at room temperature for 12 hr. It was then cooled, treated with excess of cold 10% sodium hydroxide solution, and extracted four times with a 3:1 mixture of pentane–methylene chloride. The organic layer was dried over anhydrous sodium sulfate and freed from solvents to give 135 mg. of thioketal isomer mixture as a clean viscous gum, infrared max. 5.74 μ.

The above material was then chromatographed over 10 g. of Woelm neutral Grade III alumina and eluted with a mixture of 5% methylene chloride and 95% of petroleum ether. A total of 150 fractions of 3 ml. each was collected. Fractions 22–40 gave 40 mg. of solid, m.p. 70–86°, $[\alpha]_D$ +3° (*c* 1.815, $CHCl_3$).

Rechromatography of the above 40 mg. of solid under the same conditions as above gave no further separation. It was, therefore, subjected to partition chromatography over 16 g. of Woelm neutral alumina Grade I containing 5% by weight of dimethyl sulfoxide. The column was eluted with petroleum ether and 3-ml. fractions were collected; 11 mg. of solid XX, m.p. 97–101°, was obtained, together with 21 mg., m.p. 75–85°. The 21 mg. of solid was then rechromatographed by the partition method as given above and 6 mg. of solid, m.p. 97–101°, was obtained. Thus, a total of 17 mg. of solid XX, m.p. 97–101°, was obtained and was carried through the subsequent steps.

Conversion of XX to (+)-Longicamphenylone.—A mixture of 17 mg. of XX, m.p. 97–101°, and 50 mg. of lithium aluminum hydride in 5 ml. of dry ether was refluxed under nitrogen for 5 hr., then cooled and decomposed dropwise with water till a slightly moist precipitate of alumina was obtained. The clear ether solution was decanted and the solid residue extracted thoroughly with ether. Drying and evaporation of the ether solution gave 17 mg. (quantitative) of hydroxy thioketal. Infrared showed the presence of hydroxyl at 3.0–3.3 μ and no C=O band.

A solution of 28 mg. of sodium metal in 1 ml. of dry ethylene glycol was added to a mixture of 17 mg. of this product and 0.2 ml. of 95% hydrazine, and the mixture was heated under nitrogen at bath temperature of 190–195° for 16 hr. The mixture was cooled, diluted with 2 ml. of water, and extracted with Freon 11. Drying and evaporation of the Freon gave 9 mg. (78%) of crude longicamphenylol.

A solution of the longicamphenylol (9 mg.) in Freon was tr eated in the cold with excess of a solution of ruthenium tetrox ide in Freon[25] for 3 min. The excess oxidizing agent was destroyed by adding a few drops of ether. Filtration through cotton and concentration to remove Freon gave 8 mg. of longicamphenylone, m.p. 43–46°. This product was identical with authentic material prepared from natural *d*-longifolene by infrared and v.p.c. analyses on a 20% silicone rubber column (retention times 8 min., 10 sec., at 175° with a helium flow 85 ml./min.). A sample was purified for rotation measurement by v.p.c. The rotation was measured on a Rudolph spectropolarimeter and at the same time measurements were made on an authentic sample of (+)-longicamphenylone. (We are indebted to Mr. G. Holzwarth for assistance with these measurements.) Rotation was determined at two wave lengths, 296.6 and 302 mμ (where the values are large), with solutions of the ketones in cyclohexane; found for natural ketone (0.971 mg. in 1.50 ml. of cyclohexane): at 296.6 mμ, observed rotation +0.395°, $[\alpha]$ +610°; at 302 mμ, observed rotation +0.324°, $[\alpha]$ +500°; found for synthetic ketone (1.39 mg. in 1.35 ml. cyclohexane): at 296.6 mμ, observed rotation +0.600°, $[\alpha]$ +587°; at 302 mμ, observed rotation +0.511°, $[\alpha]$ +495°.

Conversion of *d*-Longicamphenylone to *d*-Longifolene.—A sample of natural *d*-longicamphenylone (500 mg.) was treated with methyllithium (excess) in ether at reflux for 3 days and worked up as described above to give the corresponding methylated tertiary alcohol as a solid, m.p. approximately 40°. Dehydration of this alcohol as described above using thionyl chloride–pyridine in Freon 11 gave *d*-longifolene, spectroscopically and vapor chromatographically identical with the pure natural product.

Acknowledgment.—It is a pleasure to acknowledge financial support from the National Science Foundation (G-9999) and the Higgins Fund of Harvard University. We are grateful to Dr. Sukh Dev for a generous supply of *d*-longifolene and to our colleagues J. C. Fratantoni, R. T. La Londe, and J. Casanova for experimental assistance at various stages of the problem

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[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Total Synthesis of *d,l*-Caryophyllene and *d,l*-Isocaryophyllene[1]

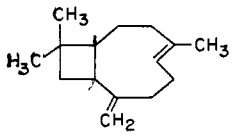
BY E. J. COREY, RAJAT B. MITRA, AND HISASHI UDA

RECEIVED JULY 12, 1963

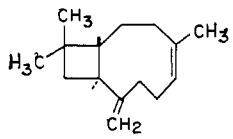
The caryophyllenes (I and II) have been synthesized starting with 2-cyclohexenone by way of a tricarbocyclic intermediate with fused four-, five-, and six-membered rings. The four-membered ring was added to the six by a photochemical cycloaddition process which formed 7,7-dimethylbicyclo[4.2.0]octanone-2 in one step; then the five-membered cycle was appended by a sequence involving methoxycarbonylation, alkylation, carbonyl addition, and Dieckmann condensation. The nine-membered ring of the caryophyllenes was then generated simply by removing the carbon-to-carbon span which served as the common bond of the six- and five-membered rings. The intermediates were selected to permit control of the 4–9 fusion (*trans*) and of the geometry of the endocyclic double bond *either* as in caryophyllene (I) *or* as in isocaryophyllene (II).

Introduction

Inspection of the molecular formulas of the sesquiterpenes caryophyllene (I) and isocaryophyllene (II) provides no more than a hint of the unusual and difficult problems which the study of these companions has entailed through successive stages over more than a century. Confronted with the complication that the reactions of these substances often lead to remarkable entanglements of the original structure, and with the fact that mixtures of isomers occur at every turn, the classical approaches, even in the hands of the most redoubtable practitioners, were for many years hopelessly inadequate.[2] Only during the past decade or so, with the help of recent improvements in reaction theory, a clearer understanding of the chemistry of large- and small-ring compounds and the application of physical methods has this quite singular puzzle been unraveled. Noteworthy



I



II

chapters include the following: structure and synthesis of the cyclobutane derivatives, norcaryophyllenic acid[3] and caryophyllenic acid,[4,5] recognition of a nine-membered ring in the caryophyllenes,[6,7] proposal of the currently accepted formulation exclusive of stereochemistry,[8] X-ray determination of the structure of caryolanyl chloride (caryophyllene hydrochloride) (III) and the

(1) This research was supported by the National Science Foundation (GP-221).

(2) See (a) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp. 39–75; (b) P. de Mayo, "Mono- and Sesquiterpenoids," Interscience Publishers Inc., New York, N. Y., 1959, pp. 286–302.

(3) H. N. Rydon, *J. Chem. Soc.*, 503 (1936); 1340 (1937).

(4) A. Campbell and H. N. Rydon, *Chem. Ind.* (London), 312 (1951); *J. Chem. Soc.*, 3002 (1953).

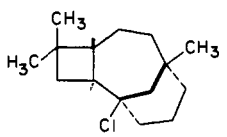
(5) A. Eschenmoser and A. Fürst, *Experientia*, **7**, 290 (1951).

(6) F. Šorm, L. Dolejš, and J. Pliva, *Collection Czech. Chem. Comm.*, **15**, 186 (1950).

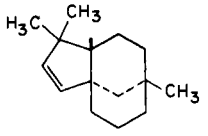
(7) D. H. R. Barton and A. S. Lindsay, *Chem. Ind.* (London), 313 (1951); *J. Chem. Soc.*, 2988 (1951).

(8) T. L. Dawson, G. R. Ramage, and B. Wilson, *Chem. Ind.* (London), 464 (1951); *J. Chem. Soc.*, 3382 (1951).

