The Total Synthesis of α- and β-Bourbonene[1]

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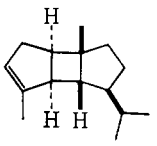
Abstract: Photochemical cycloaddition of cyclopent-2-enone to 1-methyl-3-isopropylcyclopentene (**9**) leads to norbourbonone (**10**) and a second tricyclic ketone (**11**). The structures of norbourbonone and **11** are correlated by conversion of both ketones to norbourbonane (**13**). Norbourbonone is converted to β-bourbonene (**2**) and, *via* epimeric bourbonols (**24** and **25**), to α-bourbonene (**1**). A method for the optical resolution of norbourbonone is described, and the photochemistry of nitrite ester **20** derived from **11** is discussed.

The sesquiterpenoid hydrocarbons α- and β-bourbonene have been isolated from *Geranium bourbon oil*[2] and, recently, from the oil *Mentha piperita*, of Bulgarian origin.[3] The former source has been found to contain several sesquiterpenes of novel structural types, including the furopelargones[4] and dehydrofuropelargones.[5] The stereostructures of α- and β-bourbonene have been deduced by Šorm, *et al.*, as **1** and **2**, respectively, with the absolute configuration (as shown) based upon degradation of β-bourbonene to (*S*)-(+)-isopropylsuccinic acid.[6] The tricyclo[3.3.0.0]-decane system of the bourbonenes is thus far unique among natural products, and it was this structural feature which initially attracted our interest.



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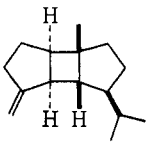
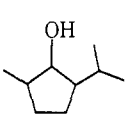


2

Our primary objective was to establish a total synthesis of the bourbonenes which would provide rigorous proof of the structural and stereochemical assignments, and which would also allow study of certain aspects of the chemistry of this interesting tricyclic system. It was felt that a particularly efficacious route to the ring skeleton of the bourbonenes lay through photochemical cycloaddition of two cyclopentanoid units, and our approach from the outset was directed along these lines.[7] An appropriate model for this synthetic plan already existed in the work of Eaton, who had shown that irradiation of cyclopent-2-enone gave a head-to-head and a head-to-tail dimer,[8] and that photolysis of a mixture of cyclopent-2-enone and cyclopentene furnished a high yield of a single crossed adduct.[9] Of special significance was the observation that all three photoadducts possessed the sterically favored *cis,anti,-cis* geometry at the cyclobutane ring, as found in the bourbonenes, and we were encouraged in believing that the principle embodied here could be applied to synthesis of the natural products. The addends of choice were cyclopentenone and 1-methyl-3-isopropylcyclopentene (**9**), and attention was initially focused on preparation of the latter compound. This was accomplished by the route described below.[10]

The imine formed by condensation of cyclopentanone and cyclohexylamine was treated with ethylmagnesium bromide, followed by 2-bromopropane, and the resulting alkylated enamine was hydrolyzed to yield 2-isopropylcyclopentanone.[11] The latter was condensed with ethyl formate in the presence of sodium methoxide to give the hydroxymethylene ketone **3**. Reduction of **3** with lithium aluminum hydride afforded mainly the allylic alcohol **5**,[12] accompanied by a small amount of the α,β-unsaturated aldehyde **6**.[13] Alternatively, **3** could be converted to its isobutyl ether **4**, which also gave a mixture of **5** and **6** upon reduction. In the latter case, appreciable amounts of undistillable material were produced, probably originating from polymerization of the unstable α-methylenecyclopentanone **7**.[14] The alcohol **5**, upon treatment with thionyl chloride in ether, was converted to the rearranged chloromethyl compound **8**.[15] Hydrogenolysis of **8** with lithium aluminum hydride in refluxing diisopropyl ether yielded



i

(1) (a) Presented at the 5th International Symposium on the Chemistry of Natural Products, London, July 1968. (b) A portion of this work has been reported in preliminary form: J. D. White and D. N. Gupta, *J. Amer. Chem. Soc.*, **88**, 5364 (1966).

(2) V. Benešová, P. N. Chou, V. Herout, Y. R. Naves, and D. Lamparsky, *Collect. Czech. Chem. Commun.*, **29**, 1042 (1964).

(3) R. Vlakhov, M. Holub, I. Ognjanov, V. Herout, and F. Šorm, *ibid.*, **32**, 808 (1967).

(4) G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron*, 20, 1789 (1964); M. Romaňuk, V. Herout, F. Šorm, Y. R. Naves, P. Tullen, R. B. Bates, and C. W. Sigel, *Collect. Czech. Chem. Commun.*, **29**, 1048 (1964); G. Büchi and H. Wuest, *J. Amer. Chem. Soc.*, **87**, 1589 (1965).

