup>. The most convincing evidence in favor of formula 41 was provided by



the n.m.r. spectrum which revealed three singlets attributable to the three magnetically different methyl groups and a doublet at 5.46  $\tau$  caused by the  $\beta$ -proton of the dihydropyran moiety.<sup>23</sup> This isomerization should proceed through a carbonium ion (25, arrows in

(21) We are indebted to Dr. R. R. Riso of this company for his help.

(22) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); *J. Chem. Phys.*, **30**, 11 (1959); H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 265.

(23) In dihydropyran itself this proton appears at 5.46  $\tau$ : L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 62.

40) which was invoked also in the formation of tricycloionone (26) from *cis*-pseudoionone (5). If these arguments are correct, it has to be assumed that tricycloionone is the kinetically controlled product resulting from carbon alkylation of the cation 25 while the dihydropyran (41) represents the less strained and thermodynamically more stable oxygen-alkylated isomer.

### Experimental

Melting points were determined in sealed, evacuated capillaries or on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 21 recording spectrophotometer, on a Baird Model B recording spectrophotometer, or on a Perkin-Elmer Model 237 recording spectrophotometer, and bands relevant to structural assignments are listed textually. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model 14. Varian Associates HR-60 and A-60 instruments were used for recording nuclear magnetic resonance (n.m.r.) spectra and peak positions are given in  $\tau$ -values. Optical rotations were determined in a Zeiss polarimeter using a 1-dm. tube. Microanalyses were performed by Dr. S. M. Nagy and associates at M. I. T. or by the Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

***cis*-Pseudoionone (5).**—Careful distillation of pseudoionone obtained from Hoffmann-LaRoche and Co., Nutley, N. J., through a 1-m. spinning band column yielded two main fractions: (1) b.p. 77° (0.1 mm.) and (2) b.p. 83.5° (0.14 mm.). Fraction 1 consisted of 85–90% of *cis*-pseudoionone (5) and 10–15% of *trans*-pseudoionone (1) according to gas chromatography and had the following properties:  $\nu$  (10% in CCl<sub>4</sub>) 1685, 1667, 1630, 1590, 975 cm.<sup>-1</sup>;  $\nu$  (pure liquid) 885, 827, 748 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  293  $\mu$  ( $\epsilon$  21,400); n.m.r. (20% in CCl<sub>4</sub>) 2.73 (1H, quadruplet),  $J = 11$  c./sec.,  $J' = 15.5$  c./sec.), 3.98 (1H, broad singlet or narrow multiplet), 4.21 (1H, unresolved multiplet), 4.93 (1H, broad multiplet), 7.80 (4H, many unresolved peaks), 7.87 (3H, singlet), 8.13 (3H, narrow multiplet), 8.39  $\tau$  (6H, multiplet).

***trans*-Pseudoionone (1).**—Fraction 2, b.p. 83.5° (0.14 mm.), from the distillation of technical pseudoionone was found to contain 85–90% of *trans*-pseudoionone (1) and 10–15% of *cis*-pseudoionone (5). This mixture had the following spectral properties:  $\nu$  (10% in CCl<sub>4</sub>) 1685, 1667, 1630, 1590, 975 cm.<sup>-1</sup>;  $\nu$  (pure liquid) 889, 828, 749 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  293  $\mu$  ( $\epsilon$  25,800); n.m.r. (20% in CCl<sub>4</sub>) 2.75 (1H, quadruplet,  $J = 10.5$  c./sec.,  $J' = 16$  c./sec.), 4.10 (2H, multiplet), 5.00 (1H, broad multiplet), 7.88 (7H, unresolved), 8.13 (3H, broad singlet), 8.37 (3H, broad singlet), 8.43  $\tau$  (3H, broad singlet).

#### Reaction of *cis*-Pseudoionone (5) with Titanium Tetrachloride.

—A solution of *cis*-pseudoionone (5, 90 g., 0.47 mole) in benzene (100 ml.) was added slowly to a solution of titanium tetrachloride (100 g., 58 ml., 0.53 mole) in a mixture of benzene (500 ml.) and heptane (100 ml.) at 5° under nitrogen. About 2 hr. was required for the addition. Anhydrous ether (200 ml.) was added slowly at 5°, and the reaction mixture was poured onto a mixture of ice (500 g.) and water (500 ml.). After separation of the phases and extraction of the aqueous phase with ether, the combined organic phase was washed in succession with 3 *N* hydrochloric acid, water, dilute sodium hydroxide solution, and water.

Collidine (100 ml.) was added to the dried organic solution, and the solvents were distilled until the pot temperature reached 160–165°. Refluxing was continued at this temperature overnight. The cooled mixture was poured onto a mixture of ice (500 g.) and concentrated hydrochloric acid (200 ml.). Extraction with ether gave a red-brown solution which was washed with 6 *N* hydrochloric acid, 3 *N* hydrochloric acid, water, and saturated sodium bicarbonate solution. Removal of the solvents from the dried extracts left a brown oil which was distilled rapidly through an 8-in. Vigreux column. A deep yellow liquid was obtained, b.p. 50–86° (0.4 mm.), which was separated by preparative scale gas chromatography into its four major components:  $\alpha$ -ionone (2, 7.2 g., 7%),  $\beta$ -ionone (3, 2.0 g., 2%), bicycloionone (6, 28.4 g., 32%), and epibicycloionone (12, 2.5 g., 3%). Considerable loss of material occurred during collection, but an estimate of yields using gas chromatography indicated: 7% of  $\alpha$ -ionone, 4% of  $\beta$ -ionone, 37% of bicycloionone, and 8% of epibicycloionone.

**Reaction of *trans*-Pseudoionone (1) with Titanium Tetrachloride.**—*Trans*-pseudoionone (1) was treated with titanium tetra-

chloride as described for *cis*-pseudoionone. Neither bicycloionone nor epibicycloionone was found among the many products.

**Identification of  $\alpha$ -Ionone (2).**— $\alpha$ -Ionone (2) obtained as described above was purified by repeated collection from a gas chromatographic column followed by short-path distillation, b.p. 125–130° (8 mm.). Its retention time on gas chromatography and its infrared spectrum were identical with those of a similarly purified sample of authentic  $\alpha$ -ionone (Givaudan Co.). Its 2,4-dinitrophenylhydrazone had m.p. 144–147.0°; authentic  $\alpha$ -ionone 2,4-DNP had m.p. 144–149°, m.m.p. 143–147°. The infrared spectra of the derivatives were identical.

