of anhydrous sodium acetate, and 250 ml of acetic anhydride was heated on a steam bath for 3.5 hr. The reaction mixture was allowed to stand overnight at 2°. The crystals were collected by filtration, washed with some hot water, and dried: 50.3 g (84%), mp 182–183°. Recrystallization from benzene gave 40 g (67%) of pale yellow crystals, mp 184–185°.

Anal. Calcd for $C_{13}H_9Cl_2NO_4$: C, 49.70; H, 2.89; Cl, 22.57; N, 4.46. Found: C, 49.66; H, 2.97; Cl, 22.33; N, 4.43.

Colorless crystals were obtained upon two more recrystallizations with charcoal (Norit A, neutral).

3,5-Dichloro-4-hydroxyphenylpyruvic Acid.—A mixture of 29.8 g (0.1 mole) of the oxazolone, 300 ml of acetic acid, and 100 ml of 3 *N* HCl was refluxed gently for 3 hr. Upon evaporation of the reaction mixture and addition of water to the residue, 15 g of crude keto acid was obtained. Recrystallization from acetic acid gave 14 g (56%) of colorless needles, mp 208–209° dec.

Anal. Calcd for $C_9H_6Cl_2O_4$: C, 43.40; H, 2.43; Cl, 28.47. Found: C, 43.17; H, 2.40; Cl, 28.74.

Detection of 2,6-Diiodohydroquinone after Reduction of an Ether Extract of an Oxygenated Solution of DIHPPA.—Oxygen was bubbled at 0° for 20 min through a solution of 0.5 g of DIHPPA in 250 ml of 0.2 *M* borate buffer, pH 7.5. The solution was adjusted to pH 5 and extracted three times with ether. The combined extracts were washed with a small amount of water, then an excess of a freshly prepared aqueous solution of $NaBH_4$ was added. After 5 min the mixture was acidified and the ether layer dried and evaporated. Both tlc in chloroform and glpc of the residue (38 mg) showed that the major part of the residue was 2,6-diiodohydroquinone. The R_f value and the retention time of an authentic sample were identical with those of the reduction product, both in separate and mixed chromatograms.

Registry No.—Enol tautomer of DIHPPA radical, 14886-10-3; keto tautomer of DIHPPA radical, 14886-11-4; DIHPPA, 780-00-7; DISQ, 14886-16-9; thyroxine, 7488-70-2; chloro analog of DIHPPA, 13990-05-1; bromo analog of DIHPPA, 13990-07-3; 4-(4-acetoxy-3,5-dichlorobenzal)-2-methyl-5-oxazolone, 14886-17-0.

The Photolysis of Some 1,6-Dienes.[1] Total Synthesis of (±)-α-Bourbonene

MORRIS BROWN

Contribution No. 3543 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109

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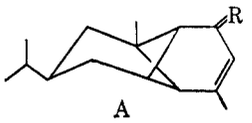
The photolysis of several 1,6-dienes has been shown to yield head-to-head cyclization products. The diketone **5c** has been converted into the naturally occurring α-bourbonene.

The sesquiterpenes are particularly interesting to the synthetic chemist because of the wide variation of structural types found in this class of compounds. Copaene (A, R = H) and mustakone (A, R = O) are

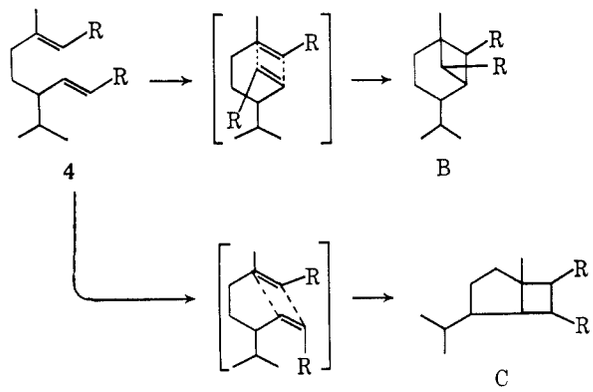


A

exceptionally interesting substances[2] which pose difficult challenges to the synthetic chemist. The presence of a four-membered ring with two fused six-membered rings is thus far unique to copaene and mustakone.