(5) C. Giannotti and H. Schwang, *Tetrahedron*, **24**, 2055 (1968); G. Büchi and H. Wuest, *ibid.*, **24**, 2049 (1968).

(6) J. Křepinský, Z. Samek, F. Šorm, and D. Lamparsky, *Tetrahedron Lett.*, 239 (1966); J. Křepinský, Z. Samek, and F. Šorm, *ibid.*, 3209 (1966); J. Křepinský, Z. Samek, F. Šorm, D. Lamparsky, P. Ochsner, and Y. R. Naves, *Tetrahedron Suppl.*, **8**, 53 (1966).

(7) A different route to α-bourbonene has recently been described: M. Brown, *J. Org. Chem.*, **33**, 162 (1968).

(8) P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962).

(9) P. E. Eaton, *ibid.*, **84**, 2454 (1962).

(10) Attempts to obtain **9** by dehydration of dihydrocamphorol (i, mixture of stereoisomers) led to unsatisfactory results. *Cf.* F. W. Semmler, *Ber.*, **37**, 234 (1904); M. Godchot and F. Taboury, *C. R. Acad. Sci., Paris*, **156**, 470 (1913). A method reported to give exclusively **9** [R. Calas, *Bull. Soc. Chim. Fr.*, **6**, 1505 (1939)] furnished low yields in our hands.

(11) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

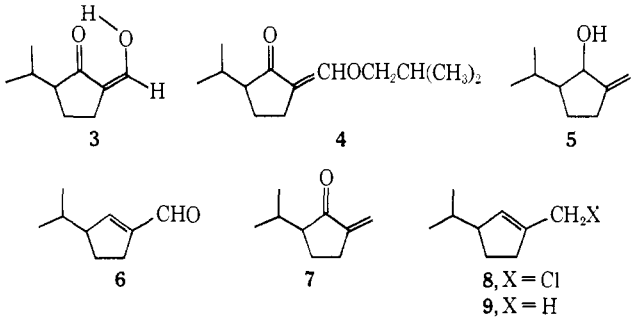
(12) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 939 (1953).

(13) M. Stiles and A. Longroy, *Tetrahedron Lett.*, 337 (1961).

(14) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960); M. Mühlstadt, L. Zach, and H. Beewar-Reinhardt, *J. Prakt. Chem.*, **29**, 158 (1965).

(15) F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *J. Amer. Chem. Soc.*, 77, 4182 (1955).

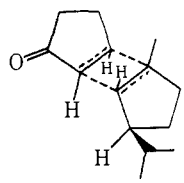
the cyclopentene **9**.[16] The over-all yield of **9** from 2-isopropylcyclopentanone was 25%.



3 **4** **5**

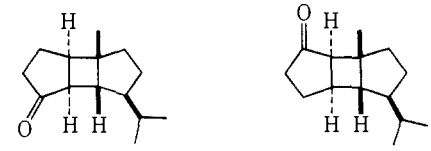
6 **7** **8**, X = Cl; **9**, X = H

Although results cited above[8,9] suggested that irradiation of a mixture of **9** and cyclopent-2-enone should lead to crossed adducts having a *cis,anti,cis* ring fusion, there remained two further stereochemical aspects of the cycloaddition to consider. These were (i) the configuration of the isopropyl substituent in the cycloadduct(s) and (ii) the orientation of the two addends in regard to head-to-head and head-to-tail modes of addition. Without specification of the precise nature of the intermediates involved,[17] it appeared likely that a transition state such as A, which would lead to the observed ring geometry of the bourbonenes, should also result in a sterically favored *exo* configuration for the isopropyl group. Factors determining the proportion of head-to-head *vs.* head-to-tail products seemed less decisive and, in fact, it has been found that cyclopentenone is rather unselective with regard to orientation in its addition to unsymmetrical olefins.[18]



A

Irradiation through Pyrex glass of a mixture of cyclopent-2-enone and **9** in pentane solution gave, as far as could be discerned, only two products. These are shown, from evidence presented below, to possess stereostructures **10** and **11**. Photodimerization of cyclopentenone occurred as a competitive process,[8] but the dimers crystallized from solution and could be removed by filtration. The photochemical reaction was carried out by adding successive quantities of cyclopentenone to the solution of **9** until about 80% of the latter had been consumed, as determined by glpc. The two tricyclic ketones **10** and **11**, which were formed in nearly equal amount, could be separated by preparative glpc, although other, more convenient methods for separation were subsequently developed and are described below.