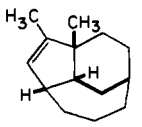
establishment of a *trans* ring fusion in caryophyllene,[9] the structure of clovene (IV),[10-12] the proposal that



III



IV

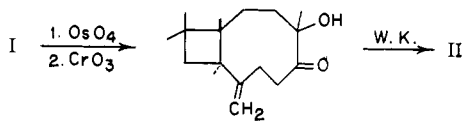


V

caryophyllene and isocaryophyllene be regarded as differing only in geometry about the endocyclic double bond,[13,14] and the establishment of V for the caryophyllene derivative isoclovene by X-ray analysis.[15]

The unusual molecular geometry of the caryophyllene ring system, from which so much extraordinary chemistry derives, has presented an interesting and challenging target for synthesis. The sections which follow describe our approach to this problem and the specific sequences by which caryophyllene and isocaryophyllene have been synthesized.[16]

Before proceeding to a discussion of the synthetic problem, it is appropriate to consider in more detail the structural relationship between caryophyllene (sometimes termed β-caryophyllene) and isocaryophyllene (also known as α-caryophyllene). These substances generally occur together as a difficultly separable mixture and almost all of the published work suffers from the ambiguity that mixtures of unknown composition were employed in the experimental work. As is described in a later part (see footnote 35) these components can now be measured analytically with precision and separated by vapor phase chromatography (v.p.c.). Consequently, it is possible at present to obtain much more reliable data on the chemistry of the individual isomers. In particular, the question of the geometry of the ring fusion in isocaryophyllene did not seem to have been settled rigorously by experiment because of the lack of suitable analytical controls. The assignment of a *trans* ring fusion as in caryophyllene (I) rested on the preparation of isocaryophyllene from "caryophyllene" of unknown composition (probably a mixture, however) *via* a "nitrosite" derivative.[13,17] Consequently, the relationship between isocaryophyllene and caryophyllene was subjected to scrutiny by rigorous experiments in our laboratories.[18] Authentic, natural caryophyllene was purified by v.p.c. and shown to be free of isocaryophyllene by v.p.c. analysis. This material was converted to a secondary–tertiary glycol by hydroxylation with osmium tetroxide–pyridine and thence to the hydroxy ketone VI by oxidation with chromic acid–acetone. Wolff–Kishner reduction–elimination of VI afforded isocaryophyllene in high yield and uncontaminated by caryophyllene as shown by v.p.c. analysis. This interconversion of caryophyllene to isocaryophyllene indicates conclusively that both compounds possess the same ring fusion, *trans*. The supposition that the double bond arrangements in caryophyllene and isocaryophyllene are *trans* and *cis*, respectively, was originally based on the finding that the rate of reaction of the endocyclic double bonds in these compounds with peracid is greater for caryophyllene than for isocarophyllene.[13] This is a reasonable, but not a compelling argument. However, it will be apparent from the synthetic work which follows that the assignments of I and II to caryophyllene and isocaryophyllene are, in fact, correct.



VI

General Plan.—Several features of the caryophyllene system represented by I and II are readily distinguished as critical units in the design of a synthetic scheme. These are the four- and nine-membered rings, the *trans* junction which unites them, the endocyclic double bond of the nine-membered ring which must be introduced in the proper location with the appropriate *cis* or *trans* configuration and, finally, the exocyclic methylene function. Provisions must be made for achieving maximum control in the formation of *each* of these units by the discriminate use of selective and interrelated operations. Various analyses of the problem led to the view that it would be advantageous to construct the four-membered ring *first* since this part of the molecule is devoid of functionality, relatively stable to a wide variety of reagents, and probably more difficult to introduce *after* the large ring has been formed. From this point *two* broad alternatives can be developed for the establishment of the desired bicyclo[7.2.0]undecane skeleton: (1) direct closure of a nine-membered ring from an appropriately substituted cyclobutane and (2) conversion of a cyclobutane derivative to a tricyclic structure of such a nature as to allow generation of the nine-membered ring from two smaller rings by bond scission.[19]

The first of these general approaches suffers from the disadvantage that there are only a very limited number of reactions which can be employed to close nine-membered rings efficiently. In addition those methods which might be used to form the nine-membered ring directly are not well suited to the selective introduction of the necessary unsaturation. Some studies were carried out to ascertain the possibility of applying the acyloin cyclization to this problem, for example, in the specific case of the compound VII, a readily available[20] degradation product of caryophyllene. These investigations seemed to yield results of only marginal interest, however.

The second alternative is exemplified by the possible application of the bridged-ring intermediate VIII or the fused-ring structure IX as precursors of the 4–9 fused-ring system of the caryophyllenes using an internal elimination reaction in the key step. A considerable number of variants on VIII are possible and might conceivably serve a useful role; however, definite disadvantages are associated with each of these. Compound IX appeared to be a more attractive key intermediate. Internal double elimination of the type reported previously for other 1,4-dihalides[21] could produce the ring system of the caryophyllenes from the

(9) J. M. Robertson and G. Todd, *Chem. Ind.* (London), 437 (1953); *J. Chem. Soc.*, 1254 (1955).

(10) A. Eschenmoser and H. H. Gunthard, *Helv. Chim. Acta*, **34**, 2338 (1951).

(11) D. H. R. Barton, T. Brunn, and A. S. Lindsay, *Chem. Ind.* (London), 1910 (1951); *J. Chem. Soc.*, 2210 (1952).

(12) A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsay, *ibid.*, 4659 (1954).

(13) A. Aebi, D. H. R. Barton, and A. S. Lindsay, *ibid.*, 3124 (1953).

(14) G. R. Ramage and R. Whitehead, *ibid.*, 4336 (1954).

(15) J. S. Clunie and J. M. Robertson, *Proc. Chem. Soc.*, 82 (1960).

(16) For a preliminary communication see E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **85**, 362 (1963).

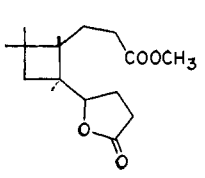
(17) K. Deussen and A. Lewinsohn, *Ann.*, **356**, 1 (1907).

(18) Performed by Dr. P. A. Vatakencherry.

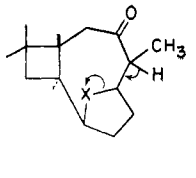
(19) Another theoretically possible route to the caryophyllene ring system is the simultaneous formation of *both* rings by an internal cycloaddition process—the probable biosynthetic pathway. This interesting approach, more adventurous and less predictable than the others here mentioned, is under investigation in our laboratories.

(20) D. J. Pasto, unpublished work in these laboratories.

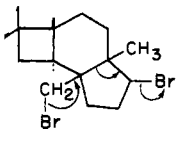
(21) See C. A. Grob, *Experientia*, **13**, 126 (1957), and more specifically for 1,4-dibromocyclohexane, see C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).



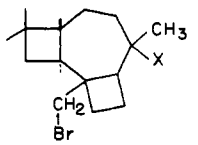
VII



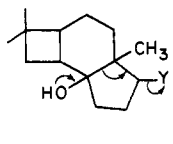
VIII; *e.g.* X = $(CH_3)_2N^+$



IX



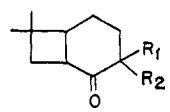
X



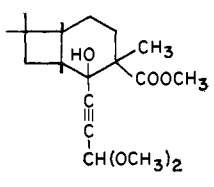
XI

dibromide IX. Further, the stereochemistry of the endocyclic double bond produced by elimination would depend on the relative orientation of the angular methyl and the adjacent bromine substituent in IX and, hence, this feature would be subject to control. A strong argument against the use of IX, however, is the necessity of having a *trans* fusion of the four- and six-membered rings in order to produce the corresponding 4–9 fusion in the internal elimination product as required for the synthesis of I and II. It will be appreciated that the construction of the required stereochemical modification of IX is not an easy task because of the angle strain involved. This is also a consideration for the alternative X. Fortunately, a simple and satisfactory alteration is available which obviates the stereochemical difficulty inherent with IX and X. This is the utilization of intermediate XI (Y is an anionic leaving group) which is still subject to internal elimination to form a nine-membered ring as are IX and X,[22] but which produces a carbonyl function adjacent to the 4–9 ring fusion instead of a terminal methylene group. Clearly, even though the 4–6 fusion in XI may be *cis*, there remains the possibility of changing the 4–9 fusion in the internal cleavage product by base-catalyzed epimerization at the junction atom alpha to the carbonyl group. The subsequent conversion of the carbonyl function to $C{=}CH_2$ is the only remaining detail, now a routine one. The following section describes the plan used for assembling structure XI and the further transformations which complete the synthesis of I and II in racemic form.