**Identification of  $\beta$ -Ionone (3).**—The ketone described above was purified by gas chromatography. Its retention time was identical with that of authentic  $\beta$ -ionone on two different gas chromatographic columns (Dow-Corning Silicone No. 11 and tetrakis[2-cyanoethoxymethyl]methane). Their behavior on thin-layer chromatograms was identical. A sample of impure compound was converted to its 2,4-DNP in methanolic hydrochloric acid and chromatography of the derivative on acid-washed Florisil followed by crystallization from isopropyl ether–methanol gave deep red flakes with a metallic luster, m.p. 128–130°. An authentic sample of  $\beta$ -ionone 2,4-DNP had m.p. 126–127°, m.m.p. 126–128°. These two derivatives were further shown to be identical by thin-layer chromatography and infrared and ultraviolet spectroscopy.

**Bicycloionone (6).**—Several crystallizations of the crude ketone from pentane at –70° followed by short-path distillation, b.p. 105–118° (5 mm.), gave pure bicycloionone as white crystals, m.p. 27–29°;  $\nu$  (10% in CS<sub>2</sub>) 3040, 1712, 1688, 706 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  278, 284  $\mu$  ( $\epsilon$  55, 54); n.m.r. (30% in CCl<sub>4</sub>) 3.80 (2H, unsymmetrical multiplet), 7.60 (1H, singlet), 7.98 (7H, strong singlet over unresolved multiplet), 8.72 (4H, strong singlet over multiplet), 8.95 (3H, singlet), 9.32  $\tau$  (3H, singlet). The ketone did not react with 2,4-dinitrophenylhydrazine.

*Anal.* Calcd. for C<sub>13</sub>H<sub>20</sub>O: C, 81.20; H, 10.48. Found: C, 81.43; H, 10.53.

**Epibicycloionone (12),** obtained by the procedure already described, did not react with 2,4-dinitrophenylhydrazine either. Several crystallizations of the ketone from pentane at –70° followed by short-path distillation, b.p. 90–105° (5 mm.), gave pure epibicycloionone which solidified and had m.p. 35–39°;  $\nu$  (10% in CS<sub>2</sub>) 3025, 1705, 713, 698 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  293  $\mu$  ( $\epsilon$  33); n.m.r. (30% in CCl<sub>4</sub>) 3.85 (quadruplet  $J = 6$  c./sec.,  $J' = 8$  c./sec.), 4.25 (doublet,  $J' = 9$  c./sec.), 7.93 (singlet), 7.97 (singlet), 8.93 (two singlets), 9.03  $\tau$  (singlet).

*Anal.* Calcd. for C<sub>13</sub>H<sub>20</sub>O: C, 81.20; H, 10.48. Found: C, 81.49; H, 10.47.

**Interconversion of the Two Ketones 6 and 12.**—Pure bicycloionone and epibicycloionone (139 mg., 0.72 mmole) were treated separately for 8 days in refluxing absolute ethanol (5 ml.) containing sodium ethoxide (10.8 mmoles). After concentration of the solutions under reduced pressure, water (5 ml.) was added and the mixtures were extracted with pentane. After removal of the solvent from the dried extracts, the residues were distilled (short-path), b.p. 110–140° (11 mm.). Identical mixtures (approximately 76% bicycloionone and 24% epibicycloionone by gas chromatography) were obtained. Infrared spectra of the samples were superimposable and corresponded to a mixture of the two ketones 6 and 12.

**Dihydrobicycloionone (8).**—Bicycloionone (2.4 g., 12.5 mmoles) dissolved in ethyl acetate (20 ml.) was hydrogenated over platinum oxide (199 mg.) at 26.6° and atmospheric pressure. Within 90 min. the reduction was complete and 308 ml. of hydrogen had been absorbed (theoretical: 307 ml. for one double bond). Filtration and distillation of the mixture afforded dihydrobicycloionone as a colorless liquid, b.p. 107–110° (10 mm.). Crystallization of the product from pentane at –70° followed by slow evaporation of the liquid onto a cold surface at atmospheric pressure furnished white crystals, m.p. 44–45.0°;  $\nu$  (10% in CCl<sub>4</sub>) 2950, 1712 cm.<sup>-1</sup>. The ketone did not give an iodoform test and did not form a 2,4-dinitrophenylhydrazone, a semicarbazone, or an oxime. It was unaffected by aqueous potassium permanganate or by concentrated sulfuric acid.

*Anal.* Calcd. for C<sub>13</sub>H<sub>22</sub>O: C, 80.35; H, 11.41. Found: C, 80.40; H, 11.47.

**Hydrogenation of Epibicycloionone (12).**—The ketone 12 (173 mg., 0.90 mmole) in ethyl acetate (2 ml.) was hydrogenated over platinum oxide (6 mg.) at 28° and atmospheric pressure. Within 30 min. hydrogen uptake was complete. Filtration of the catalyst and distillation of the filtrate gave a colorless solid (130 mg.,

0.67 mmole, 75%), b.p. 100–105° (5 mm., short path), identical with dihydrobicycloionone in regard to retention time on gas chromatography and infrared spectrum.

**Trideuteriodihydrobicycloionone.**—To a solution of sodium (48 mg., 2.09 mmoles) in deuterioethanol (10 ml.) the dihydroketone **8** (100 mg., 0.52 mmole) was added. The solution was allowed to remain at room temperature for 10 hr. Solvent was removed under reduced pressure and replaced with fresh deuterioethanol (10 ml.). After another 12 hr. the solvent was evaporated under reduced pressure and deuterium oxide (2 ml.) was added to the residue. Three extractions of the mixture with pentane followed by distillation of the extracts gave white crystals, m.p. 35–49°;  $\nu$  (10% in CCl<sub>4</sub>) 2930, 2240, 2200, 1706 cm<sup>-1</sup>. A comparison of the mass spectra of dihydrobicycloionone (**8**) and this product showed that three deuterium atoms had replaced the three protons of the acetyl group (shift of a strong peak at *m/e* 43 in the spectrum of dihydrobicycloionone to *m/e* 46 in that of trideuteriodihydrobicycloionone).

**Tetradeteriodihydrobicycloionone.**—Dihydrobicycloionone (**8**, 139 mg., 0.72 mmole) was added to a solution of sodium (248 mg., 10.8 mg.-atoms) in deuterioethanol (5 ml.), and the mixture was allowed to reflux for 24 hr. After the solvent has been replaced with fresh deuterioethanol (5 ml.), as described in the previous paragraph, the mixture was heated for 2 additional hr. Isolation of the product gave a colorless liquid which solidified slowly;  $\nu$  (10% in CCl<sub>4</sub>) 2905, 2245, 2205, 2135, 1700 cm<sup>-1</sup>. Its mass spectrum showed that four hydrogen atoms had been replaced by deuterium.