Synthesis of a complex substance such as copaene can be approached in many different ways.[3] We envisioned the synthesis of a properly substituted diene **4**, which on photolysis could yield the desired [3.1.1]bicyclohexane system B. If R were a suitably chosen group (CH_3CO–, for example) then addition of the third ring would seem to present no serious problems, and final alteration of such a tricyclic compound to the natural product should be straightforward.

However, an alternate mode of cyclization for the diene **4** is possible. This would afford the 5:4 fused-ring system C. Although there are published experimental results on the dimerization of dienes (*vide infra*), *a priori* no firm prediction could be made as to which



4 B C

product (B or C) would be produced on photolysis of diene **4**. We therefore set out to examine the synthesis and photolysis of **4**.

Production of **4** proved to be quite efficient once the proper experimental procedures were devised. The starting material was the piperidineenamine of isovaleraldehyde (**1**)[4] (see Scheme I). In the condensation of **1** with methyl vinyl ketone, the aminoenol ether **2** is first produced, as evidenced by the vinyl methyl and vinyl hydrogen singlets in the nuclear magnetic resonance (nmr) spectrum.[5] The slightly unstable ether **2** did not need to be isolated, and conversion of **1** → **3** could be accomplished in 79% yield, employing aqueous oxalic acid for the hydrolysis of **2** → **3**.[6] Ini-

(1) A preliminary communication describing some of these results has been published, M. Brown, *Chem. Commun.*, 340 (1965).

(2) (a) P. De Mayo, R. E. Williams, G. Büchi, and S. H. Feairheller, *Tetrahedron*, **21**, 619 (1965); (b) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *ibid.*, **21**, 607 (1965).

(3) For a completely different and successful approach to the problem, see C. H. Heathcock, *J. Am. Chem. Soc.*, **88**, 4110 (1966).

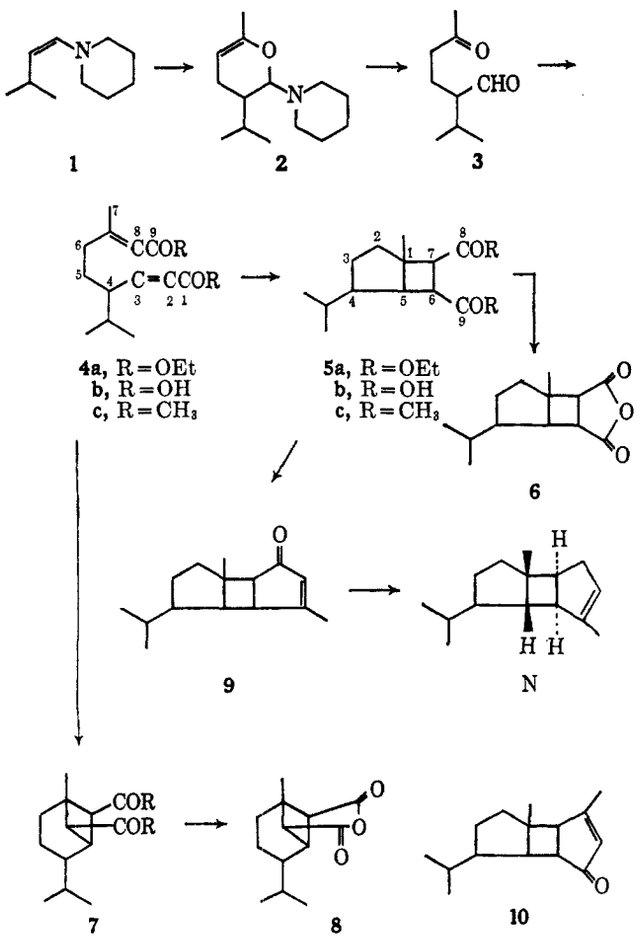
(4) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(5) See G. Opitz and I. Löschmann, *Angew. Chem.*, **72**, 523 (1960), for similar results.

(6) The ketoaldehyde **3** has apparently not been isolated before, although it or a closely related derivative is undoubtedly an intermediate in a synthesis of 4-isopropylcyclohexenone.[7a]

(7) (a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 219 (1963); (b) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

SCHEME I



tially experiments involving mineral acid for the hydrolysis were fruitless, since extensive cyclization and dehydration of the ketoaldehyde **3** occur under the conditions.