Synopsis of the Experimental Approach.—The ketone XII appeared to be the most satisfactory candidate as a precursor for the construction of the desired intermediate XI, and our initial efforts were directed toward developing a synthesis for this previously unknown substance. Two methods of synthesis, both photochemical, were investigated; one of these proved to



XII, $R_1 = R_2 = H$
XIII, $R_1 = H$, $R_2 = COOCH_3$
XIV, $R_1 = CH_3$, $R_2 = COOCH_3$



XV

be admirably suited to the need and a remarkable reaction *per se*. It was hoped that the irradiation of 2-cyclohexenone in the presence of isobutylene at high concentration would result in the intermolecular analog of previously known photochemical cycloadditions.[23] An unknown element which could not be evaluated in advance of experiment was the matter of the preferred orientational mode of cycloaddition. The experiment seemed attractive, despite this uncertainty, because the disadvantage of obtaining a mixture of the desired 7,7-dimethylbicyclo[4.2.0]octanone-2 (XII) and the undesired isomer, 8,8-dimethylbicyclo[4.2.0]octanone-2, would be counteracted by the directness of the synthesis. In actual fact it was discovered that the irradiation of a mixture of 2-cyclohexenone and a large excess of isobutylene at -40 to $-70°$ using a high-pressure mercury arc with a filter to remove wave lengths below 290 mμ resulted in a rapid reaction between the two components. Preliminary distillation of the reaction product afforded a small forerun (containing a small amount of cyclohexenone and somewhat higher-boiling ketones), and a main fraction, 65% yield, b.p. 55–57° (0.5 mm.), which contained the desired saturated ketonic material contaminated by *ca.* 30% impurity (mainly unsaturated). Chromatography of a sample of the major fraction using liquid–solid adsorption and preparative v.p.c. led to the isolation of a pure saturated ketone which was shown by analytical and physical studies to be *cis*-7,7-dimethylbicyclo[4.2.0]octanone-2, the desired product. The data include elemental analysis (showing $C_{10}H_{16}O$), infrared spectrum (carbonyl absorption at 5.84 μ), and nuclear magnetic resonance (n.m.r.) measurements. Two sharp three-proton peaks occur in the n.m.r. spectrum at 0.97 and 1.15 δ[24]; no other sharp peaks appear in this region which indicates the absence of a second isomer. Convincing evidence for the assignment of structure XII to this compound is the appearance of six sharp peaks in the region 2.6 to 3.1 δ which represent a single proton split into two overlapping triplets by coupling to a set of two protons (J = 9 c.p.s.) and additionally to a single proton (J = 7.3 c.p.s.). This proton which appears as a doublet of triplets must be alpha to the carbonyl group since it is removed from the molecule by exchange with deuterium oxide–potassium carbonate under mild conditions. The requirement of a tertiary α-hydrogen to which are attached $-CH_2-$ and $-CH-$ groups imposes structure XII on the major product of the photoreaction of 2-cyclohexenone and isobutylene.

The by-products of the photoreaction have also been examined. These are mainly unsaturated ketones.[25] The alternative cycloaddition product 8,8-dimethylbicyclo[4.2.0]octanone-2 is formed in the reaction[25] but only in minor amount. It is considerably lower boiling than the major isomer XII and is separated in the forerun by distillation. Thus the interesting result emerges that the photochemical addition of isobutylene to 2-cyclohexenone and subsequent careful distillation affords 7,7-dimethylbicyclo[4.2.0]octanone-2 (XII) (35–45% yield) uncontaminated by the isomeric 8,8-dimethyl derivative, an ideal circumstance for our synthetic purpose. The product obtained from the photoreaction by two fractional distillations proved to be satisfactory for the subsequent steps.

(22) The examples upon which our reasoning on this point was based were furnished by the work of (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. Ind.* (London), 1315 (1953); (c) R. R. Burford, F. R. Hewgill, and P. R. Jefferies, *J. Chem. Soc.*, 2937 (1957). More recently, a closely related case was described by P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

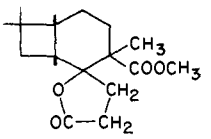
(23) See (a) G. Büchi and I. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957); (b) R. C. Cookson and E. Crundwell, *Chem. Ind.* (London), 1004 (1958); (c) S. J. Cristol and R. L. Snell, *J. Am. Chem. Soc.*, **76**, 5000 (1954); (d) A. Schönberg, "Präparative Organische Photochemie," Springer-Verlag, Berlin, 1958, pp. 22–40.

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

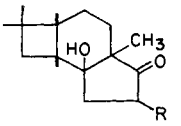
(25) The results of a study of these compounds, α- and β-methallylcyclohexanones (ratio 1.5:1), by Dr. J. D. Bass in these laboratories will be published at a later time.

Possibly the most arresting feature of the photoaddition of 2-cyclohexenone to isobutylene is that the unstable *trans* isomer of XII is produced in larger amount than the stable *cis* form. This was indicated by the appearance of peaks in the n.m.r. spectrum of distilled product which disappeared upon mild treatment with aqueous base or contact with activated alumina at room temperature or upon heating to 200° for a short time or upon v.p.c. treatment. Most prominent of these peaks was a sharp methyl resonance at 1.07 δ with about four times the intensity of a nearby peak at 0.97 δ due to the *cis*-XII which was present. In addition to these there was a sharp peak at 1.15 δ with about five times the intensity of the 0.97-δ peak. Base treatment of this product which had been subjected only to distillation resulted in loss of the peak at 1.07 δ with a corresponding increase in the 0.97-δ peak; the 1.15-δ peak was unchanged, however, and finally of the same intensity as the 0.97-δ peak, as with *cis*-XII. Furthermore, careful redistillation led to fractions containing the unstable product (higher b.p.) substantially free of the stable isomer (lower b.p.); these fractions showed methyl peaks in the n.m.r. spectra at 1.07 and 1.15 δ (equal intensity) and no peak at 0.97 δ; this spectrum changed after base treatment to that of *cis*-XII. These facts make it clear that the original photoproduct contains both *trans* and *cis* forms of XII in a ratio of approximately four to one.[26] The factors which control stereochemistry and orientation are presently under investigation; these will be considered in detail in a separate paper.[25]

With an expeditious procedure for the preparation of *cis*-XII we turned to the next stage of synthesis,[27] the addition of a third carbocyclic unit. The reaction of XII with sodium hydride–methyl carbonate in dioxane gave an enolic β-keto ester XIII which was methylated to XIV in excellent over-all yield. The methylation was not stereospecific as was shown by n.m.r. analysis of XIV which indicated a 3:1 mixture of isomers. Because this ratio seemed quite insensitive to reaction conditions and because this source of isomerism was going to be removed in the later stages of synthesis, the mixture was carried on as such; also no attempt was made to determine the stereochemistry of these isomers. Reaction of XIV with the lithio derivative of propargyl aldehyde dimethylacetal in tetrahydrofuran produced the liquid acetylenic ester XV (actually a mixture of isomers) which was hydrogenated to the corresponding tetrahydro compound using palladium–charcoal catalyst in alkaline methanol. Treatment of this tetrahydro acetal with chromic acid in aqueous acetic acid led to the ester γ-lactone XVI, the intermediate which seemed best suited for cyclization.[28] The infrared spectrum of XVI manifested both ester and γ-lactone carbonyl absorption (5.78 and 5.63 μ, respectively) as expected. Formation of a five-membered carbocyclic ring by a Dieckmann type reaction of XVI occurred rapidly and smoothly using as reagent methylsulfinylcarbanion in dimethyl sulfoxide[29]



XVI



XVII, R = $COOCH_3$
XVIII, R = H

to give the tricyclic keto ester XVII in 60% yield. An intermediate bridged lactone which undergoes attack and cleavage by methoxide ion is considered likely for this transformation. The hydroxy keto ester shows carbonyl absorption at 5.67 and 5.77 μ[30] and hydroxyl absorption at 2.8–2.9 μ; it gives a purple color with ferric chloride. It is of interest that the Dieckmann cyclization of the ester lactone XVI could not be realized under a variety of other conditions including the use of methoxide or *t*-butoxide ions as base in several different solvents.

