

Noted for subsequent elaboration are the following: The  $\beta$ -rhombohedral structure probably is thermodynamically preferred (for ordinary pressures) at every temperature below the melting point. Establishment of the partial framework having 84-atom subunits, but with a different internal crosslinking (probably influenced by foreign atoms), is the obvious, if inconclusive, interpretation of X-ray powder data from some boron samples crystallized too far below the melting point. At still lower temperatures kinetic mechanism determines the choice of framework.<sup>3</sup>

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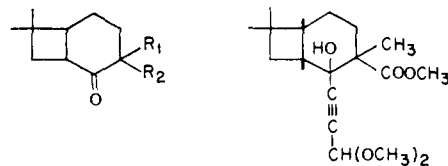
### TOTAL SYNTHESIS OF *d,l*-CARYOPHYLLENE AND *d,l*-ISOCARYOPHYLLENE

Sir:

The hydrocarbons known as the caryophyllenes have occupied a unique position in the terpene field for more than a century because of the unusual array of difficulties which have been encountered during their study.<sup>1</sup> We describe here the total synthesis of XI and XV, now commonly known as isocaryophyllene and caryophyllene, respectively, as the racemates.

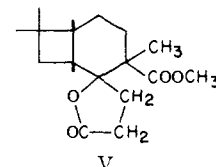
The ketone I, one of the compounds which appeared suitable as a starting material, was obtained by a new and remarkable reaction, the photochemical addition of 2-cyclohexenone to isobutylene at *ca.*  $-40^{\circ}$ . This process affords *ca.* 58% of 7,7-dimethylbicyclo[4.2.0]octanone-2 (I) and *none* of the isomeric 8,8-dimethylbicyclo[4.2.0]octanone-2.<sup>2</sup> Further, both *cis* and *trans* isomers of the bicyclic ketone I are formed, with *trans* predominating by a factor of about four. These isomers are readily distinguished by n.m.r.; two sharp peaks due to methyl protons occur at 0.97 and 1.15  $\delta^3$  in the spectrum of the *cis* ketone and at 1.07 and 1.15  $\delta$  for the *trans* ketone. The configurations indicated are assigned from the fact that the predominating ketone in the photoreaction is completely isomerized to the minor isomer by treatment with dilute base.<sup>4-6</sup> The  $\alpha$ -proton at C<sub>1</sub> in the *cis* photo adduct, infrared max. 5.84  $\mu$ , b.p. 72° (1 mm.), (C, 78.78; H, 10.50), gives rise to six sharp peaks in the n.m.r. spectrum (a pair of triplets downfield from the remaining peaks) which disappear on base-catalyzed deuteration.

The *cis* ketone I was further transformed according to the sequence: to II (methyl carbonate-sodium hydride-dioxane), b.p. 82-83° (0.3 mm.), infrared



I, R<sub>1</sub> = R<sub>2</sub> = H  
II, R<sub>1</sub> = H, R<sub>2</sub> = COOCH<sub>3</sub>  
III, R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = COOCH<sub>3</sub>

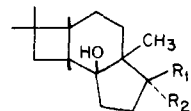
IV



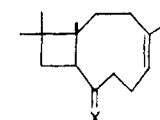
V

VI, R = COOCH<sub>3</sub>

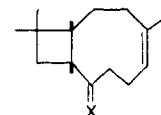
VII, R = H



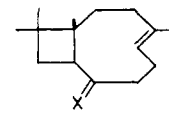
VIII, R<sub>1</sub> = H, R<sub>2</sub> = OH  
IX, R<sub>1</sub> = OH, R<sub>2</sub> = H