10 **11**

One of the two ketones appeared to be identical with norbourbonone,[19] derived from ozonolysis of β-bourbonene,[6] and its structure was established as **10** by a single-crystal X-ray analysis of its thiosemicarbazone. Unequivocal proof of identity of synthetic and naturally derived norbourbonones was provided by a second X-ray structure determination of the thiosemicarbazone of the natural ketone.[20] We subsequently learned that norbourbonone itself occurs in nature, and comparison of infrared and nmr spectra of our synthetic material with those of the natural compound confirmed their identity.[21]

There remained the problem of identifying the second tricyclic ketone obtained in the addition of cyclopentenone to **9**, and to this end we sought a correlation between this photoproduct and ketone **10** of established configuration. It soon became apparent that, in order to carry out transformations on these two ketones individually, a technique more efficient than preparative glpc would be needed for separation of the two compounds. Examination of a molecular model of **11** showed that the angular methyl substituent lay directly over the carbon atom of the carbonyl group, at a distance sufficiently close to suggest that intermediates having tetrahedral geometry at the carbonyl carbon would be sterically crowded. The carbonyl group of **10**, on the other hand, appeared to be relatively unhindered. Assuming the structure of **11** to be correctly assigned, it therefore seemed likely that an appreciable difference in carbonyl reactivity would exist between the two ketones. When **11** (in contrast to **10**) failed to react with thiosemicarbazide and only very slowly with several other carbonyl reagents, it became apparent that this hypothesis was well founded. A convenient method for separation of **10** and **11** involved formation of the 5-(α-phenylethyl)semioxamazone derivative **12** of **10**, by a procedure which left **11** unreacted.[22] The mixture of **11** and **12** could be separated rapidly by chromatography on an alumina column, and ketone **10** was recovered in high yield by hydrolysis of **12** with warm sulfuric acid.

It was our intention to correlate the configuration of **11** with that of **10** by converting each ketone to the same tricyclic hydrocarbon **13** (norbourbonane). Attempted Wolff–Kishner reduction of **11** failed to yield a hydrocarbon, but a closer examination of the reaction revealed that a hydrazone (**14**) was formed which was exception-

(16) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, 70, 3738 (1948); L. F. Hatch and J. J. D'Amico, *ibid.*, 73, 4393 (1951).

(17) There presently exist several ambiguities in the photochemical reactions of alicyclic enones which are not easily accounted for by current mechanistic theory, and a case in point is the nature of excited cyclopentenone. Initially believed to be a singlet [N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 203; J. G. Calvert and J. N. Pitts, "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 537], this species has been found to have properties more consistent with those of a triplet [P. E. Eaton and W. S. Hurt, *J. Amer. Chem. Soc.*, **88**, 5038 (1968); J. L. Ruhlen and P. A. Leermakers, *ibid.*, **89**, 4944 (1967)], although recent evidence suggests that it may not be the lowest triplet state which is involved in photochemical cycloadditions of this molecule [P. de Mayo, J. P. Pete, and M. Tchir, *ibid.*, **89**, 5712 (1967)].

(18) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968).

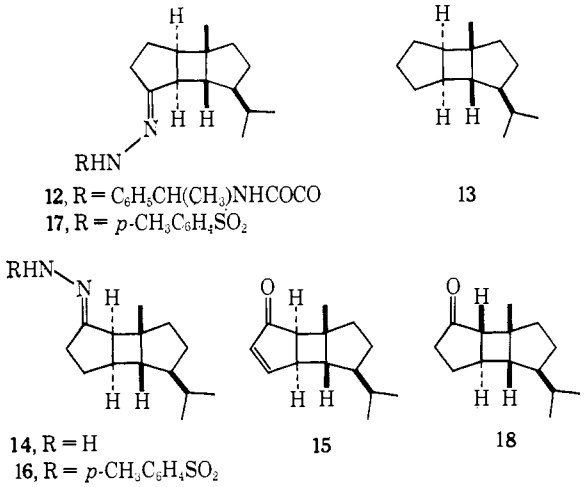
(19) We are indebted to Professor Šorm for samples of authentic β-bourbonene and norbourbonone.

(20) We acknowledge with appreciation the skillful collaboration of Professor J. Z. Gougoutas, Mrs. K. Gold, and Mr. P. C. Manor in carrying out these structure determinations. Full details of the molecular structures, as well as a comparison of molecular packing modes between racemic and optically active forms of norbourbonone thiosemicarbazone, will be presented in a separate publication.

(21) Professor E. Lederer, private communication. We are grateful to Professor Lederer for making this comparison.