Hydrolysis of keto ester XVII (still a mixture of stereoisomers) by aqueous alkali at room temperature yielded an acid which underwent decarboxylation upon heating in pyridine to give as a major product a crystalline hydroxy ketone XVIII, m.p. 126–127°, infrared maxima 2.7–2.9 and 5.76 μ. Three sharp methyl peaks appear in the n.m.r. spectrum of XVIII which indicates it to be a pure isomer[31]; these peaks are at 0.98, 1.10 and 1.22.

Although the structure of the hydroxy ketone can be assigned as XVIII with confidence, the stereochemistry of this substance is not defined by the method of synthesis. The fact that the 4–6 ring fusion must be *cis* coupled with the probability that the addition of the anion from propargyl aldehyde dimethyl acetal to the ketone function of XIV proceeds from the side of the synclinal system *cis* to the hydrogens of the ring junction would indicate only two alternatives for the hydroxy ketone XVIII. These are (starting from the 4–6 fusion): *cis, anti, cis* and *cis, anti, trans*. Which of these possibilities is correct is not known at present and, fortunately, this knowledge is not essential to our purpose. The important point of stereochemistry is the geometrical configuration of the endocyclic double bond generated in the nine-membered ring by internal scission of the bond common to the six- and five-membered rings and the bonds to the leaving groups. Assuming that the internal elimination is concerted with respect to the breaking of the various bonds and that the stereoelectronically favorable *coplanar* mode of elimination will prevail, the control of olefin configuration during internal elimination is governed by the relative orientation of the angular methyl group and the vicinal leaving group, the secondary *p*-toluenesulfonate function in the experiments which follow. When these groups are *cis* (as in XX) a *trans* olefinic linkage should result. Thus it is necessary to control the stereochemistry of the reduction of the hydroxy ketone XVIII so as to produce either XIX or XX in order to achieve syntheses of both the caryophyllene and isocaryophyllene systems.

Reduction of the hydroxy ketone XVIII with a variety of reagents, including sodium borohydride, lithium aluminum hydride, lithium tri-*t*-butoxyaluminum hydride, and sodium–moist ether, produced a single crystalline diol, m.p. 122.5–124°, which from the data which follow must be XIX (methyl and secondary

(26) The formation of the *trans* isomer of XII in the photoaddition of 2-cyclohexenone to isobutylene and the orientational specificity were unexpected on the basis of earlier studies (see ref. 23) and also stand in contrast to some more recent work; see (a) P. de Mayo, H. Takeshita, and A. B. Sattar, *Proc. Chem. Soc.*, 119 (1962), and (b) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344, 2554 (1962). One very recent communication reports another photochemical route to the *trans*-bicyclo[4.2.0]octane system: (c) P. de Mayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc.*, 54 (1963).

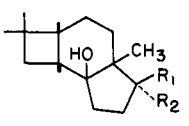
(27) The alternative approach to the synthesis of XII utilizes the photolysis of 2-*t*-butylcyclohexanone which produces 7,7-dimethylbicyclo[4.2.0]-octanol-1 in *ca.* 15% yield. This is clearly not competitive with the photoaddition route. Further discussion of this reaction series will be given in a subsequent paper.

(28) Acid catalyzed hydrolysis of tetrahydro XV afforded a cyclic hemiacetal ester which did not appear to undergo the desired ring closure under a variety of conditions.

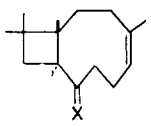
(29) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(30) Ethyl cyclopentanone-2-carboxylate shows carbonyl absorption at 5.70 and 5.80 μ: N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Petersen, *ibid.*, **74**, 4070 (1952).

(31) Another crystalline hydroxy ketone, m.p. 140–141.5°, a stereoisomer of XVIII, has been isolated in small amount from the crude decarboxylation product.

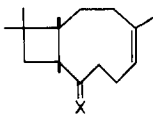


XIX, R_1 = H, R_2 = OH
XX, R_1 = OH, R_2 = H

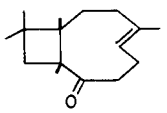


XXI, X = O
II, X = CH_2

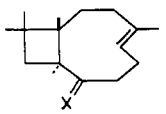
hydroxyl *trans*). This was transformed readily into a mono-*p*-toluenesulfonate. Generation of the fused 4–9 ring system of the caryophyllenes was accomplished by internal elimination *via* the γ-oxide anion derived from the toluenesulfonate,[22] as projected in the preceding section. Thus, treatment of the hydroxy-*p*-toluenesulfonate with methylsulfinylcarbanion[29] (3 equivalents) at 25° in dimethyl sulfoxide for 30 min. followed by addition of several equivalents of *t*-butyl alcohol and a further 2 hr. for isomerization of the 4–9 ring fusion afforded the ketone XXI, infrared max. 5.90 μ in excellent yield. The methylsulfinylcarbanion seems admirably suited for this application and, indeed, the cleavage reaction appears to proceed in just a few minutes. Reaction of the ketone XXI with methylenetriphenylphosphorane–dimethyl sulfoxide[32] gave the hydrocarbon II identical with a sample of natural isocaryophyllene (kindly provided by Dr. F. Sorm) as shown by vapor chromatography and spectroscopy. When the internal elimination of the above hydroxy toluenesulfonate was allowed to proceed for only 15 min. at 10° and worked up without delay, a ketone XXII isomeric with XXI was formed. This yielded by Wittig transformation a hydrocarbon isomeric with the caryophyllenes. This substance which differs in physical properties from both caryophyllene and isocaryophyllene must be the unknown *cis,cis* isomer XXIII.



XXII, X = O
XXIII, X = CH_2



XXIV



XXV, X = O
I, X = CH_2

The synthesis of *d,l*-caryophyllene (I) was also accomplished starting from the hydroxy ketone XVIII used above. Reduction of this substance with hydrogen–Raney nickel afforded a mixture of two diols, XIX and XX, in roughly equal amounts; these were separated readily by chromatography, and XIX could be oxidized back to the starting material quantitatively (chromium trioxide–pyridine). The other diol XX (methyl and secondary hydroxyl *cis*), m.p. 112.5–113°, gave a crystalline mono-*p*-toluenesulfonate, m.p. 100.5–101.5°, which was converted by base-catalyzed internal elimination to a bicyclic unsaturated ketone different from the isomers XXI and XXII described above. This substance must be the *trans*-cycloolefin with *cis* 4–9 fusion (XXIV) since upon prolonged (15 hr.) treatment with sodium *t*-butoxide–dimethyl sulfoxide it is changed to an isomeric ketone (XXV) which is transformed by the Wittig process to *d,l*-caryophyllene (I). The synthetic material was identical with a sample of natural caryophyllene, which had been purified by v.p.c., as determined by a comparison of infrared spectra and vapor chromatographic behavior.

It is noteworthy that the initial cleavage product from the crystalline monotoluenesulfonate of XX, the ketone XXIV, is much more slowly isomerized at the ring junction than is the ketone XXII, a *cis*-cycloolefin with *cis* ring fusion. The isomer XXIV is also much less reactive toward the Wittig reagent than any of the other ketones, XXI, XXII or XXV and, in fact, it is completely unreactive under conditions which are conducive to essentially complete reaction of XXI, XXII, or XXV. The unreactive isomer XXIV must have a *trans* endocyclic double bond since this structure is the only possibility which serves to explain the unreactivity of this substance in carbonyl addition or enolate formation. Examination of Dreiding models of XXII and XXIV indicates that the nine-membered ring in the latter is much more rigid than that of the former and shows clearly the difference in carbonyl environment. These differences in reactivity of XXII and XXIV and the conversions to isocaryophyllene and caryophyllene, respectively, provide convincing evidence of the correctness of the assigned structures; isocaryophyllene must have a *cis* endocyclic double bond and caryophyllene must have the *trans* olefinic geometry.