The ketoaldehyde **3** was then converted into the desired diester **4a**, by condensation with triethyl phosphonoacetate in dimethoxyethane. This modified Wittig reaction, developed by Wadsworth and Emmons,[7b] afforded the desired diene in 50% yield, bp 120–132° (0.08 mm). Vapor phase chromatography (vpc) revealed the diene to be a mixture of double-bond isomers. However, the nmr indicated that the 2,3 double bond is *trans*, since the coupling constant of the vinyl hydrogens is 15 cps. The remaining features of the nmr spectrum are also in accord with assignment of structure **4a** to the diene.

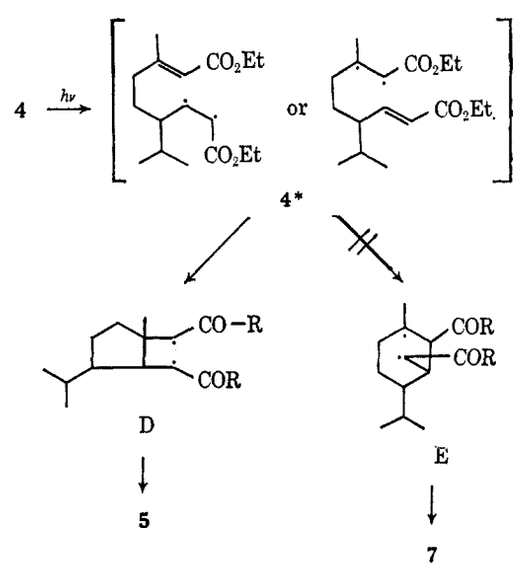
Photolysis of the diene **4a** could be carried by direct irradiation in a quartz tube at 2537 Å, or by using acetophenone as a sensitizer and employing a high-pressure mercury lamp in a Pyrex apparatus. In either case, a saturated diester mixture is produced which appeared from the infrared and nmr spectra to be consistent with the formation of saturated cyclic products.

Assignment of structure **5a** to the photoproduct was achieved as follows. When the diester mixture is saponified with aqueous sodium hydroxide, a crystalline diacid **5b**, mp 148–150°, is obtained in 53% yield. This diacid on distillation from phosphorous pentoxide yields an anhydride in 90% yield which has absorption in the infrared at 5.38 and 5.61 μ. This absorption is clearly consistent only with structure **6**, since the alternate anhydride structure **8** would have quite different infrared absorption.[8] The nmr is also consistent only with **6**. A multiplet, at δ 3.0, is clearly an ABX-type spectrum and the coupling constants are J_{AB} = 6.5 cps, J_{AX} = 0 cps, and H_{BX} = 3 cps.

When the remaining noncrystalline diacids, obtained for the mother liquors of crystallization **5c**, are submitted to the phosphorus pentoxide distillation, the resulting distillate (90% yield) again shows absorption only at 5,38 and 5.61 μ in the infrared. Thus it appears that only 1,2-diacids (**5b**) are produced in the photocyclization.[9]

Several points should be mentioned about this photolysis. Since both the sensitized and unsensitized photolysis yield the same mixture of diesters, the cyclization is probably proceeding *via* the triplet state. The photolysis is not solvent sensitive, since it can be carried out equally well in benzene, ethanol, ether, or acid with the same results. The photolysis of the diketone **4c**, which was prepared from the diacid **4b** and methyllithium, also yielded only head-to-head cyclization product **5c**. This same diketone **5c** was prepared from the diacid **5a** (see below), thus establishing its structure.