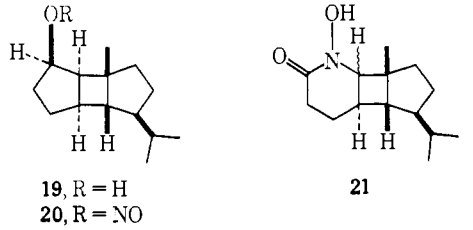
(22) N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).

ally resistant to the action of base. Wolff–Kishner reduction of **15** is also reported to fail (although the reason here was ascribed to the presence of a conjugated double bond rather than the operation of steric hindrance).[7] It did prove possible to prepare the tosylhydrazone **16**, and this was reduced with sodium borohydride in refluxing methanol to **13**.[23] Reduction of **10** presented no problems, and either the Wolff–Kishner method or treatment of tosylhydrazone **17** with sodium borohydride produced a hydrocarbon (**13**) identical with that obtained from **11**. Since both tricyclic ketones yield norbourbonane upon reduction, **11** must have a *cis,anti,cis* ring geometry and *exo* configuration of the isopropyl group. The remote possibility that one (or both) ketones might have a *trans,anti,cis* fusion (*e.g.*, **18**),[24] which could isomerize to the more stable *cis,anti,cis* structure under the reduction conditions, is ruled out by the observation that both ketones are recovered unchanged after treatment with sodium hydroxide. The two photoproducts must therefore differ only in the orientation of the carbonyl group, and evidently result from head-to-head and head-to-tail modes of addition.



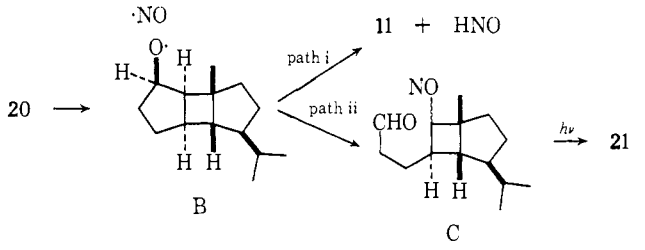
The chemical shifts of the angular methyl protons in the nmr spectra of **10** and **11** are in agreement with the stereochemical assignment, and show differences clearly related to the orientation of the carbonyl group. In **10** a three-proton singlet occurs at 1.12 ppm, whereas the angular methyl protons in **11** are shifted upfield to 0.9 ppm and merge with signals due to the isopropyl group. The relative shielding of the methyl group in **11** is ascribed to the anisotropic effect of the carbonyl group,[25] which results in an upfield shift of protons situated above the plane of the carbon–oxygen double bond.[26]

An attempt was made to establish directly the configurational relationship between the carbonyl and angular methyl groups in **11** by intramolecular functionalization of the latter. The three-dimensional structure of **11** appeared to suggest that a Barton reaction[27] was well suited to this purpose. Ketone **11** was reduced with sodium borohydride in methanol to give a quantitative yield of a single alcohol, and, on the assumption that hydride is delivered to the less hindered, *exo* face of the carbonyl group, the stereochemistry of this alcohol is designated as **19**. Treatment of **19** with nitrosyl chloride in pyridine produced an unstable nitrite ester[28] (**20**) which, from the presence of strong bands in the infrared spectrum at 1640 and 1595 cm^{-1}, was taken to be a mixture of *syn* and *anti* isomers.[29] Within a few hours at room temperature, the nitrite had decomposed with regeneration of **11** and evolution of brown fumes. Photolysis of a pentane solution of **20** through Pyrex at 0° resulted in complete decomposition within minutes and led to a 60% recovery of **11**. A minor product was also isolated and, on the basis of spectral evidence and formation of a red color with ferric chloride, is assigned the hydroxamic acid structure **21**. No evidence for formation of an oxime could be found and examination of the crude photolysate by nmr suggested that the angular methyl group was retained intact.



The decomposition of nitrite ester **20** to **11** and **21** is represented in Scheme I. Dissociation to form

Scheme I



alkoxy radical **B**, followed by hydrogen atom abstraction giving ketone **11** and unstable nitroxyl (path i), has ample precedent in nitrite photochemistry.[30] Formation of hydroxamic acids has also been observed in the photolyses of certain steroidal nitrites[31] and, by

(23) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963); L. Caglioti and P. Grasselli, *Chem. Ind.* (London), 153 (1964).

(24) The *trans*-bicyclo[3.2.0]hexane system is well known [N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Amer. Chem. Soc.*, **81**, 4074 (1959); J. Meinwald, P. Anderson, and J. J. Tufariello, *ibid.*, **88**, 1301 (1966); J. Meinwald, J. J. Tufariello, and J. J. Hurst, *J. Org. Chem.*, **29**, 2914 (1964)] and appears to be conformationally quite stable. The stability of this system undoubtedly derives from the ability of both the cyclobutane and cyclopentane rings to assume folded conformations, the latter adopting an extreme envelope configuration. The tricyclo[3.3.0.0]decane system, however, is constrained such that the cyclobutane ring must be almost planar, and models suggest that the system is rigid. The X-ray structure of norbourbonone thiosemicarbazone provides clear evidence that the cyclobutane ring is virtually planar [see also T. N. Margulis, *Acta Crystallogr.*, **18**, 742 (1965)].

(25) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 124.

(26) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(27) M. Akhtar, "Advances in Photochemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1964, p 263.