(32) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

Experimental

Infrared and n.m.r. spectra were determined using carbon tetrachloride as solvent unless otherwise indicated.

Photoaddition of Isobutylene to 2-Cyclohexenone.—The apparatus used for the photochemical reaction consisted of a cylindrical Pyrex reaction vessel having a neck for sampling and addition, a neck for a Dry Ice condenser, and a neck to accommodate a quartz-jacketed, water-cooled Hanovia type-L, 450-w., high-pressure (immersion type) mercury arc lamp with an outer Corex filter sleeve. An atmosphere of pure argon was obtained in the reactor by alternately evacuating and filling with argon through a three-way stopcock attached to the top of the condenser. The reactor (800 ml. capacity with immersion well) was charged with 350 ml. of pentane and cooled by means of an external Dry Ice–ethanol bath (reactor fully immersed). Isobutylene (300 ml.) and 2-cyclohexenone (28 g.) were then added to the cold pentane, an atmosphere of argon was imposed (slight positive pressure with a slow flow of argon past the top of the condenser into a mercury valve) and irradiation was commenced. An excess of Dry Ice was kept in the bath and in the condenser all during the reaction. The water used to cool the mercury lamp was precooled to 5°. The progress of the reaction was followed by removing aliquots by hypodermic syringe and measuring the infrared spectrum. As the reaction proceeded the carbonyl band of 2-cyclohexenone (5.94 μ) gradually disappeared and another due to nonconjugated carbonyl developed at 5.84 μ. On this scale the reaction was essentially complete in 14 hr.; in smaller scale runs less time was required (6 hr. with 5 g. of 2-cyclohexenone). The crude product was obtained by removal of pentane and isobutylene on a water bath and then distilled through a 1-m. spinning-band column (Nester and Faust). After a forerun of 2.45 g. (b.p. up to 55° (0.45 mm.)), the main fraction (29.5 g.) was collected at b.p. 55–57° (0.45 mm.). This fraction contained mainly 7,7-dimethylbicyclo[4.2.0]octanone-2 but also at least three minor impurities. Two of these were revealed by v.p.c. analysis on a 20% fluorosilicone (1265) on Chromosorb-P column (8 ft.) at 175° (helium flow 60 ml./min.) as an unresolved double peak, retention time 12.3, 12.6 min., which accompanied the main peak of retention time 17.3 min.; the minor peaks and the major peak correspond to 15 and 85% of the total material. The material corresponding to this major peak was collected by preparative v.p.c. on a fluorosilicone column; the infrared spectrum showed no hydroxyl absorption, a strong carbonyl band at 5.84 μ, and a weak band at 11.1 μ which arises from two impurities having an olefinic terminal methylene group; the n.m.r. spectrum confirms the presence of olefinic impurity since absorption occurs at 4.7–4.8 δ which amounts quantitatively to only 0.2 proton, *i.e.*, 0.1 $C{=}CH_2$. The olefinic impurities (roughly 10%) were removed by careful chromatography using methylene chloride–chloroform mixtures as eluting solvents and silica gel as adsorbant. The n.m.r. spectrum of 7,7-dimethylbicyclo[4.2.0]-octanone-2 obtained indicated the compound to be pure and supported the assigned structure: six peaks due to *one* proton at 162, 168, 171, 178, 179, and 185 c.p.s. downfield from tetramethylsilane (at 60 Mc.) (no peaks at lower field), and sharp methyl peaks at 58.2 and 69 c.p.s. (0.97 and 1.15 δ, 3 protons each). Warming XII to 50° with a large excess of deuterium oxide containing 5% anhydrous potassium carbonate, followed by extraction with pentane and distillation gave trideuterio-XII which lacked the peaks at 162–185 c.p.s. as well as some of the original absorption at 1.6–2.3 δ. The peaks at 162–185 c.p.s. in the undeuteriated compound can only be interpreted as due to a single hydrogen attached to an α-carbon atom, the resonance of which is split into a triplet by an adjacent methylene and further into a pair of overlapping triplets by another vicinal proton; thus the assignment of XII seems unambiguous. The major

fraction (29.5 g.) of the distilled product (before further purification), which according to the data above should be *ca.* 70% XII, did not show the expected intensities of the methyl peaks at 0.97 and 1.15 δ in the n.m.r. spectrum; the observed methyl peak at 0.97 δ was far too weak relative to the observed peak at 1.15 δ (ratio approximately 1:5) and further there was a new peak at 1.07 δ of about four times the intensity of the 0.97-δ peak. This discrepancy was explained when it was noted that by treatment of the distilled product with aqueous or methanolic base at 25°, by passage through alumina (using ether as solvent) or by short heating to 200°, the expected n.m.r. spectrum was developed. That is, the peak at 1.07 δ disappeared and two methyl peaks at 0.97 and 1.15 δ (of approximately equal intensity) remained. Thus it is clear that the original reaction product contains stable and unstable isomers of XII; the obvious and most likely interpretation is that these are the geometrical forms with *cis* and *trans* ring fusion, respectively (ratio about 1:4). The unstable isomer was rapidly isomerized during v.p.c. treatment using a fluorosilicone–Chromosorb-P column, but not on a fluorosilicone–Diatoport (F. and M. Scientific Co.) column. The *trans* isomer can in fact be purified with the latter column at minimal temperatures.[25] It shows only two peaks in the n.m.r., 1.07 and 1.15 δ; treatment with alumina produces pure *cis* isomer, n.m.r. peaks at 0.97 and 1.15 δ (exactly equal intensity).

Careful redistillation of the major distillation fraction led to a partial purification of the various components; the *trans* isomer of XII is higher boiling than the *cis* isomer and the last distillation fractions are enriched in this substance (n.m.r. peaks at 1.07 and 1.15 δ (equal intensity), negligible peaks at 0.97 δ) and in the olefinic impurity with v.p.c. retention time 17.3 min. (same as XII). The impurities with shorter v.p.c. retention time (12.3, 12.6 min.) can be separated quite efficiently in the forerun, b.p. 50–55° (1.3 mm.). The main fractions, b.p. 56–58.5° (1.1 mm.), estimated to be 85–90% pure by v.p.c. and n.m.r. were found to be free of the 8,8-dimethyl isomer[25] of XII and these were satisfactory for the synthetic operations described below. The total yield of material of this purity was *ca.* 50%; the yield of pure XII calculated on the basis of v.p.c. and n.m.r. analysis on the distilled reaction product was *ca.* 35–45%.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.78; H, 10.50.

In a separate control experiment[25] it was found that irradiation of *cis*-XII under standard reaction conditions left this ketone mainly unchanged; none of the *trans* isomer could be detected by n.m.r.

3-Carbomethoxy-7,7-dimethylbicyclo[4.2.0]octanone-2 (XIII).—A solution of 9.56 g. (0.063 mole) of the ketone XII in 25 ml. of dry dioxane was added dropwise over 3 hr. under nitrogen to a stirred mixture of 3.02 g. (0.126 mole) of sodium hydride and 28 g. of dimethyl carbonate in 50 ml. of dry dioxane at a bath temperature of 80–85°. Initially, the reaction was very sluggish but gradually hydrogen evolution grew more rapid, and as the sodium hydride disappeared the solution became pale red. After the addition of the ketone, the mixture was stirred for a further 2 hr. at 80–85°, then cooled with an ice-water bath and acidified with a slight excess of aqueous acetic acid. The solvent was removed *in vacuo* and the residue was diluted with water and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate to remove acetic acid, then with saturated brine, dried, and freed from ether to give 13 g. of crude keto ester. Distillation *in vacuo* gave 11.36 g. (86%) of colorless liquid, b.p. 82–83° (0.3 mm.). The infrared spectrum showed double-bond stretching at 5.7, 5.86 (both medium intensity), 6.05, and 6.19 μ (strong). The product gave a deep purple color with alcoholic $FeCl_3$.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.84; H, 8.55.