**Carboxylic Acid 10.**—Concentrated nitric acid (5 ml.) was added to dihydrobicycloionone (310 mg., 1.59 mmoles) and the mixture was heated on a steam bath for 2 min. with constant agitation. Addition of cold water to the reaction mixture caused precipitation of a solid which was extracted into pentane, re-extracted into dilute sodium hydroxide solution, and reprecipitated with dilute hydrochloric acid. After the acid was washed and dried, it was sublimed at 130–145° (13 mm.) to yield crystals (173 mg., 55%), m.p. 166–167.0°. Further purification raised the m.p. to 168°;  $\nu$  (10% in CCl<sub>4</sub>) 3307–2467, 1702 cm<sup>-1</sup>; neut. equiv. 195. The acid was recovered unchanged after further exposure to boiling nitric acid.

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>: C, 73.42; H, 10.27. Found: C, 73.41; H, 10.29.

**Reconversion of the Acid 10 to Dihydrobicycloionone (8).**—A mixture of the acid (196 mg., 1.0 mmole) and thionyl chloride (1.64 g., 1 ml., 13.9 mmoles) was allowed to reflux for 5–10 min. and excess thionyl chloride subsequently was evaporated under reduced pressure. A solution of methylmagnesium iodide, prepared from methyl iodide (142 mg., 1.0 mmole) and magnesium (24 mg., 1.0 mg.-atom) in ether (1 ml.), was added dropwise to the residue, causing a violent reaction. Water was added, the mixture was extracted with ether, and the ether solution was washed with dilute aqueous sodium hydroxide and dried over anhydrous potassium carbonate. Distillation of the product (short path) gave a colorless liquid (69 mg., 36%) which was found by gas chromatography to be essentially pure dihydrobicycloionone (**8**). Further purification of the product by gas chromatography furnished a white solid exhibiting an infrared spectrum identical with that of the pure dihydroketone **8**.

**Methyl Ester 11.**—The carboxylic acid **10** (1.171 g.) was converted into its methyl ester **11** by means of an ether solution of diazomethane. The product, a colorless liquid, b.p. 115° (13 mm., short path), was purified by gas chromatography to yield pure ester (1.003 g., 80%);  $\nu$  (10% in CCl<sub>4</sub>) 1735 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>13</sub>H<sub>22</sub>O<sub>2</sub>: C, 74.24; H, 10.54. Found: C, 74.57; H, 10.45.

**(-)-Carboxylic Acid 10.**—A solution of the racemic acid **10** (6.00 g., 30.6 mmoles) in benzene (60 ml.) was added to a hot solution of quinine (4.96 g., 15.6 mmoles) and the benzene was removed under reduced pressure. Dissolving the oily residue in hot hexane (150 ml.) and adding water (60 ml.) with cooling and agitation caused precipitation of a hydrated quinine salt. Filtration and repeated crystallization of the precipitate from acetone–water to constant rotation yielded the presumably pure hydrated quinine salt of the (-)-carboxylic acid (4.60 g.), m.p. 104–113° dec.,  $[\alpha]_D -89.7 \pm 0.3^\circ$  (*c* 2.34 in ethanol). This salt was dissolved in ether, the solution was washed several times with concentrated hydrochloric acid and with water, and finally extracted several times with dilute sodium hydroxide solution. Acidification of the basic extracts followed by extraction with ether gave the crude acid **10** (2.59 g.). Sublimation of this

material at 128° (7 mm.) gave the pure optically active acid (2.28 g.), m.p. 167–168°,  $[\alpha]_D -14.5 \pm 0.2^\circ$  (*c* 5.20 in ethanol), infrared spectrum identical with that of the racemic acid **10**.

**(-)-Methyl Ester 11.**—The optically active acid **10** was converted by excess diazomethane in ether solution to its methyl ester in 84% yield,  $[\alpha]_D -11.8 \pm 0.2^\circ$  (*c* 10.98 in methanol). Its retention time in the gas chromatogram and its infrared spectrum were identical with those of the racemic ester **11**.

**Racemization of (-)-Methyl Ester 11.**—A solution of the optically active ester **11** (1.10 g., 5.24 mmoles) in dry tetrahydrofuran (10 ml.) containing a trace of methanol was heated under reflux with sodium hydride (480 mg., 20 mmoles). After 4 days, methanol (3 ml., 75 mmoles) was added and heating was continued for another 10 days. The solvents were removed by distillation under reduced pressure, and the residue was taken up in ether, washed with water, and dried over sodium bicarbonate and anhydrous calcium chloride. Removal of the ether and distillation of the residue afforded a colorless ester (399 mg., 1.90 mmoles, 36% recovery), b.p. 104–110° (4 mm.),  $[\alpha]_D -0.58 \pm 0.07^\circ$  (*c* 12.95 in methanol), corresponding to 95% racemization. The gas chromatographic retention time and infrared spectrum of the product were identical with those of racemic and optically active esters **11**.

**$\alpha$ -Diketone 7.**—A solution of bicycloionone (1.00 g., 5.2 mmoles) in acetone (100 ml.) and acetic acid (10 ml.) was treated at 0° with a solution of potassium permanganate (1.90 g., 12.0 mmoles) in water (30 ml.). After remaining at room temperature for 30 min., the mixture was heated on a steam bath. Aqueous sodium bisulfite was added to decolorize the solution, which then was poured into ether (100 ml.). Evaporation of the dried and filtered ether solution gave a yellow oil which, when dissolved in a small amount of ether, deposited yellow crystals. Evaporation of the mother liquors gave a yellow gum which was redissolved in acetone (10 ml.) and acetic acid (5 ml.), warmed to the boiling point, and treated with approximately 2 ml. of a saturated solution of calcium permanganate tetrahydrate in acetone. After a few minutes, the mixture was worked up as described, yielding an additional crop of yellow crystals. Repetition of the calcium permanganate oxidation of the mother liquors resulted in the accumulation of 900 mg. of yellow material, which on chromatography over acid-washed Florisil afforded 680 mg. of a bright yellow gum. Crystallization from benzene–ether gave the  $\alpha$ -diketone **7** (344 mg., 1.55 mmoles, 30%) as fine rods, changing to anvil-shaped crystals at 160°, m.p. 187–188°,  $\nu$  (Nujol mull) 1720, 1691 cm<sup>-1</sup>;  $\nu$  (5% in CHCl<sub>3</sub>) 1748 (sh), 1735, 1708 cm<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  249, 434 m $\mu$  ( $\epsilon$  706, 31);  $\lambda_{\text{max}}^{\text{EtOH-KOH}}$  249, 432 m $\mu$  ( $\epsilon$  697, 30);  $\lambda_{\text{max}}^{\text{CHCl}_3}$  437 m $\mu$  ( $\epsilon$  33); no color reaction with ferric chloride in ethanol solution.