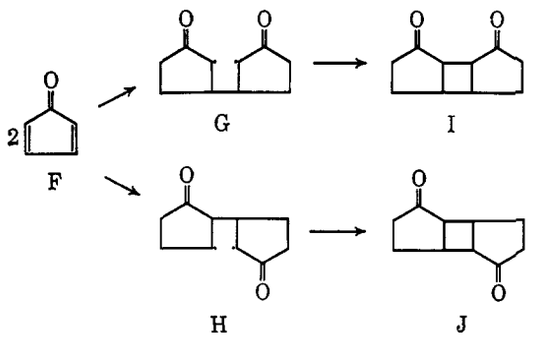
The rationalization for exclusive formation of the head-to-head type of product is not obvious. One could argue that in a head-to-head type of cyclization, you pass through a diradical intermediate D in which both radicals are stabilized by conjugation with a carbonyl group. On the other hand, the intermediate E, from a head-to-tail cyclization, is certainly of higher energy (and therefore not formed) since only one radical is stabilized by conjugation. However, in the dimerization of cyclopentenone (F)[10] both the head-to-head I and head-to-tail J type of products are formed. Clearly the stability of the diradical is not the only factor influencing the formation of product in this case.



(8) K. Nakanishi, Infrared Absorption Spectroscopy, Holden Day, Inc., San Francisco, Calif., 1962, p 45.

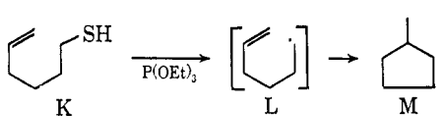
(9) Cyclobutane-1,3-dicarboxylic acid has been submitted to this distillation also, and found to produce the anhydride in high yield. Thus we would certainly expect the 1,3-dicarboxylic acid (**7**) to form an anhydride if it were present.

(10) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344, 2454 (1962).

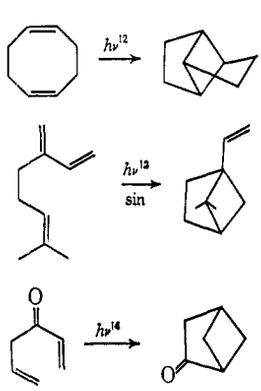


A much better explanation can be found by examining the preferential formation of D over E from an excited state such as is shown by **4***. If one makes the gross assumption that the exicted state will behave much like a diradical, then it is quite reasonable to expect the higher energy β radical to add first to the double bond, rather than the conjugated α radical.

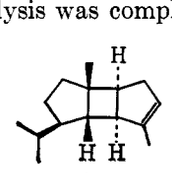
The problem then boils down to whether preferential addition of a radical to a double bond prefers to form five-membered rings (**4*** → D) or prefers six-membered rings (**4*** → E). There now exists ample precedence in the literature for a preference for five-membered rings over six- in simple radical additions.[11a] The conversion of K into M is an example of such a



preference.[11b] Such an explanation would serve to predict the formation of D. This explanation would also predict the formation of five-membered rings in other photochemical cyclizations. Indeed it would appear that five-membered rings are preferred in the following cases.



The production of the diacid **5b** did, however, allow for an efficient synthesis of the sesquiterpene α-bourbonene (N), which was found[15] after much of the initial work on the photolysis was completed.[16]



N

(11) (a) R. C. Lamb, P. W. Ayers, and M. K. Tomy, *J. Am. Chem. Soc.*, **85**, 3483 (1963); (b) C. Walling and M. S. Pearson, *ibid.*, **86**, 2262 (1964).

(12) R. Srinivasan, *ibid.*, **85**, 819 (1963).

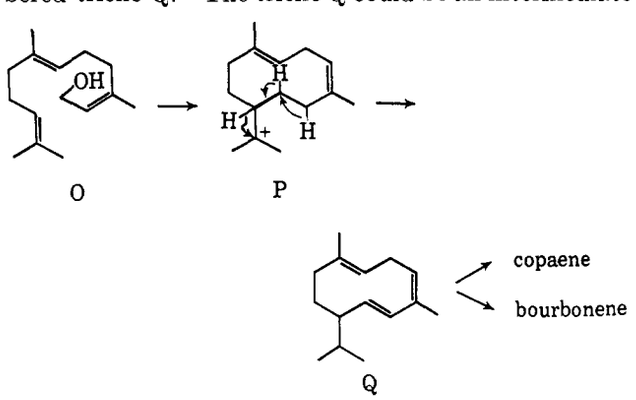
(13) R. S. H. Liu and G. S. Hammond, *ibid.*, **86**, 1892 (1964).

(14) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Letters*, 4685 (1965).