3-Carbomethoxy-3,7,7-trimethylbicyclo[4.2.0]octanone-2 (XIV).—A solution of 11.2 g. (0.0534 mole) of the β-keto ester in 15 ml. of dry dioxane was added gradually under nitrogen to a stirred suspension of 1.92 g. of sodium hydride in 60 ml. of dry dioxane. A very vigorous evolution of hydrogen was observed. To this mixture, after 5 min., was added excess of methyl iodide and the reaction mixture was stirred for 2.5 hr. at 40°. It was then cooled and acidified with a mixture of water and 5 ml. of acetic acid. After removal of solvents *in vacuo*, the residue was diluted with water and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate and saturated brine, then dried, and freed from ether. The residual liquid was distilled *in vacuo* to give 11.15 g. (94%) of colorless liquid, b.p. 80–85° (0.3 mm.). The infrared spectrum showed strong carbonyl peaks at 5.84 (ketone) and 5.74 μ (ester). The n.m.r. spectrum of XIV showed the presence of two isomers in a ratio of *ca.* 3:1. The major isomer showed *gem*-dimethyl equally intense peaks at 1.05 and 1.25 δ; the minor isomer showed *gem*-dimethyl peaks at 0.98 and 1.15 δ (of equal intensity). In each isomer the 3-methyl group appeared in the n.m.r. at 1.36 δ. The carbomethoxy methyl was split into 2 peaks (intensity ratio 1:3) at 3.89 and 3.93 (major) δ.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61, H, 8.99 Found: C, 69.98; H, 9.19.

Addition of Propargyl Aldehyde Dimethyl Acetal to XIV. Propargyl aldehyde[33] was converted to the dimethyl acetal by treatment with methanol–sulfur dioxide–calcium chloride.[34] A solution of *n*-butyllithium in hexane (10 ml., 15.25%) was added at once to a solution of 3 g. (0.03 mole) of the propargyl aldehyde dimethyl acetal in 40 ml. of freshly distilled anhydrous tetrahydrofuran at 0° with stirring and under nitrogen. The mixture turned immediately to light yellow brown. After 15 min., 2.24 g. (0.01 mole) of the keto ester XIV in 10 ml. of tetrahydrofuran was added at once through a rubber stopple with a syringe and the mixture was stirred at 0° for 1 hr. Then 16 ml. of water was added and almost all of the tetrahydrofuran was removed under reduced pressure. The separated oily material was extracted with 1:1 pentane–ether and the extract was washed with water and saturated salt solution. After removal of the solvent, carbon tetrachloride was added and evaporated; this operation was repeated three times in order to expel the remaining acetal. Finally 3.29 g. of the adduct XV was obtained as a liquid, the infrared spectrum of which showed a hydroxyl band (at 2.83 μ), carbonyl bands (at 5.74 and 5.85 μ), and strong acetal bands (at 8.93 and 9.41 μ). Integration of the peak intensities in the n.m.r. spectrum confirmed the assigned structure XV, *e.g.*, the methyl peaks at 4.0 δ ($COOCH_3$) and at 3.48 δ ($>C(OCH_3)_2$) are in the ratio 1:2.

Attempts to purify further the liquid reaction product by distillation under high vacuum or chromatography did not seem promising and so further analytical data were not obtained.

Conversion of the Acetylenic Acetal XV to the Ester Lactone XVI.—A mixture of 500 mg. of 5% palladium on carbon in 50 ml. of methanol containing 13 mg. of potassium hydroxide was saturated with hydrogen, and then 6.63 g. of the adduct XV in methanol was added and hydrogenated at 1 atm. overnight. A total of 890 ml. of hydrogen was absorbed. After removal of the catalyst, hydrogenation was continued using 400 mg. of fresh catalyst. The total uptake of hydrogen was 1035 ml. (theoretical amount is 1010 ml.). Filtration of the catalyst through Hyflo Super-Cel, followed by evaporation of the methanol afforded viscous material. The product was dissolved in ether and washed with water and saturated salt solution and then freed of the ether under reduced pressure to give 6.48 g. of the tetrahydro derivative of XV, infrared max. 2.82, 5.79, and 5.87 μ.

A solution of this material (6.48 g.) in 26.5 ml. of acetic acid and 6.6 ml. of water at 15° was treated dropwise with a solution of 13 g. of chromium trioxide in 33 ml. of acetic acid and 13 ml. of water with stirring. The time of addition was 40 min. and the temperature was maintained at 15° during this time. The cooling bath was then removed and the reaction was allowed to proceed for a further 2 hr. The reaction mixture was treated with 250 ml. of pentane–ether (2:1), ice, and 220 ml. of 10% sodium hydroxide (with external cooling). The phases were separated and the aqueous part extracted twice with the same solvent. The organic extracts were combined, washed successively with potassium carbonate solution and saturated salt solution, dried over sodium sulfate, and concentrated. The ester lactone XVI, 4.81 g. (86%), was obtained as a colorless liquid which showed lactone and ester peaks in the infrared at 5.63 and 5.78 μ and no hydroxyl absorption. A sample was prepared for analysis by evaporative distillation (120–130° bath temp. at 0.08 mm.).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.51; H, 8.86.

Dieckmann Cyclization of the Ester Lactone XVI to Keto Ester XVII.—Sodium methylsulfinylcarbanion was prepared in the usual manner from 1 g. of sodium hydride and 29 ml. of dry dimethyl sulfoxide. A solution of 5.78 g. of the ester lactone XVI in 30 ml. of dimethyl sulfoxide was added at room temperature with stirring and under nitrogen; the mixture turned immediately to dark brown. After 20 min. dilute acetic acid (5.8 ml. in 12 ml. of water) was added with cooling. The resulting solution was transferred in a separatory funnel with the aid of more water (300 ml.) and 2:1 pentane–ether and extracted with the same solvent four times. The combined extracts were successively washed with dilute sodium bicarbonate solution, water, and saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 3.27 g. (57%) of oily hydroxy keto ester XVII, which showed infrared absorption at 2.80 μ (OH) and at 5.69 and 5.78 μ (keto ester) and gave a purple color with ferric chloride.

Because this product was unstable to attempted distillation, an analytical sample was not prepared.

Conversion of the Hydroxy Keto Ester XVII to the Hydroxy Ketone XVIII.—The hydroxy keto ester from the preceding ex-

(33) *Org. Syn.*, **36**, 66 (1956).

(34) H. Pasedach and G. Schmidt-Thomée, U. S. Patent 2,879,305 (March 24, 1959).

periment (3.27 g.) was treated with 95 ml. of 1 *N* sodium hydroxide at 30° for 13 hr. and then at 40° for an additional 7 hr. with stirring and under nitrogen. The cooled mixture was extracted with 2:1 pentane–ether three times. The extracts were washed with saturated salt solution and evaporated to give 0.7 g. of neutral material which showed a weak hydroxyl band and three carbonyl bands at 5.65, 5.78, and 5.86 μ in the infrared spectrum.

The water layer was acidified (congo red) with 6 *N* hydrochloric acid (*ca.* 22 ml.) at 0°, saturated with salt, and extracted with ether four times. Washing the combined extracts with saturated salt solution, followed by evaporation of the ether, afforded 2.58 g. (83%) of free acid which showed the characteristic infrared absorption of a carboxylic acid at 2.8–3.2 and 5.90 μ in addition to a cyclopentanone band at 5.75 μ.

All of this material was dissolved in 40 ml. of pyridine and the solution was heated at 110–115° for 40 min. under nitrogen. After cooling to 0° the reaction mixture was carefully acidified (to congo red) using 6 *N* hydrochloric acid and extracted with three portions of ether. The ethereal extract was washed successively with brine, sodium bicarbonate, and brine, dried, and concentrated *in vacuo* to give 1.80 g. of crude hydroxy ketone which partially crystallized on standing chromatography on neutral alumina. Separation of the crystals followed by recrystallization from pentane–ether afforded 400 mg. of pure hydroxy ketone XVII, m.p. 126–127°, infrared max. 5.76 μ, n.m.r. peaks due to methyl groups at 0.98, 1.10, and 1.22 δ.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.48; 75.67; H, 10.02, 9.91.