*Anal.* Calcd. for C<sub>13</sub>H<sub>18</sub>O<sub>3</sub>: C, 70.14; H, 8.16. Found: C, 70.20; H, 8.04.

**Epimeric  $\alpha$ -Diketone 13.**—Epibicycloionone (**12**, 2.2 g., 11.4 mmoles), dissolved in reagent grade acetone (100 ml.) and water (5 ml.), was slurried with powdered magnesium sulfate (5 g.). A solution of potassium permanganate (1.6 g., 10 mmoles) in water (50 ml.) was added dropwise to the stirred mixture at 0° over a period of 35 min. After coming to room temperature the mixture was filtered, the precipitate of manganese dioxide was washed thoroughly with acetone, and the filtrate was concentrated to a volume of 75 ml. Continuous extraction with ether gave a yellow oil (1.6 g.) which was dissolved in acetone (100 ml.) and treated dropwise with 8 *N* Kiliani reagent until an excess of oxidizing agent was indicated by the color of the solution. After evaporation of the solution to near dryness, the residue was dissolved in benzene, and the solution was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent left a yellow gum (1.7 g.) which was chromatographed on neutral alumina. Repeated crystallization of the yellow product from chloroform–hexane and from isopropyl ether, followed by sublimation (85–90° (1.5 mm.)) and final crystallization from *n*-hexane, gave yellow needles (144 mg., 0.65 mmole, 5.7% yield) of the  $\alpha$ -diketone **13**, m.p. 98–99°;  $\nu$  (5% in CHCl<sub>3</sub>) 1746, 1727, 1708 cm<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  462 m $\mu$  ( $\epsilon$  48), shoulders at  $\lambda$  457 and 446 m $\mu$ .

*Anal.* Calcd. for C<sub>13</sub>H<sub>18</sub>O<sub>3</sub>: C, 70.14; H, 8.16. Found: C, 70.08; H, 8.05.

**Adol 9.**—A solution of the  $\alpha$ -diketone **7** (150 mg., 0.675 mmole) in boiling ethanol (1.5 ml.) was treated with a solution of sodium hydroxide (0.3 g.) in water (1.5 ml.) with swirling and heating until the yellow color was discharged (about 2 min.). The nearly colorless solution was neutralized with 20% phos-

phoric acid and extracted with ether 5 times. The product was crystallized from cyclohexane and sublimed at 110° (1.3 mm.) to yield white crystals (125 mg., 83% yield), sublimes >200°, softens at 215–225°, m.p. 225–226° (rapid heating);  $\nu$  (10% in  $\text{CHCl}_3$ ) 3560, 3480, 1742, 1725  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CDCl}_3$ ) 6.24 (1H, broad singlet), 7.5–8.5 (8H, many peaks), 8.79 (3H, singlet), 8.96 (3H, singlet), 9.16  $\tau$  (3H, singlet). The aldol was completely stable under the conditions used for its formation.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}_3$ : C, 70.14; H, 8.16. Found: C, 69.91; H, 7.87.

**Base Treatment of the  $\alpha$ -Diketone 13.**—During an attempt to measure the visible spectrum of the  $\alpha$ -diketone 13 in ethanol the yellow color of the solution disappeared gradually. The compound 13 (10 mg.) dissolved in boiling absolute ethanol (0.1 ml.) was treated with 0.1 ml. of a solution of sodium hydroxide (0.3 g.) in water (1.5 ml.). The yellow color disappeared instantly, but the solution was stirred at 80–90° for 2 min. (conditions used for the preparation of the aldol) before being cooled. When the reaction mixture was neutralized with 20% phosphoric acid, the yellow color reappeared. Water (3 ml.) was added and the solution was extracted with ether. Examination of the product by thin-layer chromatography revealed the absence of the  $\alpha$ -diketone 7 and the aldol 9. In addition to starting material 13, several other products were present.

**Reaction of *cis*-Pseudoionone (5) with Vanadium Tetrachloride.**—A solution of *cis*-pseudoionone (45 g., 0.24 mole) in benzene (100 ml.) was added dropwise to a solution of vanadium tetrachloride (technical grade, 100 g.) in a mixture of benzene (500 ml.) and heptane (50 ml.) below 5° under nitrogen with vigorous mechanical stirring. As soon as addition was complete, ether (250 ml.) was added and the reaction mixture was poured onto ice (250 g.) and water (250 ml.). Extraction with pentane gave a brown solution which was treated with collidine (100 ml.). Solvent was distilled until the pot temperature reached 160°, and this temperature was maintained overnight. After work-up, the crude product was distilled through an 8-in. Vigreux column, b.p. 70–112° (2.8 mm.), to give a yellow oil (12.1 g., 27% recovery of monomeric material). Gas chromatography showed the presence of  $\alpha$ -ionone (2),  $\beta$ -ionone (3), bicycloionone (6), and epibicycloionone (12) in the product, along with other compounds. Treatment of the crude product with Girard reagent "P" removed all ketones except the bicycloionones 6 and 12, 2.55 g. A sample of pure bicycloionone was obtained from this mixture by repeated crystallization from pentane at –70° followed by distillation. Its gas chromatographic behavior and its infrared spectrum were identical with those of authentic bicycloionone.

**Cyclization of *cis*-Pseudoionone (5) with Boron Trifluoride in Benzene.**<sup>14</sup>—*cis*-Pseudoionone (10.0 g., 52 mmoles) dissolved in benzene (50 ml.) was added dropwise to a saturated solution of boron trifluoride in a mixture of benzene (100 ml.) and heptane (10 ml.) with stirring and cooling in an ice bath. A slow stream of boron trifluoride was bubbled through the reaction mixture during addition of the ketone. Sodium hydroxide solution (5%, 100 ml.) was added dropwise to destroy excess boron trifluoride, and the mixture was extracted with pentane. Distillation of the crude product yielded a yellow oil (8.46 g., 84.6% yield), b.p. 80–88° (1.0 mm.), which consisted of  $\alpha$ -ionone (2, 86%) and  $\beta$ -ionone (3, 14%) as ascertained by gas chromatography. Neither bicycloionone (6) nor tricycloionone (26) was detected.