(28) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **82**, 2640 (1960).

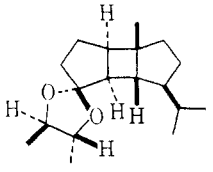
(29) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 304.

(30) J. G. Calvert and J. N. Pitts, "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 480.

(31) C. H. Robinson, O. Gnoj, A. Mitchell, R. Wayne, E. R. Townley, P. Kabasakalian, E. P. Oliveto, and D. H. R. Barton, *J. Amer. Chem. Soc.*, **83**, 1771 (1961).

analogy with these and other cases,[32] **21** is presumed to arise by ring cleavage of B to give nitroso aldehyde C (path ii), followed by recyclization. There is likely to be considerable relief of steric crowding in paths i and ii, which would not be available through a Barton reaction, and this could presumably provide driving force in the observed directions.

We next turned our attention to resolution of **10**, with the aim of obtaining (−)-norbourbonone corresponding to natural material. A variety of methods for the resolution of ketones has been described,[33] although few of these are general in their applicability. It had been the intention in using 5-(α-phenylethyl)-semioxamazide for separation of **10** and **11** to employ this reagent as a means of resolving **10** as well, since both enantiomeric forms of the reagent are available from (+)- and (−)-α-phenylethylamine.[22] Separation of the diastereomeric forms of **12**, prepared from either enantiomer of the semioxamazide, proved difficult and, at best, only partial resolution could be accomplished by this method. A more promising approach appeared to lie through ketalization of **10** with an optically active diol (or dithiol), since this would provide structurally compact and rigid diastereomers which would be amenable to gas–liquid partition chromatography.[34] Treatment of **10** with (*R*)-(−)-2,3-butanediol and a trace of *p*-toluenesulfonic acid in refluxing benzene gave diastereomeric ketals **22** and **23**,[35] which were separable by preparative glpc. Hydrolysis of the separate ketals with hydrochloric acid in ethanol, followed by passage through alumina, produced (+)- and (−)-norbourbonones. Both ketones were homogeneous according to glpc analysis, but in separation of the two ketals, one of the diastereomers had become slightly contaminated with the other, resulting in (−)-norbourbonone of 80–85% optical purity. (+)-Norbourbonone was apparently optically pure. Not unexpectedly, **11** failed to react with (−)-2,3-butanediol, and it thus proved possible to use this resolving agent on the mixture of **10** and **11** to obtain, first, pure racemic **11**, followed by enantiomeric norbourbonones.



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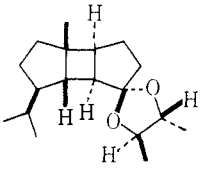
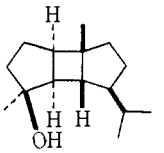


23

It now remained to convert norbourbonone to α- and β-bourbonene, and for this purpose the racemic ketone was used. Treatment of **10** with triphenylmethylenephosphorane afforded synthetic β-bourbonene (**2**), indistinguishable from natural material on the basis of infrared, nmr, mass spectral, and vpc properties.[19] Ketone **11**, on the other hand, was recovered unchanged after treatment with the Wittig reagent, providing further evidence for a sterically hindered carbonyl group in this structure. With methylmagnesium iodide, **10** gave a mixture of two alcohols, **24** and **25**, in the ratio 4:1. The major alcohol is presumably derived from attack of the Grignard reagent at the more exposed *exo* side of the carbonyl group and is therefore designated as **24**. Reconstitution of α-bourbonene (**1**) from this alcohol has been described previously,[3] and we were able to confirm that dehydration of **24** and **25** with phosphorus oxychloride in pyridine gives α-bourbonene, accompanied by a small amount of the β isomer. The facile *exo* to *endo* double bond isomerization in the bourbonenes provides an alternative route to **1**, brief treatment of β-bourbonene with ethanolic hydrogen chloride effecting a clean conversion to the endocyclic isomer. Although we were unable to secure a sample of natural α-bourbonene, the synthetic compound had spectral properties in accord with those reported[6] and was identical with material prepared by similar acid-catalyzed isomerization of natural β-bourbonene.