The crystalline diacid **5b** was converted into the diketone **5c** by the multistep procedure of Stork[17] in 77% over-all yield. The diketone was then smoothly cyclized to the unsaturated ketone **9** in 78% yield with potassium *t*-butoxide in *t*-butyl alcohol. The infrared, 5.95 μ, ultraviolet, λ_{max} 239 mμ (ϵ 14,200), and nmr spectra were all in accord with structure **9**. We first assumed that cyclization of **5c** would lead to a mixture of **9** and **10**. However, the gas chromatogram for the cyclization product had only a single peak and the nmr had only one quarternary methyl signal at δ 1.02. The position of the methyl group appears to be shifted by proximity to carbonyl, since, on reduction of the ketone to the alcohol, the signal moves to δ 1.25. These facts then all seemed to point toward a single product **9** rather than a mixture of **9** and **10**. The exclusive formation of **9** must be attributed to a steric interaction of the quaternary methyl group in the aldol condensation.

Attempted Wolff–Kishner reduction of **9** failed, which is perhaps not too surprising since this type of reaction is often poor on α,β-unsaturated ketones. The ketone was successfully removed, utilizing the method of Broome,[18] by reduction with lithium aluminum hydride–aluminum chloride. In this manner the olefin obtained proved to be identical in all respects with bourbonene. Since the configuration of the natural product is known,[14] the configuration of the crystalline diacid **5b** and all further transformation products must be the same in centers 1, 4, and 5.

It is perhaps interesting to note that a very similar *in vivo* synthesis of copaene and bourbonene is possible. Thus, farnesol (O) could first cyclize to the ten-membered triene Q. The triene Q could be an intermediate



for both copaene and bourbonene, since a head-to-tail cyclization yields the copaene, while a head-to-head cyclization would afford bourbonene.

Experimental Section[19]

2-Isopropyl-5-ketohexanal (3).—To a 1-l. round-bottom flask cooled in ice and stirred magnetically was placed 41 g of the

(15) J. Křepinský, Z. Samek, and F. Šorm, *ibid.*, 359 (1966); J. Křepinský, Z. Samek, F. Šorm, D. Lamparsky, P. Ochsner, and Y.-R. Nayes, *Tetraherdron, Suppl. No. 8*, 53 (1966).

(16) A different synthesis of α-bourbonene has been recently reported: J. D. White and D. N. Gupta, *J. Am. Chem. Soc.*, **88**, 5364 (1966).

(17) G. Stork and F. H. Clarke, Jr., *ibid.*, **83**, 3114 (1961).

(18) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

(19) Nuclear magnetic resonance spectra were determined at 60 Mc on a Varian A-60 spectrometer with tetramethylsilane as internal standard. Ultraviolet spectra were determined on a Cary Model 14. Infrared spectra were determined on a Perkin Elmer Model 137. Melting points are corrected and were determined on a Kofler hot stage.

piperidineenamine of 3-methylbutryaldehyde.[4] A 71.0-g portion of freshly distilled methyl vinyl ketone was added dropwise over 30 min and the resulting solution was stirred for 2.5 hr at room temperature. The solution was again cooled in ice and 50 g of oxalic acid dissolved in 500 ml of water was added. After stirring at 0° for 1.5 hr the solution was transferred to a separatory funnel and extracted well with ether. The ether layer was washed with water and dried over sodium sulfate. After removal of the solvent, the product was distilled affording 125.5 g of the ketoaldehyde **3**, bp 79–81° (1.2 mm) (79% over-all yield), λ_{max}^{film} 5.85 μ (C=O). Nmr showed the expected isopropyl methyls at δ 1.0 (J = 6 cps) and acetyl methyl at δ 2.07.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.04; H, 10.27.