**Cyclization of *trans*-Pseudoionone (1) with Boron Trifluoride in Benzene.**<sup>14</sup>—Reaction of *trans*-pseudoionone (1) with boron trifluoride using the conditions described in the preceding paragraph gave an identical result.

**Reaction of *cis*-Pseudoionone (5) with Boron Trifluoride in a Benzene–Acetic Acid Mixture.**<sup>14</sup>—*cis*-Pseudoionone (5, 10 g., 52 mmoles) dissolved in benzene (50 ml.) was added dropwise at 0–5° to a mixture of glacial acetic acid (50 ml.) and benzene (50 ml.) in which was dissolved boron trifluoride (approximately 7 g., 100 mmoles). After addition was complete, water (100 ml.) was added dropwise, and the mixture was poured onto a mixture of ice and a solution of sodium hydroxide (50 g.) and water (200 ml.). Work-up gave a product containing very little  $\alpha$ -ionone (2) and  $\beta$ -ionone (3), but neither bicycloionone (6) nor tricycloionone (26).

**Reaction of *trans*-Pseudoionone (1) with Boron Trifluoride in a Benzene–Acetic Acid Mixture.**<sup>14</sup>—Under the conditions given above, *trans*-pseudoionone gave a product containing unreacted starting material (75%),  $\alpha$ -ionone (2, 25%), and a trace of  $\beta$ -ionone (3), but no bicycloionone (6) and no tricycloionone (26).

**Photopseudoionone.**—Irradiation of either *cis*-pseudoionone (5) or *trans*-pseudoionone (1) in 1% solutions in either pentane or ether with a low-pressure mercury discharge lamp yielded a mixture of *cis*-pseudoionone, *trans*-pseudoionone, and a new isomer, photopseudoionone, in the proportions 33:49:18, respectively (by gas chromatography). A large amount of polymeric material was also formed. Irradiation for a period longer than that required to reach this steady-state composition (about 4–8 hr. depending on the light source used) resulted only in more extensive polymerization. Ten "large-scale" irradiations were performed as follows. *trans*-Pseudoionone (10 g.) in ether (1000 ml.) was irradiated for 8 hr. under nitrogen gas at reflux temperature. Removal of the solvent from the combined products left approximately 100 g. of residue which on repeated fractional distillation through an 18 in. spinning-band column afforded 3.3 g. of a mixture containing photopseudoionone (75%), *cis*-pseudoionone (5, 20%), and *trans*-pseudoionone (1, 5%) (by gas chromatography), b.p. 50–54° (0.14 mm.);  $\nu$  (10% in  $\text{CCl}_4$ ) 1682, 1623, 1573, 971  $\text{cm}^{-1}$ ;  $\nu$  (10% in  $\text{CS}_2$ ) 758  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{EosH}}$  297  $\mu$  ( $\epsilon$  14,700); n.m.r. (20% in  $\text{CCl}_4$ ) 2.70 (1H, doublet with much fine splitting,  $J = 12$  c./sec.), 3.22–4.28 (2H, many peaks), 4.94 (1H, broad band), 7.88 (7H, strong singlet over multiplet), 8.14 (3H, multiplet), 8.37  $\tau$  (6H, two methyl singlets).

**Treatment of Bicycloionone (6) with Hydrogen Chloride.**<sup>24</sup> (a).—A solution of bicycloionone (6, 200 mg.) in benzene (2 ml.) was saturated with dry hydrogen chloride at 0–5°, and allowed to remain at this temperature for 2.5 hr. Addition of ice and water and extraction with pentane gave a yellow oil (167 mg.) which was distilled. The colorless product was identical with starting material in its gas chromatogram and its infrared spectrum.

(b).—A solution of bicycloionone (6) in benzene at ca. 0° was saturated with hydrogen chloride (Matheson purified) under anhydrous conditions for 15 min. One equivalent of titanium tetrachloride was added and the resulting mixture was held at ca. 0° for 2.5 hr. It was then worked up as above and yielded a brown oil. Thin-layer and gas chromatographic analyses showed it to be a mixture of at least three compounds, none of which was bicycloionone. This oil was dissolved in 10 times its weight of collidine (redistilled and dried over BaO) and heated in an oil bath at 180°. After 12 hr. the dark brown solution was cooled and poured onto a mixture of ice and concentrated hydrochloric acid. This was extracted with pentane, and the combined extracts were washed with 10% hydrochloric acid solution, water, diluted sodium carbonate solution, and water. After drying ( $\text{MgSO}_4$ ) the solvent was evaporated under reduced pressure. Thin-layer and gas chromatographic analyses revealed the presence of one major product, which was also present before collidine treatment; but bicycloionone was not detectable. The oil gave a positive Beilstein test.

**Isolation of Tricycloionone Semicarbazone.**—Redistilled "ionone forerun" (2 kg., b.p. 102–112° (5.5 mm.)) from the Maywood Chemical Works, Maywood, N. J., was allowed to react in absolute methanol solution with Girard reagent "T" (600 g.) and glacial acetic acid (360 g.) for 5 hr. at 65°. After remaining at room temperature overnight, the mixture was cooled to 0° and poured into a mixture of ice (8 kg.), water (8 l.), and sodium carbonate (300 g.). Extraction with ether gave the "nonketonic" material. The aqueous phase was acidified to congo red indicator with 6 N hydrochloric acid (1700 ml.) and allowed to remain at room temperature for 3 hr. Extraction with ether yielded a yellow oil (393 g.) from which residual methanol was removed by distillation with benzene (400 ml.). Treatment of an acetone (2750 ml.) solution of the residue with potassium permanganate (350 g.) produced an exothermic reaction. The temperature was kept at 40–45° during the addition of permanganate, which required 8 hr. Stirring was continued overnight at room temperature, excess permanganate was destroyed by addition of a small amount of methanol, and the manganese dioxide was filtered and washed with acetone and ether. Removal of the solvents from the filtrates by distillation under reduced pressure furnished a yellow residue which was taken up in pentane, washed consecutively with 2 N sodium hydroxide solution and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the oil gave a pale yellow liquid, b.p. 95–113° (5 mm.) (232 g.), which was estimated by gas chromatography to contain not more than 25% of tricycloionone (26).