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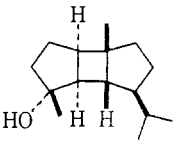

25

Experimental Section

General. Melting points were determined on a Kofler hot stage and are corrected. Boiling points are uncorrected. Infrared spectra were measured, except where otherwise indicated, as liquid films, on a Perkin-Elmer Model 137 or 237 spectrometer. Nmr spectra were measured in deuteriochloroform on a Varian A-60 spectrometer, and chemical shifts are reported as parts per million downfield from tetramethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra were determined with an Associated Electronics Industries MS-9 spectrometer at 70 eV, using direct insertion into the ion source. Glpc analyses were carried out, except where otherwise indicated, with a 0.25 in. × 8 ft column of 5% silicon rubber (Hewlett-Packard SE 30) on acid-washed 60–80 mesh Chromosorb W, using an F & M Model 609 gas chromatograph equipped with flame ionization detector. Preparative glpc separations were carried out on a Wilkens Autoprep 700 instrument. Column chromatographic separations were performed, except where otherwise indicated, on Woelm (activity I) alumina. Microanalyses were carried out by Micro-Tech Laboratories, Inc., Skokie, Ill., or by Dr. S. M. Nagy and associates, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

2-Isopropylcyclopentanone. A solution of ethylmagnesium bromide was prepared from 9.61 g (0.40 g-atom) of magnesium turnings and 33.0 ml of dry tetrahydrofuran, and 62.7 g (0.38 mol) of N-cyclopentylidenecyclohexylamine[36] was added to it with stirring. The mixture was heated under reflux for 1 hr. After the mixture had cooled to room temperature, 37.8 ml (0.40 mol) of 2-bromopropane was added with stirring. When addition was complete, the mixture was stirred under reflux for 15 hr. A solution of 18 g of sodium acetate in 36 ml of glacial acetic acid and 36 ml of water was added to the cooled reaction mixture, which was then heated under reflux for a further 4 hr. Separation of layers and extraction of the aqueous phase with benzene gave a combined extract, which was washed with 10% hydrochloric acid and saturated sodium bicarbonate solution. The solvent was removed and the residue distilled on a spinning-band column to give 25.0 g (53%) of 2-isopropylcyclopentanone: bp 69–70° (25 mm) (lit.[37] bp 86° (40 mm)); ir 1740, 1380, 1360, and 1155 cm^{-1}; nmr, δ 0.81 and 0.97 ppm (6 H, pair of doublets, J = 6.5 Hz, $CH(CH_3)_2$).[38]

(32) P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 27, 2918, 3562 (1962).

(33) For a summary, see W. R. Adams, O. L. Chapman, J. B. Sieja, and W. J. Welstead, *J. Amer. Chem. Soc.*, **88**, 162 (1966), ref 1–8.

(34) J. Casanova and E. J. Corey, *Chem. Ind.* (London), 1664 (1961).

(35) Structures **22** and **23** denote absolute configurations since the absolute configuration of (−)-2,3-butanediol has been established [S. A. Morell and A. H. Auernheimer, *J. Amer. Chem. Soc.*, **66**, 792 (1944)].

(36) K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).

(37) J. Golé, *Bull. Soc. Chim. Fr.*, 894 (1949).

(38) Diastereotopic methyl protons are due to asymmetry at the carbon atom bearing the isopropyl group [H. J. Jakobsen, P. Madsen, and S. O. Lawesson, *Tetrahedron*, **22**, 1851 (1966)].

2-Isopropyl-5-hydroxymethylenecyclopentanone (3). To an ice-cold, rapidly stirred suspension of 64.8 g (1.2 mol) of sodium methoxide in 600 ml of dry benzene was added 76.0 g (0.60 mol) of 2-isopropylcyclopentanone and 88.8 g (1.2 mol) of freshly distilled ethyl formate. Stirring was continued overnight and cold water added to the mixture. The alkaline layer was separated, washed once with ether, and acidified with 10% hydrochloric acid. Extraction of the acidified mixture with ether, followed by removal of solvent and distillation of the residue, gave 65.0 g (80%) of **3** as a colorless liquid: bp 75° (1.5 mm); ir 3400, 1753, 1670, and 1605 cm^{-1}; nmr, δ 7.33 ppm (1 H, multiplet, C*H*OH). The ketone solidified upon refrigeration.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.37; H, 9.29.

2-Isopropyl-5-isobutyloxymethylenecyclopentanone (4). A mixture of 13.0 g (0.083 mol) of **3**, 11.8 g (0.16 mol) of isobutyl alcohol, and 50 mg of *p*-toluenesulfonic acid in 100 ml of dry benzene was heated under reflux with azeotropic removal of water. When the theoretical quantity of water had been collected (*ca.* 1.5 hr), solvent and unreacted isobutyl alcohol were removed *in vacuo*, and the residue was distilled to give 15.2 g (89%) of **4** as a colorless oil: bp 90–93° (0.3 mm); ir 1705, 1640, 1200, 1140, and 1040 cm^{-1}; nmr, δ 7.38 ppm (1 H, triplet, J = 2 Hz, C*H*OR).