1,7-Dicarbethoxy-3-isopropyl-6-methyl-1,6-heptadiene (4a).—A 10.9-g portion of sodium hydride (56% dispersion in mineral oil) was added to a dry 250-ml, three-necked, round-bottom flask. The sodium hydride was washed twice with dry pentane to remove the mineral oil and then 100 ml of dimethoxyethane previously distilled from lithium aluminum hydride was added. The flask was cooled in ice and 57.0 g of triethyl phosphonoacetate was added dropwise with mechanical stirring under an atmosphere of nitrogen (hydrogen evolved). After stirring for 1 hr a solution of 18.7 g of ketoaldehyde **3** in 50 ml of dimethoxyethane was added over 30 min. The solution was warmed to room temperature and then heated at reflux overnight. After cooling to room temperature, water was added and the solution was extracted with ether, washed with water, and dried over sodium sulfate. Removal of the solvent and distillation afforded, after a lower boiling forerun, 17.6 g, bp 120–132° (0.08 mm) (50% yield), of the diester **4a**, λ_{max}^{film} 5.85 μ, λ_{max} 216 mμ (ϵ 23,800).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.14; H, 9.21.

1,7-Dicarboxy-3-isopropyl-6-methyl-1,6-heptadiene (4b).—A 11.5-g portion of the diester **4a** and 100 ml of 1 N aqueous sodium hydroxide were heated at 90° under nitrogen for 24 hr. The cooled solution was extracted with ether. The aqueous phase was acidified with hyrochloric acid and reextracted with chloroform. This chloroform extract was dried and removal of the solvent afforded the product which soon crystallized. Recrystallization from acetonitrile gave colorless crystals, mp 125–127°, 5.0 g (53% yield).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.85; H, 8.32.

1,7-Diacetyl-3-isopropyl-6-methyl-1,6-heptadiene (4c).—To a stirred solution of 2.56 g of diacid **4b** in 400 ml of anhydrous ether was added 30 ml of 2.0 M methyllithium in ether. The solution was then heated for 5 hr at reflux. After cooling to room temperature, the solution was washed well with water. These aqueous washes on acidification and extraction yielded 0.60 g of starting diacid **4b**.

The ethereal solution was dried and after removal of the solvent afforded 0.425 g (22% yield) based on 2.0 g of starting acid. The analytical sample was obtained by evaporative distillation: bp 100° (0.1 mm); λ_{max}^{film} 5.93 (C=O), 6.18 (C=C).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.19; H, 10.52.

Photolysis of 4a. Preparation of 6,7-Dicarbethoxy-4-isopropyl-1-methyl[3.2.0]heptane (5a).—A solution of 5.5 g of the diester **4a** and 0.480 g of acetophenone in 80 ml of ethanol was irradiated with a 450-w Hanovia high-pressure lamp in a Pyrex immersion well for 48 hr. The reaction was followed by vpc (10% silicone oil column at 220°), which clearly indicated that some *cis–trans* isomerism of the double bonds was taking place before cyclization. The solvent was removed and the material was then distilled to yield 2.9 g (53% yield) of cyclized diester **5a**, bp 121° (0.04 mm), λ_{max}^{film} 5.78 μ, no vinyl hydrogens in the nmr spectrum.

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.12; H, 9.40.

6,7-Dicarboxy-4-isopropyl-1-methyl[3.2.0]heptane (5b).—A solution of 3.8 g of the diester **5a**, 10 ml of methanol, and 25 ml of 1 N sodium hydroxide was heated at 90° under nitrogen for 16 hr. The solution was cooled, diluted with 50 ml of water, and extracted with ether. The aqueous solution was then acidified with hydrochloric acid and extracted well with chloroform. The chloroform extract was dried and after removal of the solvent gave 2.1 g (68% yield) of crystalline material. Recrystallization from acetonitrile gave the analytical sample, mp 148–150°.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.95; H, 8.45.

Anhydride of Diacid 5b. Preparation of 6.—The diacid **5b** (0.50 g) was placed in a tube suitable for evaporative distillation and mixed with approximately 5 g of phosphorous pentoxide. The mixture was then heated to 160° under high vacuum and the anhydride distilled from the mixture as an almost colorless oil (0.45 g, 90% yield), λ_{max}^{film} 5.38 and 5.61 μ. The nmr spectrum showed an ABX-type spectrum at δ 3.0 (J_{AB} = 6.5 cps, J_{BX} = 3 cps, J_{AX} = 0 cps).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.84; H, 8.16.

The mother liquors from crystallization of **5b** could also be treated in a similar manner to afford isomeric anhydrides with very similar infrared spectra.