X, X = O  
XI, X = CH<sub>2</sub>



XII, X = O  
XIII, X = CH<sub>2</sub>



XIV, X = O  
XV, X = CH<sub>2</sub>

max. at 5.70, 5.86, 6.05 and 6.19  $\mu$  (C, 68.84; H, 8.55); then to III (methyl iodide-base), b.p. 80-85° (0.3 mm.), infrared max. 5.84 and 5.74  $\mu$  (C, 69.98; H, 9.19), as a 3:1 mixture of isomers (v.p.c. analysis); further to the acetylene IV (propargyl aldehyde dimethyl acetal lithio derivative in tetrahydrofuran) and beyond to the lactone V (hydrogenation with Pd-C catalyst in methanol followed by oxidation with chromic acid in aqueous acetic acid), b.p. *ca.* 120-130° (bath) (0.08 mm.), infrared max. at 5.63 and 5.78  $\mu$  (C, 68.51; H, 8.86); additionally to the keto ester VI (methylsulfinylcarbanion in dimethyl sulfoxide) infrared max. 5.67 and 5.77  $\mu$ , purple color with ferric ion; then to the hydroxy ketone VII (by hydrolysis with cold aqueous base and decarboxylation at 115° in pyridine), m.p. 126-127°, infrared max. 2.7-2.9 and 5.76  $\mu$  (C, 75.57; H, 9.96), sharp n.m.r. peaks at 0.93, 1.10 and 1.21  $\delta$  (three methyl groups).<sup>8</sup>

Reduction of the hydroxy ketone VII with either sodium borohydride in methanol, lithium aluminum hydride, lithium aluminum tri-*t*-butoxyhydride or sodium-moist ether produced a crystalline diol (VIII, methyl and OH *trans*), m.p. 122.5-124° (C, 73.90 (low); H, 10.90), which was transformed readily into a mono *p*-toluenesulfonate. Generation of the fused 4-9 ring fusion of the caryophyllenes was accompanied by internal elimination *via* the  $\gamma$ -oxide anion<sup>9</sup> derived from the toluenesulfonate. Thus, treatment of the hydroxy *p*-toluenesulfonate with methylsulfinylcarbanion<sup>7</sup> (3 equivalents) at 25° in dimethyl sulfoxide for 30 minutes followed by addition of several equivalents of *t*-butyl alcohol and a further 2 hours for isomerization of the 4-9 ring fusion afforded the ketone X, infrared max. 5.90  $\mu$  (C, 81.65; H, 10.90). Reaction of this ketone with methylenetriphenylphosphorane-dimethyl sulfoxide

(7) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(8) The stereochemistry of this hydroxy ketone may be either (starting from the 4-6 fusion) (1) *cis,anti,cis* or (2) *cis,anti,trans*.

(9) See (a) A. Eschenmoser and A. Frey, *Helv. Chim. Acta*, **35**, 1660 (1952); (b) R. B. Clayton, H. B. Henbest and M. Smith, *J. Chem. Soc.*, 1983 (1957); also *Chem. and Ind.*, 1315 (1953); (c) P. S. Wharton, *J. Org. Chem.* **26**, 4781 (1961).

(1) For a recent review see P. de Mayo, "Mono- and Sesquiterpenes," Interscience Publishers, Inc., New York, N. Y., 1959, p. 286.

(2) In addition *ca.* 30% of a non-distillable resin and 12% of a C<sub>10</sub> unsaturated ketone are produced.

(3) All n.m.r. data were obtained at 60 Mc. and are expressed as p.p.m. shift from tetramethylsilane as internal standard.

(4) *trans*-I is not produced by irradiation of *cis*-I under preparative conditions (experiment by Dr. J. D. Bass).

(5) For related studies see (a) G. Büchi and I. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957); (b) R. C. Cookson and E. Crundwell, *Chem. and Ind.*, 1004 (1958); (c) P. de Mayo, H. Takeshita and A. B. Sattar, *Proc. Chem. Soc.*, 119 (1962); (d) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344, 2554 (1962).

It is clear that the photoaddition of 2-cyclohexenone to isobutylene does not proceed as might have been anticipated from previous results and discussions. We are presently investigating the factors which control orientation and stereochemistry in such addition processes.