2-Isopropyl-5-methylenecyclopentanol (5). A. Reduction of 3. A solution of 64.7 g (0.42 mol) of **3** in 100 ml of ether was added dropwise to a well-stirred suspension of 40 g (1.05 mol) of lithium aluminum hydride in 1 l. of ether at room temperature. After stirring for 2 hr, the mixture was cooled in ice and excess hydride destroyed by cautious addition of water. The salts were filtered and washed with ether. The filtrate was dried and the solvent removed to leave a colorless oil. Distillation gave 41.0 g (70%) of **5**: bp 94–95° (25 mm); ir 3450, 1662, and 895 cm^{-1}; nmr, δ 4.95 and 5.11 (1 H each, multiplet, =CH_2), and 4.20 ppm (1 H, multiplet, C*H*OH).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.87; H, 11.49.

The forerun from the distillation contained a fraction, bp 63–65° (25 mm), which was purified by preparative glpc and identified as **6**: ir 2740, 1680, and 1610 cm^{-1}; nmr, δ 9.71 (1 H, singlet, C*H*O) and 6.88 ppm (1 H, multiplet, C*H*=C).

B. Reduction of 4. A solution of 13.0 g (0.062 mol) of **4** in 50 ml of methanol was added slowly to a well-stirred suspension of 6.5 g of sodium borohydride in 200 ml of methanol at −10°. The mixture was stirred overnight at 0 to −10° and decomposed with dilute sulfuric acid. Extraction with ether, removal of solvent, and distillation as described above gave 4.2 g (49%) of **5** and 2.2 g (26%) of **6**, identical with compounds prepared by method A.

1-Chloromethyl-3-isopropylcyclopentene (8). A solution of 42.0 g (0.30 mol) of **5** in 150 ml of ether was added to a stirred solution of 28 ml (0.39 mol) of thionyl chloride in 150 ml of ether at room temperature under a nitrogen atmosphere. After gas evolution had ceased (*ca.* 10 min), excess thionyl chloride and ether were removed *in vacuo*. The dark residue was rapidly distilled under high vacuum to yield 32.0 g (67%) of **8** as a light green, unstable oil: bp ~36° (0.3 mm); ir 1645 and 690 cm^{-1}; nmr, δ 4.12 (2 H, singlet, CH_2Cl) and 5.71 ppm (1 H, multiplet, C*H*=C). The chloride was used immediately for the next step.

1-Methyl-3-isopropylcyclopentene (9). A mixture of 15.6 g (0.099 mol) of **8** and 3.80 g (0.10 mol) of lithium aluminum hydride in 250 ml of dry diisopropyl ether was heated under reflux for 7 hr. The mixture was cooled in ice and excess hydride was decomposed by cautious addition of cold water. The salts were filtered and washed with ether, and the combined ether extract was dried. After removal of solvent *in vacuo*, the residue was distilled, giving 8.2 g (67%) of **9** as a colorless oil: bp 55° (25 mm); ir 1650 and 830 cm^{-1}; nmr, δ 5.21 (1 H, multiplet, C*H*=C), 1.63 (3 H, singlet, =CCH_3), and 0.8 ppm (6 H, pair of doublets, J = 5 Hz, CH(CH_3)$_2$). An analytical sample was obtained by chromatography on a column of silica gel, impregnated with 10% silver nitrate, and eluting with benzene.

Anal. Calcd for C_9H_{16}: C, 87.03; H, 12.97. Found: C, 86.90; H, 12.87.

Photoaddition of Cyclopent-2-enone to 9. A solution of 4.01 g (0.033 mol) of **9** and 2.0 g of cyclopent-2-enone[39] in 175 ml of pentane was irradiated in a water-cooled Pyrex immersion apparatus with a Hanovia Type L 450-W lamp. Nitrogen was passed continuously through the irradiated mixture. At intervals of 2, 4, and 6 hr the apparatus was disassembled, the deposited solids were removed, and a further 2.0 g quantity of cyclopentenone was added to the mixture before irradiation was resumed. Total irradiation time was 8 hr, after which glpc analysis indicated that about 80% of **9** had been consumed. The pentane solution was filtered and the filtrate concentrated to give a colorless oil. Distillation afforded 4.35 g (66% based on **9**) of a mixture of **10** and **11**, bp 90–95° (0.3 mm). Glpc analysis indicated that the mixture consisted of 48% **10** and 52% **11**. Separation of the mixture of ketones by preparative glpc on a $^3/_8$ in. × 12 ft column containing 20% fluorosilicon (Hewlett-Packard QF-1) on Diatoport S at 175° (flow rate 60 ml/min) gave **10** as the first eluted fraction: ir 1735 and 1422 cm^{-1}; nmr, δ 1.12 (3 H, singlet, CCH_3) and 0.88 ppm (6 H, unsymmetrical doublet, J = 6 Hz, CH(CH_3)$_2$).