Treatment of this oil (228 g.) with a solution of semicarbazide

(24) We are indebted to Dr. S. H. Fearheller for these two experiments.



acetate, prepared from semicarbazide hydrochloride (190 g.), sodium acetate trihydrate (304 g.), and enough methanol to bring the volume to 765 ml., gave crystals (126.5 g.), which were recrystallized from methanol, ethyl acetate, and finally methanol to yield tricycloionone semicarbazone (60.5 g.), m.p. 214–215°. A mixture with an authentic sample, m.p. 211–212°, kindly provided by Dr. Y.-R. Naves, had m.p. 211–213°. The infrared spectra of the two specimens in KBr were identical.

**Tricycloionone (26).**—Tricycloionone semicarbazone (59 g.), phthalic anhydride (59 g.), and water (360 ml.) were steam distilled. Two liters of distillate was collected and extracted with pentane. Distillation of the oil through an 8 in. Vigreux column gave pure tricycloionone (26) as a colorless liquid, b.p. 90–91° (1.6 mm.) (41.7 g., 92% yield from the semicarbazone, 2% from 'ionone forerun');  $\nu$  (10% in  $\text{CCl}_4$ ) 2920, 2860, 1702  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{EtOH}}$  286  $\mu$  ( $\epsilon$  40); n.m.r. (20% in  $\text{CCl}_4$ ) 7.4–7.9 (3H, many peaks), 7.97 (3H, singlet), 8.1–9.0 (8H, many peaks), 9.06 (3H, singlet), 9.13  $\tau$  (3H, singlet); mass spectrum:  $m/e$  43 (11,600), 192 (100).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}$ : C, 81.20; H, 10.48. Found: C, 81.20; H, 10.49.

**Epitricycloionone (27).**—Tricycloionone (10.0 g.) was heated in a solution of sodium (1.0 g.) in absolute methanol (50 ml.) under nitrogen for 20 hr. Water (100 ml.) was added to the cooled mixture and the ketones were extracted into pentane. Distillation of the total product, b.p. 60–80° (0.34 mm.), gave a colorless oil containing tricycloionone (26, 69%) and epitricycloionone (27, 31%). Preparative gas chromatography followed by crystallization of the lower-boiling epimer from pentane and ether at  $-70^\circ$  afforded a sample of pure epitricycloionone (27), b.p. 84–95° (2 mm.);  $\nu$  (10% in  $\text{CCl}_4$ ) 1700  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 7.15–8.00 (3H, many peaks), 8.06 (3H, singlet), 8.10–8.88 (8H, many peaks), 8.88 (3H, singlet), 9.20  $\tau$  (3H, singlet); mass spectrum:  $m/e$  43 (75,000), 192 (100). When epitricycloionone (27, 100 mg.) was heated with a solution of sodium (20 mg.) in methanol (2 ml.) overnight and worked up, a colorless oil, b.p. 75–85° (2 mm.), was obtained which had the same composition as that obtained by epimerization of tricycloionone (26).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}$ : C, 81.20; H, 10.48. Found: C, 81.32; H, 10.39.

**Tetradeteriotricycloionone.**—Tricycloionone (26) (5 g.) was added to a solution of sodium (0.6 g.) in absolute deuterioethanol (30 ml.), and the mixture was allowed to reflux under nitrogen for 13 hr. Deuterium oxide (30 ml.) was added to the cooled solution and extraction with pentane afforded a mixture of the epimeric ketones. Preparative scale gas chromatography on a column flushed several times with deuterioethanol, followed by crystallization of the product from pentane at  $-70^\circ$ , gave tetradeteriotricycloionone, b.p. 90–95° (2.8 mm.) (short-path);  $\nu$  (10% in  $\text{CCl}_4$ ) 2250, 2150, 1695  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 7.4–8.1 (2H, many peaks), 8.20–9.05 (8H, many bands), 9.05 (3H, singlet), 9.12  $\tau$  (3H, singlet); mass spectrum:  $m/e$  43 (1870), 46 (25,700), 192 (5), 195 (41), 196 (100).

**Tetradeterioepitricycloionone.**—The preparation of tetradeteriotricycloionone furnished also tetradeterioepitricycloionone which was purified in the same manner, b.p. 88–93° (2.7 mm.);  $\nu$  (10% in  $\text{CCl}_4$ ) 2245, 2130, 1697  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 7.39 (1H, broad triplet,  $J = 5.5$  c./sec.), 7.90–8.10 (1H, unresolved), 8.10–8.90 (8H, many peaks), 8.90 (3H, singlet), 9.22  $\tau$  (3H, singlet); mass spectrum:  $m/e$  43 (1580), 46 (22,800), 192 (5), 195 (37), 196 (100).

**Acetate 28.**—Tricycloionone (26, 4.0 g., 20.8 mmoles) was dissolved in approximately 20% peracetic acid (a commercial solution in acetic acid; 54 g. of solution, approximately 10.8 g. of peracetic acid, 140 mmoles), and the solution was stored in the dark at room temperature for 48 hr. Water (400 ml.) was added and the mixture was extracted with pentane. Chromatography of the crude product on neutral alumina gave the ester, which was crystallized from pentane at  $-70^\circ$  and distilled, b.p. 65–85° (2.2 mm., short path), to give a colorless liquid (2.64 g., 61% yield);  $\nu$  (10% in  $\text{CCl}_4$ ) 1735, 1245  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 5.76 (1H, singlet), 7.60–8.00 (2H, broad band), 8.00 (3H, singlet), 8.10–8.90 (8H, broad band), 9.10 (3H, singlet), 9.15  $\tau$  (3H, singlet).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}_2$ : C, 75.04; H, 9.68. Found: C, 75.19; H, 9.59.

**Epimeric Acetate 31.**—A solution of epitricycloionone (27, 953 mg., 4.95 mmoles) in 13.5 g. of peracetic acid solution (see above) was allowed to remain in the dark for 20 hr. It was subsequently worked up, chromatographed, crystallized, and dis-

tilled to yield the epiacetate 31 (107 mg., 0.52 mmole, 10% yield), b.p. 65–80° (3 mm.);  $\nu$  (5% in  $\text{CCl}_4$ ) 1738, 1240  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 5.67 (1H, doublet,  $J = 6$  c./sec.), 7.48 (1H, quadruplet,  $J' = 6$  c./sec.,  $J'' = 11.5$  c./sec.), 7.8–9.0 (9H, unresolved), 7.99 (3H, broad singlet), 9.01 (3H, singlet), 9.16  $\tau$  (3H, singlet).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}_2$ : C, 75.04; H, 9.68. Found: C, 75.00; H, 9.66.