Chromatography of the noncrystalline material on neutral alumina (Grade III–IV) and storage of the oily fractions for several weeks yielded an additional 380 mg. of the above hydroxy ketone. In addition another isomeric hydroxy ketone, m.p. 140.5–141.5°, was obtained in very small amount by catalytic reduction (over Ni) of crude solid fractions followed by chromatography and oxidation with chromium trioxide–pyridine (see below). An analytical sample was prepared by sublimation *in vacuo*.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.49; H, 10.01.

Reduction of the Hydroxy Ketone XVIII to the Diol XIX.—To a cold solution of 1.5 g. of sodium borohydride in 28 ml. of methanol containing a small amount of sodium hydroxide was added dropwise a solution of 170 mg. of the crystalline hydroxy ketone XVIII in 2 ml. of methanol, and the mixture was stirred at 0° for 30 min. and at room temperature for 15 hr. Cold aqueous tartaric acid solution was added with ice-cooling until the white precipitate redissolved. Almost all of the methanol was evaporated under reduced pressure and the aqueous solution (crystals separated) was extracted with ether three times. The extracts were washed with dilute sodium hydroxide and saturated salt solution and evaporated to give 180 mg. of crystalline diol XIX, m.p. 122.5–124°, intense infrared max. at 2.7–3.0 (hydroxyl) and 9.82 μ (C–O stretching). Analytical samples were prepared both by recrystallization from ether–pentane and by sublimation, but the observed carbon content was somewhat low in each case.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 73.90; H, 10.90 (average).

This same product was obtained from the hydroxy ketone XVIII in good yield with either excess sodium (0.4 mm. diameter shot) in moist ether, lithium aluminum hydride in ether at room temperature, lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran at 50° for 16 hr., or sodium borohydride in pyridine using minimal reaction and isolation conditions.

Reduction of the Hydroxy Ketone XVIII with Hydrogen–Raney Nickel.—Crystalline XVIII, m.p. 124–126° (200 mg.), in 25 ml. of ethanol was hydrogenated using freshly prepared Raney nickel catalyst (from 1.25 g. of alloy) at atmospheric pressure until 1 mole of hydrogen was absorbed. After removal of the catalyst and ethanol, the residue was dissolved in ether and the insoluble material was filtered. Evaporation of the ether afforded 200 mg. of a mixture of diols. The mixture was dissolved in 2 ml. of benzene and 8 ml. of cyclohexane and chromatographed on 5 g. of neutral alumina activity V with cyclohexane and then with 4:1 cyclohexane–benzene as eluting solvents. The more rapidly eluted fraction consisted of *ca.* 100 mg. of crystalline product which showed a different infrared spectrum from that of diol XIX obtained by the above mentioned methods. Recrystallization from pentane–ether twice gave pure diol XX, m.p. 112.5–113.0°, infrared max. 2.7–3.0 (OH), and 9.92 and 10.05 μ.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.91; H, 10.76.

After elution of 8 mg. of a mixture, 70 mg. of diol XIX was obtained by washing the alumina column with ether.

In runs where crude hydroxy ketone XVIII was used in the above reduction a third diol was obtained by chromatography, as the most rapidly eluted product, m.p. 154.5–157.5° after recrystallization from carbon tetrachloride. The infrared spectrum, different from those of XIX and XX, showed bands at 2.7–3.0, 9.69, and 10.14 μ.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.95; H, 10.77.

Oxidation of this diol with chromium trioxide–pyridine gave the hydroxy ketone, m.p. 140.5–141.5°, described above and isomeric with XVIII.

Oxidation of Diol XIX to Hydroxy Ketone XVIII.—To the complex prepared from 40 mg. of chromium trioxide and 1.5 ml. of pyridine was added 20 mg. of diol XIX; after 15 min. the color turned to brown and then gradually dark brown. The mixture was stirred at room temperature for 8 hr., then 3–4 ml. of water was added at 0°, and the resulting dark brown solution was transferred into a separatory funnel with the aid of more water and 1:1 pentane–ether, and extracted with the same solvent four times. The combined extracts were successively washed with 2 *N* sulfuric acid, 5% sodium bicarbonate, and saturated salt solution. Evaporation of the solvent gave the original hydroxy ketone XVIII, identified by infrared spectrum and melting point, in quantitative yield.

Mono-*p*-toluenesulfonate of the Diol XIX.—To a solution of 286 mg. (1.5 mmoles) of *p*-toluenesulfonyl chloride in 0.82 ml. of dry pyridine was added a solution of 220 mg. of diol XIX in 4 ml. of dry methylene chloride with ice-cooling and under nitrogen. The temperature was kept at 0° for 30 min. and then at 22° for 10 hr. Several pieces of chopped ice were added and then the mixture was stirred for 30 min. More water was added and the water layer was extracted with methylene chloride. The combined extracts were washed with 11 ml. of cold 1 *N* hydrochloric acid and then with saturated salt solution containing sodium carbonate. Evaporation of the solvent gave 360 mg. (97%) of noncrystalline tosylate which showed strong bands in the infrared typically due to tosylate at 7.23, 8.34, and 8.42 μ. This product was satisfactory for subsequent reactions; storage was at −20°.

Internal Elimination to Form the *trans,cis*-Bicyclic Ketone XXI.—A solution of 250 mg. of tosylate from XIX described immediately above, in 5 ml. of dimethyl sulfoxide, was added to a solution of sodium methylsulfinyl carbanion, prepared from 47.5 mg. of sodium hydride and 3 ml. of dimethyl sulfoxide in the usual manner, at 20° with stirring and under nitrogen; the mixture turned immediately to dark brown and was stirred at 20° for 30 min. Then, 300 mg. (0.38 ml.) of dry *t*-butyl alcohol was added and stirring was continued at room temperature for 2 hr. Finally, 8 ml. of cold water was added dropwise with water cooling and the mixture was diluted with an additional 30 ml. of water containing sodium chloride (*ca.* 2 ml. of saturated solution) and extracted with 2:1 pentane–ether three times. The combined extracts were washed with half-saturated and then saturated salt solution. Careful distillation of the solvent gave 128 mg. (94%) of pale yellow viscous unsaturated ketone XXI, infrared max. 5.92 μ. Vapor phase chromatography showed one peak at a retention time of 30 min. on a 10-ft. 20% nitrile silicone column at 180° (He flow 55–60 ml./min.). An analytical sample was prepared by v.p.c.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.65; H, 10.90.

***d,l*-Isocaryophyllene (II).**—Sodium methylsulfinycarbanion was prepared in the usual manner from 36 mg. of sodium hydride and 2.5 ml. of dimethyl sulfoxide. Then a solution of 675 mg. of methyl triphenylphosphonium bromide in 3 ml. of dimethyl sulfoxide was added at room temperature. The mixture turned immediately to orange. After stirring for 10 min., a solution of 113 mg. (0.55 mmole) of the unsaturated ketone XXI in 1.5 ml. of dimethyl sulfoxide was added. The resulting mixture was stirred at room temperature for 3 hr. These operations were carried out under nitrogen and the solutions were injected through a rubber stopple with a syringe. Then 4 ml. of water was added with water cooling and the resulting yellow solution was extracted with 23 ml. of pentane first, followed by two 8 ml. portions of pentane. Each pentane extract was separately washed with 1:1 dimethyl sulfoxide–water (6 ml.) and then half-saturated salt solution (6 ml.), passed through *ca.* 800 mg. of neutral alumina activity I, and evaporated carefully to give 81 mg. of colorless crude isocaryophyllene (II). Analysis by v.p.c. using a nitrile silicone column indicated that this product was essentially pure; its behavior on both nitrile silicone and tricyanoethoxypropane (TCEP) columns (at 150 and 125°, respectively) matched exactly that of pure, natural isocaryophyllene. The infrared and n.m.r. spectra of samples of the product collected by v.p.c. were completely indistinguishable from those of the authentic natural product II. In the n.m.r. spectra a peak due to two methyls occurs at 0.95 δ and one due to methyl attached to C=C at 1.57 δ; olefinic peaks (2 protons) are at 4.63 and 4.70 δ. The analytical specimen was prepared by v.p.c. using a nitrile silicone column.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.16; H, 11.74.