6,7-Diacetyl-4-isopropyl-1-methyl[3.2.0]heptane (5c).—A 1.1-g portion of the diacid **5b** in 30 ml of dry benzene and 0.5 ml of pyridine were stirred while 1.5 ml of thionyl chloride was added. After stirring for 1 hr the solution became homogeneous. The benzene was then removed under reduced pressure and more benzene was added which was also removed. Finally, more benzene was added, the solution was filtered, and the benzene was removed to afford the crude acid chloride which was used directly in the next stage.

The acid chloride was dissolved in 30 ml of ether and a solution of diazomethane in ether was added until the yellow color persisted. The solution was allowed to stand at room temperature for 4 hr, followed by removal of the ether on a steam bath. More ether was then added, the solution was cooled in an ice bath, and HCl gas was bubbled through the solution (10 min is sufficient). The ether was then removed and 20 ml of acetic acid was added, followed by 1.0 g of potassium iodide and 10 g of zinc dust.

After stirring overnight, 30 ml of methanol was added, the solution was filtered, and the precipitate was washed well with methanol. The methanolic solution was diluted with water and the aqueous solution was extracted with ether. After drying over sodium sulfate the solvent was evaporated and the residue was evaporatively distilled, bp 100° (0.1 mm), to afford 0.84 g of colorless oil (77% yield), homogeneous on vpc, λ_{max}^{film} 5.85 μ.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.18; H, 10.21.

Preparation of (±)-Bourboneneone (9).—A solution of 0.200 g of potassium in 10 ml of dry *t*-butyl alcohol was prepared under nitrogen. Then 0.84 g of the diketone **5c** in 4 ml of dry *t*-butyl alcohol was added. The solution was stirred at 75° for 1 hr and 15 min. After cooling the solution was diluted with water and extracted with ether. After drying, 50 ml of benzene was added to the ethereal solution and the solvent was removed under reduced pressure to afford after evaporative distillation (100° (0.1 mm)) a colorless oil: 0.61 g (78% yield); λ_{max} 239 mμ (ϵ 14,200); nmr spectrum, δ 0.88, 0.94 (isopropyl methyls), 1.02 (saturated methyl), 2.12 (vinyl methyl), and 5.90 (vinyl hydrogen).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.39; H, 10.24.

α-Bourbonene (N).—Authentic natural β-bourbonene[20] (0.080 g) was isomerized by heating at 60° in 2 ml of ethanol with 0.3 ml of concentrated hydrochloric acid. The solution was diluted with water and extracted with ether. Afford drying over sodium sulfate, the ether was carefully removed and the product was evaporatively distilled (100° (1 mm)). The material was then separated from some small amounts of impurities by preparative vpc on 10% polyphenyl ether (six ring): nmr spectrum δ 0.85 (6 H, doublet, J = 6 cps, isopropyl), 1.00 (3 H, singlet, methyl), and 5.18 (1 H, multiplet, vinyl hydrogen).

(±)-α-Bourbonene (Synthetic) (N).—The ketone 9 (0.100 g) was reduced with 0.100 g of $LiAlH_4$ in 25 ml of anhydrous ether at room temperature for 1 hr. The 1.0 g of $AlCl_3$ was added and the solution was heated at reflux for 2 hr. The solution was cooled and 1.0 ml of 5% sodium hydroxide was added. The solution was stirred at room temperature for 2 hr and then filtered; the precipitate was washed well with ether. The ethereal solution was washed with water and dried over sodium sulfate; the solvent was carefully removed. The product was then purified by preparative vpc as above to yield 0.020 g of α-bourbonene,

(20) Authentic natural β-bourbonene was kindly provided by Professor F. Sorm.

identical on all respects (infrared and nmr spectra) with the material prepared from natural sources.

Registry No.—**3**, 15303-46-5; **4a**, 5909-78-4; **4b**, 5909-84-2; **4c**, 5909-85-3; **5a**, 15303-50-1; **5b**, 5909-79-5; **5c**, 5909-83-1; **6**, 5909-80-8; **9**, 15303-54-5; (±)-α-bourbonene, 13828-07-4.