(6) A subsequent paper will deal with another approach to the ring system of I, the photolysis of 2-*t*-butylcyclohexanone which produces 7,7-dimethylbicyclo[4.2.0]octanol-1.

ide<sup>7</sup> gave the hydrocarbon XI identical with a sample of natural isocaryophyllene (kindly provided by Dr. F. Sorm) vapor chromatographically and spectroscopically (infrared, n.m.r.) (C, 88.16; H, 11.74). When the internal elimination of the above hydroxy toluenesulfonate was allowed to proceed for only 15 minutes at 10° and worked up without delay a ketone (XII) isomeric with X was formed which yielded after a Wittig transformation a hydrocarbon (XIII) isomeric with XI (C, 87.75; H, 11.78). This substance, which differs from both caryophyllene and isocaryophyllene clearly must be the unknown *cis-cis* isomer.

Reduction of the hydroxy ketone VII with hydrogen-Raney nickel afforded a mixture of two diols, VIII and IX, in roughly equal amount; these were separated readily by chromatography and VIII could be oxidized back to starting material quantitatively (chromium trioxide-pyridine). The other diol IX (methyl and OH *cis*), m.p. 112.5–113° (C, 74.91; H, 10.76), gave a crystalline mono *p*-toluenesulfonate, m.p. 100.5–101.5°, which was converted by methylsulfinylcarbanion to a bicyclic unsaturated ketone different from the isomers X and XII described above, infrared max. 5.89  $\mu$  (C, 81.19; H 10.73). This substance must be the *trans* cycloolefin with *cis* 4-9 fusion since upon prolonged (15 hours) treatment with sodium *t*-butoxide-dimethyl sulfoxide it is isomerized to the ketone XIV, infrared max. 5.89  $\mu$  (C, 81.42; H, 10.74), which is transformed by the Wittig process to *d,l*-caryophyllene, identical with natural material spectroscopically and vapor chromatographically (C, 88.04; H, 11.97).

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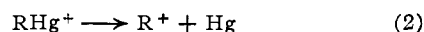
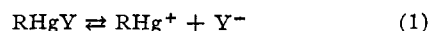
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THE EFFECT OF STRUCTURE AND SOLVENT ON THE RATES OF DEMERCURIZATION. REHYBRIDIZATION OF LEAVING GROUP AS AN IMPORTANT FACTOR IN SOLVOLYSIS REACTIONS<sup>1,2</sup>

Sir:

In previous papers<sup>3</sup> it was demonstrated that alkylmercuric salts undergo loss of mercury to form carbonium ions. By the observed change in kinetic order and rate of solvolysis of ionized and partially ionized alkylmercuric salts with added common ions, it was shown that the material which undergoes decomposition in water solution is the alkylmercuric cation. In less



polar solvents, where the concentration of free ions is low, the reaction apparently occurs largely through the ionized but not dissociated salt.<sup>4</sup>

In accord with our earlier conclusions that these are S<sub>N</sub>1 reactions, we have found that in acetic acid D-(+)-*sec*-butylmercuric perchlorate (from D-(+)-*sec*-butylmercuric bromide,  $[\alpha]_D +7.50$ ) gives mostly racemized but partially inverted *sec*-butyl acetate,  $[\alpha]_D -0.58$ . (The starting compound is optically stable to the reaction conditions.) Furthermore, *n*-butylmercuric perchlorate gives 16% rearranged acetate. By comparison, *n*-butylamine (amine-nitrous acid reaction) gives 25% rearranged acetate, while

(1) Organomercurials. X.

(2) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society.

(3) F. R. Jensen and R. J. Ouellette, *J. Am. Chem. Soc.*, **83**, 4477, 4478 (1961). Also, see L. H. Gale, F. R. Jensen and J. A. Landgrebe, *Chem. and Ind.*, 118 (1960).

(4) R. J. Ouellette, Ph.D. Thesis, University of California, 1961.