Unsaturated Ketone XXII and Hydrocarbon XXIII.—A solution of 18 mg. of sodium hydride in 1 ml. of dimethyl sulfoxide was added to a solution of 95 mg. of monotosylate from diol XIX in 1 ml. of dimethyl sulfoxide at 10° with stirring and under nitrogen; an immediate greenish brown coloration developed. After 15 min., the reaction mixture was worked up in the manner described above to give 45.4 mg. of a viscous liquid. The crude material in pentane was passed through a short column of 500 mg. of activity III neutral alumina, giving 29.5 mg. of unsaturated ketone XXII, purified by distillation *in vacuo* and then by v.p.c. on a 4-ft. 20% fluorosilicone column at 175° (retention time different from XXI; found: 8 min. at He flow 100 ml./min.). The product showed carbonyl absorption at 5.90 μ and differed clearly from XXI in the infrared.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.48; H, 10.71.

Treatment of the ketone XXII with methylenetriphenylphosphorane in dimethyl sulfoxide as described above for XXI, and isolation also in the same way afforded a hydrocarbon (XXIII), v.p.c. retention time 19.6 min. using a 10-ft. 20% nitrile silicone column (He flow rate 60 ml./min.) which differed from isocaryophyllene (retention time under exactly the same conditions 17.4 min.). The v.p.c. retention time of XXIII happens to be the same as that of caryophyllene (I) under the same conditions. However, the infrared and n.m.r. spectra of XXIII are distinctly different from those of I or II.

The analytical specimen of XXIII was collected by v.p.c. on a 10 ft. 20% nitrile silicone column at 150° and He flow 55–60 ml./min.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.75; H, 11.78.

Mono-*p*-toluenesulfonate of Diol XX.—To a solution of 80 mg. of diol XX in 0.3 ml. of dry pyridine and 1.0 ml. of methylene chloride was added 138 mg. (2 equiv.) of *p*-toluenesulfonyl chloride. The reaction mixture was stored at 0° for 30 min. and then at room temperature for 24 hr. under nitrogen. Several pieces of chopped ice were added and the mixture was stirred for 1 hr., during which period almost all of the methylene chloride had evaporated leaving an oil which gradually solidified. The solid was collected by filtration, washed thoroughly with water, and then dissolved in ether. Washing with saturated salt solution, followed by evaporation of the ether gave 125 mg. (93%) of pale yellow crystalline tosylate, m.p. 100.5–101.5°, the infrared spectrum of which showed two strong bands at 7.28 and 8.49 μ due to tosylate and "fingerprint" absorption clearly different from that of the monotosylate from XIX described above.

Unsaturated Ketone XXV.—A solution of excess sodium *t*-butoxide (140 mg. of sodium hydride and 1.1 ml. of *t*-butyl alcohol were used) in dimethyl sulfoxide (11 ml.) was added to a solution of 302 mg. of the monotosylate from diol XX in 2 ml. of dimethyl sulfoxide at 20° with stirring and under nitrogen; in this run no significant color change developed. The reaction mixture was stored at room temperature for 17 hr. and worked up by dilution with water and extraction in the usual manner to give a single unsaturated ketone XXV by v.p.c. analysis (nitrile silicone column) in essentially quantitative yield, infrared max. 5.89 μ. This product was clearly different from ketones XXI and XXII and also XXIV (see below) by both v.p.c. and infrared spectral measurements. The same product XXV was also obtained using methylsulfinylcarbanion followed by *t*-butyl alcohol as reagent with 20 hr. for isomerization of the ring fusion. The analytical specimen was collected by v.p.c.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.42; H, 10.74.

***d,l*-Caryophyllene (I).**—The Wittig reagent methylenetriphenylphosphorane was prepared in dimethyl sulfoxide as described above for the synthesis of *d,l*-isocaryophyllene (II) and 5 equivalents (3 ml. of solution) were added to a solution of the ketone XXV (41 mg.) in 1 ml. of dimethyl sulfoxide. After 4 hr. at room temperature the product was isolated exactly as described for synthetic II. Evaporation of the washed pentane extracts left 44 mg. of liquid with v.p.c. retention time (only one peak) on a 10 ft. 20% TCEP column (He flow 55 ml./min.) of 27 min. at 125°, identical with a sample of natural I; with a 10-ft. 20% nitrile silicone column at 150° (He flow 55 ml./min.) the retention time was 20.3 min., again identical with natural I. Under the same v.p.c. conditions on the TCEP column isocaryophyllene has a retention time of 22 min. and is cleanly resolved from caryophyllene.[35] Thus the yield of synthetic *d,l*-I obtained was essentially quantitative. The infrared spectra of synthetic and natural I were absolutely identical.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.04; H, 11.97.

Unsaturated Ketone XXIV.—A solution of sodium *t*-butoxide in dimethyl sulfoxide was prepared from 43 mg. of sodium hydride, 0.34 ml. (266 mg.) of *t*-butyl alcohol, and 3 ml. of dimethyl sulfoxide and 1.8 ml. of this solution was injected into a solution of 112 mg. of the monotosylate of XX in 3 ml. of dimethyl sulfoxide at 20° under nitrogen. The resulting brown solution was stored at room temperature for 4 hr. and 4.5 ml. of water was added with water cooling. The milky mixture was transferred into a separatory funnel with the aid of 15 ml. of water containing salt and a 2:1 pentane–ether mixture. The water layer was extracted with the same solvent four times and the combined extracts were washed with half-saturated (10 ml.) and saturated salt solution (10 ml.). Removal of the solvent gave a pale brown liquid in quantitative yield. This product consisted of two isomeric unsaturated ketones XXIV and XXV in ratio of about 3:2 which as determined by v.p.c. on a 10-ft. 20% nitrile silicone column showed two peaks at retention times of 23.2 min. (major) and at 25.8 min. (minor) (165° and He flow 60 ml./min.). The major unsaturated ketone XXIV was isomerized upon prolonged (15 hr.) treatment with sodium *t*-butoxide in dimethyl sulfoxide to the minor one XXV identical with the compound described above. Interestingly, this unstable *cis*-fused ketone XXIV did not react appreciably with the Wittig reagent in dimethyl sulfoxide under the conditions which completely transformed the isomeric ketones XXI, XXII, and XXV. An analytical sample was prepared by v.p.c., infrared max. 5.89 μ.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.19; H, 10.73.

(35) The "natural caryophyllene" used in our studies was obtained from the Aldrich Chemical Co. and was labeled β-carophyllene. However, this material was a mixture of caryophyllene (I) and isocaryophyllene (II) in ratio 3:1 as shown clearly by v.p.c. The pure components were obtained by preparative v.p.c. The component of shorter retention time proved to be identical with a sample of pure isocaryophyllene provided by Dr. F. Sorm.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF.]

Optical Rotatory Dispersion Studies. XCI.[1] The Use of Low-Temperature Circular Dichroism Measurements for "Fingerprinting" of Steroidal Ketones[2]

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For purposes of locating a carbonyl group on a steroid skeleton, optical rotatory dispersion curves are generally more useful than circular dichroism curves, because the former exhibit characteristically different shapes (as well as signs) due to the operation of background rotation effects, which are absent in circular dichroism. It has now been noted that when circular dichroism measurements of such ketones are performed near the boiling point of liquid nitrogen (*ca.* −192°), vibrational fine structure is usually developed or intensified, which in many instances is characteristic of a carbonyl group in a given (bicyclic) environment and can thus be employed for purposes of "fingerprinting." Similar low-temperature measurements of the ultraviolet absorption spectrum in the $n \rightarrow \pi^*$ region are not as useful; vibrational fine structure is not as well developed as in the circular dichroism spectrum and furthermore larger amounts of material are required because of the low extinction.

In an earlier article,[4] where the relative advantages of the closely related phenomena optical rotatory dispersion (O.R.D.) and circular dichroism (C.D.) were compared, it was noted that for structural purposes, O.R.D. will often be preferable. This is due to the

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(3) National Institutes of Health Postdoctoral Research Fellow, 1962–1963.

(4) C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **84**, 4552 (1962).