**Alcohol 29.**—The acetate 28 (2.08 g., 10 mmoles) was added to a solution of potassium hydroxide (1.12 g., 20 mmoles) in water (2 ml.) and enough methanol was added to produce a homogeneous solution (total volume approximately 25 ml.). After remaining at room temperature under nitrogen for 2 hr., the solution was diluted with water (100 ml.) and extracted with pentane. Crystallization of the crude product (1.66 g., quantitative yield) from ether and pentane at  $-70^\circ$  followed by sublimation at 55° (2 mm.) gave the alcohol 29 (1.40 g.), m.p. 56–57°;  $\nu$  (10% in  $\text{CCl}_4$ ) 3650, 3370 (broad)  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 6.63 (1H, doublet,  $J = 3$  c./sec.), 6.97 (1H, doublet,  $J = 3$  c./sec.), 7.66–8.14 (2H, several broad bands), 8.14–8.96 (8H, many peaks), 9.14 (3H, singlet), 9.16  $\tau$  (3H, singlet).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{18}\text{O}$ : C, 79.46; H, 10.91. Found: C, 79.57; H, 11.00.

**Deuterioalcohol.**—A sample of the alcohol 29 was dissolved in deuterioethanol and the solvent was removed by distillation. This operation was repeated, and the residue was sublimed; n.m.r. (20% in  $\text{CCl}_4$ ) 6.63 (1H, singlet), 6.92 ( $1/3$  H, singlet), 7.65–8.14 (2H, unresolved), 8.14–8.92 (8H, many peaks), 9.13 (3H, singlet), 9.16  $\tau$  (3H, singlet).

**Cyclobutanone (32).**—The alcohol 29 (300 mg., 1.8 mmoles) in acetone (30 ml.) was treated dropwise with an excess of 8 N Kiliani reagent at 0°. Water (50 ml.) was added and the product was extracted into pentane. Crystallization from pentane and ether followed by short-path distillation, b.p. 100–115° (13 mm.), gave a ketone 32 (100 mg., 0.6 mmole, 33% yield);  $\nu$  (10% in  $\text{CCl}_4$ ) 1772 (very strong)  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 7.13 (1H, multiplet), 7.55–8.85 (9H, many peaks), 9.01 (3H, singlet), 9.10  $\tau$  (3H, singlet). A less pure crop weighed 80 mg. (27% total yield 60%). Its semicarbazone had m.p. 205–207° dec.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{16}\text{O}$ : C, 80.44; H, 9.82. Found: C, 80.18; H, 9.66.

**Carboxylic Acid 33.**—A solution of sodium hypochlorite was prepared by adding chloride (7.3 g., 100 mmoles) to a cooled solution of sodium hydroxide (13.2 g., 325 mmoles) in water (33 ml.). This solution was added dropwise to a stirred solution of tricycloionone (26, 4.0 g., 2.1 mmoles) in dioxane (100 ml.) at 12° over a period of 1 hr. After addition was complete the mixture was stirred another 2 hr. at 11°. Water (75 ml.) was added and the mixture was stirred at room temperature overnight. The acidified reaction mixture was extracted with ether, which in turn was extracted with sodium carbonate solution. Acidification and extraction gave the crude acid 33 which was crystallized from petroleum ether to yield white crystals (2.7 g.), m.p. 104–105°. Further crystallization and sublimation (85° (1 mm.)) raised the m.p. to 108°;  $\nu$  (5% in  $\text{CCl}_4$ ) 3200–2500 (broad band), 1695  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : C, 74.19; H, 9.34. Found: C, 74.30; H, 9.37.

**Methyl Ester 34.**—The carboxylic acid 33 was treated with excess diazomethane in ether solution to convert it in about 70% yield to the ester 34, which was crystallized several times from pentane at  $-70^\circ$  and distilled to give the pure ester, b.p. 55–60° (1.2 mm.);  $\nu$  (10% in  $\text{CCl}_4$ ) 1727, 1035  $\text{cm}^{-1}$ ; n.m.r. (20% in  $\text{CCl}_4$ ) 6.38 (3H, singlet), 7.4–7.8 (2H, several peaks), 7.91 (1H, singlet), 8.0–9.0 (8H, unresolved), 9.10  $\tau$  (6H, two singlets).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}_2$ : C, 74.96; H, 9.67. Found: C, 74.88; H, 9.75.

**endo-1,3-Dimethyl-5-(2,2-diphenylethyl)bicyclo[2.2.2]octene-2 (36).**—A solution of phenylmagnesium bromide was prepared from magnesium (7.00 g., 288 mg.-atoms) in dry ether (50 ml.) and a solution of bromobenzene (45.3 g., 288 mmoles) in ether (150 ml.) at 0°. The ester 33 (3.0 g., 14.4 mmoles) in benzene (150 ml.) was added to the cooled solution of the Grignard reagent. Approximately 150 ml. of solvent was distilled from the mixture, which was then allowed to reflux at 75° overnight. Work-up gave a dark brown oil (8.6 g.) which appeared already to contain some of the hydrocarbon. Treatment of this material with acetic acid (20 ml.) and acetic anhydride (10 ml.) under



reflux for 4.5 hr. gave a product which was filtered through alumina to yield a mixture of the hydrocarbon **36** and biphenyl. Steam distillation removed biphenyl and the residue was crystallized from methanol-ether to yield colorless crystals (2.85 g., 9.1 mmoles, 63% yield), m.p. 83–84°;  $\nu$  (10% in  $\text{CCl}_4$ ) 3050, 3015, 2925, 2855, 1650, 1598  $\text{cm}^{-1}$ ; (10% in  $\text{CS}_2$ ) 802, 774, 763, 732, 701  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  258  $\text{m}\mu$  ( $\epsilon$  15,300); n.m.r. (30% in  $\text{CCl}_4$ ) 2.7–3.0 (10 H), 4.35 (2H, doublet over broadened singlet), 7.47 (1H, very broad multiplet), 7.80 (1H, multiplet), 8.13 (3H, doublet,  $J = 1.5$  c./sec.), 8.2–9.2 (6H, unresolved), 8.93  $\tau$  (3H, singlet).

*Anal.* Calcd. for  $\text{C}_{24}\text{H}_{26}$ : C, 91.67; H, 8.33. Found: C, 91.89; H, 8.38.

**Dehydrogenation of the Hydrocarbon 36.**—Hydrocarbon **36** (2.00 g., 6.4 mmoles) and 30% palladium-on-charcoal (250 mg.) were heated together in a slow stream of nitrogen which was passed into a Dry Ice trap. The mixture was boiled (approximately 325°) for 1.5 hr. (until evolution of volatile materials ceased). *m*-Xylene (**38**) was isolated from the volatile products in the trap by gas chromatography and short-path distillation (109 mg., 16% yield). Its gas chromatographic retention time and its infrared and n.m.r. spectra were identical with those of authentic *m*-xylene.