primary arylsulfonates yield essentially no rearranged acetate.<sup>5</sup>

Earlier<sup>3</sup> it was shown that the central carbon atom attains a large positive charge in going to the transition state as indicated by the sensitivity of the reaction to change in structure; thus,  $k_{t\text{-butyl}}/k_{\text{methyl}} \cong 10^{13}$ . These results were explained on the basis of very low susceptibility to nucleophilic attack on carbon. Although these conclusions find support in the rearrangement reported above for the *n*-butyl system, it has been found that the reaction is actually sensitive to changes in nucleophilicity of the solvent. These results can be expressed most conveniently by comparing the effect of  $\alpha$ -carbon substitution on the rates of reaction for various leaving groups in different solvents. In Table I,<sup>6</sup> considering as examples the  $k_{\text{isopropyl}}/k_{\text{ethyl}}$  ratio differences for mercury and tosylate as leaving groups in acetic and formic acid, the difference in rate for mercury is  $10^1$  (a factor of ten) and for tosylate  $10^{0.6}$  (a rate factor of four). This same general behavior is observed in all examples. (It should be noted that in these considerations it is assumed that solvent interacts equally with the mercuronium groups in each pair of compounds.)

The apparent contradiction that the reaction occurs with low solvent-on-carbon participation, but yet is sensitive to the nucleophilicity of solvent, is explained as follows: in the related tosylate and bromide reactions, the developing positive charge is stabilized by both the leaving group and by nucleophilic participation of solvent. However, with the mercury compounds a significantly different process is occurring. As the mercury-carbon bond is broken, mercury undergoes rehybridization to the 6S<sup>2</sup> (spherical) configuration and is less able to provide stabilization to the developing carbonium ion. Due to the change in hybridization, the function of the leaving group has become more important and less participation by solvent is required. Therefore, the carbon moiety must obtain stabilization from the groups attached to the central carbon atom, leading to large differences in rate with increasing  $\alpha$ -methyl substitution. Similarly, even though the relative amount of nucleophilic participation by solvent

TABLE I  
EFFECT OF DEGREE OF  $\alpha$ -CARBON SUBSTITUTION ON THE RATES OF SOLVOLYSIS FOR DIFFERENT LEAVING GROUPS IN VARIOUS SOLVENTS

Ratio	Leaving group	HCO <sub>2</sub> H	HOAc	EtOH	H <sub>2</sub> O
$k_{t\text{-butyl}}$	Hg	...	10 <sup>6.2</sup>	10 <sup>4.2</sup>	...
$k_{\text{isopropyl}}$	OTs <sup>-</sup>	...	...	...	...
	Br <sup>-</sup>	...	...	10 <sup>8.1</sup>	...
	Hg	10 <sup>6.6</sup>	10 <sup>4.6</sup>	10 <sup>2.8</sup>	10 <sup>4.3</sup>
$k_{\text{isopropyl}}$	OTs <sup>-</sup>	10 <sup>2.3c</sup>	10 <sup>1.7c</sup>	10 <sup>0.7c</sup>	10 <sup>1.8d</sup>
$k_{\text{ethyl}}$	Br <sup>-</sup>	10 <sup>1.4e</sup>	...	10 <sup>-0.12f</sup>	10 <sup>1.0f</sup>
	Hg	...	10 <sup>3.1</sup>	10 <sup>1.2</sup>	10 <sup>2.5</sup>
$k_{\text{ethyl}}$	OTs <sup>-</sup>	10 <sup>0.2g</sup>	10 <sup>-0.4g</sup>	10 <sup>-0.4g</sup>	10 <sup>-0.02g</sup>
$k_{\text{methyl}}$	Br <sup>-</sup>	10 <sup>0.2b</sup>	...	10 <sup>-0.4f</sup>	10 <sup>0.03f</sup>

<sup>a</sup> At 75°, S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952). <sup>b</sup> At 95°, I. Dostrovsky, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 173 (1946). <sup>c</sup> At 75°, using the brosylate, from reference in footnote a. <sup>d</sup> At 50°, using benzenesulfonate, P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **33**, 1207 (1955). <sup>e</sup> At 100°, L. C. Bateman and E. D. Hughes, *J. Chem. Soc.*, 945 (1940). <sup>f</sup> At 50°, S. Winstein, E. Grunwald and H. W. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951).

(5) A. J. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 6233 (1957).

(6) The results reported in this and the next paper were carried out in the indicated solvent in the presence of a small controlled amount of water. All reactions in Table I were carried out using 1 mole equivalent of perchloric acid except for *t*-butyl which was studied utilizing a small amount of acid under pseudo zero order conditions.