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Structure of Anisomycin

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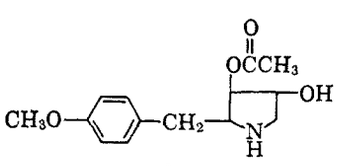
A three-dimensional X-ray diffraction analysis of N-acetylbromoanisomycin has been carried out and the results have been used to determine the structure of anisomycin. The crystals are monoclinic, space group $P2_1$, with a = 11.25 A, b = 7.16 A, c = 11.44 A, β = 112.8°, z = 2. The molecule is a substituted pyrrolidine in which the *p*-methoxy-*m*-bromobenzyl moiety on the 2 position is *cis* to the 3-acetate group which is, in turn, *trans* to a 4-hydroxy function. An analysis of stereoelectronic factors governing ring-opening reactions of cyclopentane derivatives is presented.

The antibiotic anisomycin (**1**) is a fermentation product of various species of *Streptomyces* and has been shown to have widespread activity against certain pathogenic protozoa.[3,4] It has been found to be effective in the treatment of amoebic dysentery and has been used for that purpose.[5] In a recent study of the ipecac alkaloids, Grollman[6] has found that these alkaloids block the aminoacyl–sRNA transfer reaction in protein biosynthesis and that anisomycin effects a similar inhibition.[7] On the basis of these results and certain common structural features between the ipecac alkaloids and anisomycin, Grollman has formulated a structural basis for the inhibition of protein synthesis.

Early chemical studies indicated that **1** has a formula corresponding to $C_{14}H_{19}NO_4$ and possesses a methoxyl group, an acetyl group, and two active hydrogens.[3,8] The basicity of **1** (pK_a 7.75) indicates that the compound is an amine, and subsequent degradation confirmed the presence of a pyrrolidine ring.[8] Further studies established that the gross structural features of anisomycin are best accommodated by the formula of compound **1**.



1

To establish the relative stereochemical relationships of the substituents on **1**, a complex series of transformations of the hydroxyl and acetate groups was undertaken (*vide infra*). As a result of these studies, the groups on the pyrrolidine ring were assigned the all-*trans* configuration. More recent studies[9] have, however, led to results which are difficult to rationalize in terms of this configuration for **1**. As a result, we have determined the crystal structure of a derivative of **1**, N-acetylbromoanisomycin (**2**), to clarify any ambiguity which may exist in the stereochemical assignments.

Experimental Section

N-Acetylbromoanisomycin, $C_{16}H_{20}NO_5Br$ (386.2), is a monoclinic crystal with a = 11.254 ± 0.017, b = 7.160 ± 0.013, c = 11.439 ± 0.018 A, β = 112.8 ± 0.2°; U = 849.7 A³, D_m = 1.501, D_c = 1.506, Z = 2, $F(000)$ = 396; space group $P2_1$ (C^2_2, No. 4); single crystal oscillation and Weissenberg photographs (λ = 1.5418 A).

The crystals (mp 177°) were grown from ethyl acetate as colorless needles elongated along [*b*]. Equi-inclination Weissenberg photographs of the h0l through h4l levels were taken with Cu K radiation, and the relative intensities were obtained by visual estimation against a calibrated strip. Reflections which were too weak to observe were included at one half the local minimum observable value. A total of 1000 independent reflections were recorded.

The structure was solved by the heavy-atom technique. The coordinates of the bromine atom were found from a three-dimensional Patterson synthesis, and the positions of the lighter atoms were obtained from successive two- and three-dimensional Fourier syntheses. Refinement was carried out by differential syntheses until R had dropped to a final value of 10.5%. Hydrogen atoms were ignored throughout. All calculations were carried out on an IBM 7072 computer with programs written in Professor G. A. Jeffrey's laboratory at the University of Pittsburgh.

Results

The final atomic coordinates, with standard deviations given as units in the last place, are shown in Table I. The anisotropic thermal factors of the form

$$B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{23}klb^*c^* + 2B_{13}hla^*c^*$$

are given in Table II. Table III shows an analysis of the agreement between observed and calculated structure factors in terms of the layer index k and of the magnitude of F_0. Bond lengths and angles are given in Table IV. The molecule as it appears in projection

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