Chromatography of the nonvolatile residue from the reaction gave a hydrocarbon mixture which was distilled (short path), b.p. 90–200° (3 mm.). Gas chromatography of the distillate yielded a small amount of 1-phenylnaphthalene (**39**) which was crystallized three times from pentane-ether at –70° and distilled to give a colorless, viscous oil (33 mg., 0.16 mmole, 2.5% yield). Its infrared spectrum was identical with that of authentic 1-phenylnaphthalene (Aldrich Chemical Co.). Nitration<sup>25</sup> of these samples gave 4-nitro-1-phenylnaphthalene, m.p. 129–130° and 129–130°, respectively, m.m.p. 129–130° (lit.<sup>25</sup> m.p. 132°).

**Synthesis of 1-Phenylnaphthalene (39) from 1,1-Diphenylbutadiene (37).**—A solution of allyl chloride (1.53 g., 20 mmoles) in ether (5 ml.) was added slowly to a mixture of magnesium (0.97 g., 40 mg.-atoms) in ether (5 ml.) with cooling in an ice bath.

(25) R. Weiss and K. Woidich, *Monatsh.*, **46**, 453 (1925).

When addition was complete (15 min.) stirring was continued at 0° for 15 min. To this suspension of allylmagnesium chloride was added a solution of benzophenone (1.82 g., 10 mmoles) in ether (5 ml.) and the reaction mixture was allowed to come to room temperature. After another 2.5 hr. of stirring, work-up yielded crude allyldiphenylcarbinol, which was dissolved in a mixture of phosphorus oxychloride (5 ml.) and pyridine (10 ml.) and stored at room temperature overnight. Work-up with ice gave a product which was chromatographed on Florisil to give a colorless hydrocarbon, probably 1,1-diphenylbutadiene (**37**) which had a marked tendency to polymerize. Dehydrogenation of this product under the same conditions used for the dehydrogenation of the hydrocarbon **36** gave a mixture in which 1-phenylnaphthalene (**39**) was detected by gas chromatography. Nitration of the entire product gave 4-nitro-1-phenylnaphthalene, m.p. 128–129°, undepressed by admixture with authentic material.

**Dihydropyran (41).**—Tricycloionone (**26**, 1.00 g.) was cooled to 0° and treated with cold concentrated sulfuric acid (1 ml.). The mixture was stirred for 1 min. at 0°; then water (10 ml.) was added. Extraction with pentane yielded an oil which was distilled (short path), b.p. 30–35° (3 mm.). Redistillation, b.p. 70–75° (3 mm.), gave a colorless oil (**41**, 455 mg., 45% yield),  $\nu$  (10% in  $\text{CCl}_4$ ) 3045, 2920, 1630, 1605  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{heptane}}$  199  $\text{m}\mu$  ( $\epsilon$  4680); n.m.r. (pure liquid) 5.46 (1H, doublet,  $J = 6$  c./sec.), 7.9 (1H, multiplet), 8.1–9.2 (9H, unresolved), 8.38 (3H, broadened singlet), 8.73 (3H, singlet), 9.22  $\tau$  (3H, singlet). The spectra of this material indicated the presence of a single compound, but it decomposed on thin-layer or on column chromatography and on gas chromatography, and it resinified easily unless stored under nitrogen in a refrigerator. It reacted slowly with 2,4-dinitrophenylhydrazine reagent, but gave a mixture of derivatives which was not separated.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}$ : C, 81.20; H, 10.48. Found: C, 80.62; H, 10.44.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASSACHUSETTS]

## A Total Synthesis of Holomycin

By G. BÜCHI AND GEORGE LUKAS<sup>1</sup>

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S-Benzyl-L-cysteine ethyl ester was acylated with diketene to form the N-acetoacetyl derivative which was cyclized with sodium ethoxide to racemic 3-acetyl-4-hydroxy-5-(S-benzylthio)methyl-3-pyrrolin-2-one. A novel dehydrogenation reaction using thionyl chloride gave 3-acetyl-4-hydroxy-5-(S-benzylthio)methylene-3-pyrrolin-2-one. This yellow ketone was converted to an oxime which on treatment with *p*-toluenesulfonyl chloride and sodium hydroxide rearranged to 3-acetamido-4-hydroxy-5-(S-benzylthio)methylene-3-pyrrolin-2-one. Tosylation followed by exposure to sodium benzylmercaptide furnished 3-acetamido-4-S-benzylthio-5-(S-benzylthio)methylene-3-pyrrolin-2-one. Removal of the two benzyl groups was accomplished with lithium in liquid ammonia. Air oxidation of crude 3-acetamido-4-sulfhydryl-5-sulfhydrylmethylene-3-pyrrolin-2-one in methanol solution containing hydrochloric acid gave synthetic holomycin identical in every respect with the natural antibiotic.

Certain *Streptomyces* species elaborate yellow-colored metabolites containing the pyrrolinodithiole nucleus. The four substances thiolutin (**1**),<sup>2</sup> aureothricin (**2**),<sup>2</sup> isobutyropyrrrothine (**3**),<sup>3</sup> and holomycin (**4**)<sup>4</sup> are of some interest because of their pronounced activities against a variety of Gram-positive and Gram-negative bacteria, amoeboid parasites, and fungi.

The synthesis of holomycin (**4**) described in this

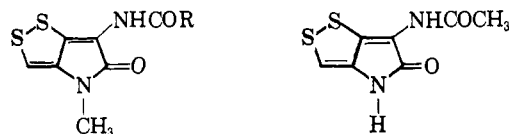
(1) National Institutes of Health Predoctoral Fellow 1961–1963.

(2) W. D. Celmer and I. A. Solomons, *J. Am. Chem. Soc.*, **77**, 2861 (1955), and earlier papers cited.

(3) D. S. Bhate, R. K. Hulyalkar, and S. K. Menon, *Experientia*, **16**, 504 (1960).

(4) L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, and H. Zähner, *Helv. Chim. Acta*, **42**, 563 (1959).

paper is based on the principle of building the two five-membered rings present in the structure at different



1, R =  $\text{CH}_3$   
2, R =  $\text{CH}_2\text{CH}_3$   
3, R =  $\text{CH}(\text{CH}_3)_2$

4

stages. A reasonable possibility was first to construct an appropriately substituted pyrrolone and to close the disulfide ring in a final stage. Treatment of