A mixture of 0.057 g (0.28 mmol) of **10** and 0.030 g (0.33 mmol) of thiosemicarbazide in 6 ml of ethanol and 2 ml of water was heated under reflux for 5 hr. After cooling, the mixture was filtered and the collected solid was crystallized twice from chloroform–hexane to give 0.030 g (39%) of norbourbonone thiosemicarbazone: mp 181–182°; ir ($CHCl_3$) 3600, 3450, and 1580 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}N_3S$: C, 64.69; H, 9.02; N, 15.04; S, 11.45. Found: C, 64.40; H, 9.00; N, 15.01; S, 11.34.

Collection of the second fraction to be eluted on preparative glpc of the mixture of photoproducts gave **11**: ir 1735 and 1420 cm^{-1}; nmr, δ 0.8–1.0 (9 H, multiplet, CCH_3 and CH(CH_3)$_2$). A mixture of 0.062 g (0.30 mmol) of **11** and 0.059 g (0.32 mmol) of tosylhydrazide in 10 ml of methanol was heated under reflux for 4 hr. The oily residue, which remained after removal of the solvent, solidified upon trituration with ether and was crystallized from methanol–ether to give 0.112 g (99%) of tosylhydrazone **16**: mp 170–171°; ir (mull) 3300, 1640, 1600, 1370, 1320, and 1160 cm^{-1}; nmr, δ 7.86 (2 H, doublet, J = 8 Hz, aromatic *H*), 7.27 (2 H, doublet, J = 8 Hz, aromatic *H*), 2.41 (2 H, singlet, aromatic CH_3), and 0.8–0.9 ppm (9 H, multiplet, CCH_3 and CH(CH_3)$_2$).

Anal. Calcd for $C_{21}H_{30}N_2O_2S$: C, 67.36; H, 8.06; N, 7.48; S, 8.54. Found: C, 67.57; H, 8.08; N, 7.46; S, 8.61.

Separation of 10 and 11 *via* Norbourbonone 5-(α-Phenylethyl)-semioxamazone (12). A solution of 3.80 g (0.018 mol) of the mixture of **10** and **11**, 2.04 g (0.010 mol) of 5-(α-phenylethyl)-semioxamazide,[22] and a trace of iodine in 100 ml of dry benzene was heated under reflux for 30 min. Solvent was removed and the residue was chromatographed on an alumina column packed in hexane. Elution with a 1:1 mixture of hexane–benzene gave 1.30 g (72% of the amount present in the mixture) of **11**, shown to be homogeneous by glpc and identical with the second fraction eluted on preparative glpc of the mixture of photoproducts. Further elution of the column with benzene containing 5% methanol yielded 3.19 g of **12** as a semisolid residue. The semioxamazone **12** was hydrolyzed without further purification by heating under reflux with 200 ml of 20% sulfuric acid for 15 min. Extraction of the hydrolyzate with pentane, followed by passage through a short column of alumina (benzene eluent), gave 1.35 g (68% of the amount present in the mixture) of pure **10**. This material was identical with that obtained by collection of the first eluted fraction on preparative glpc of the ketone mixture.

Norbourbonane (13). A. Reduction of Tosylhydrazone 16. To a solution of 0.112 g (0.30 mmol) of **16** in 10 ml of methanol was added 0.20 g of sodium borohydride. The mixture was heated under reflux for 8 hr. Water was added and the mixture extracted with ether. The ether extract was washed with water and saturated sodium bicarbonate solution, and solvent was removed to give 60 mg of a viscous oil. Chromatography on alumina and eluting with light petroleum gave a hydrocarbon fraction containing a trace of unsaturated material. The latter was removed by chromatography on silica gel impregnated with 10% silver nitrate. Elution with light petroleum containing 5% ether gave 0.025 g (43%) of norbourbonane (**13**) as a colorless oil, homogeneous on glpc: ir 1375 and 1360 cm^{-1}; nmr, δ 1.24 (singlet overlying multiplet, CCH_3) and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.14; H, 12.40.

B. Reduction of Norbourbonone Tosylhydrazone (17). The tosylhydrazone **17** was prepared from 0.050 g (0.24 mmol) of **10** and 0.048 g (0.26 mmol) of *p*-toluenesulfonylhydrazide in 10 ml of methanol by heating under reflux for 2 hr. The crude tosylhydrazone was reduced with 0.10 g of sodium borohydride in 10 ml of methanol under reflux (4 hr) to give, after chromatography on alumina, 0.023 g (49%) of **13**, identical according to glpc retention time, ir, nmr, and mass spectrum with norbourbonane prepared as described by method A.

(39) K. Alder and F. Flock, *Ber.*, **89**, 1732 (1956).

C. Wolff–Kishner Reduction of Norbourbonone (10). A mixture of 141 mg (0.68 mmol) of **10** and 1 ml of 85% hydrazine hydrate in 3 ml of freshly distilled diethylene glycol was heated under reflux for 15 min. The mixture was allowed to cool to 60–70° and 0.42 g of potassium hydroxide added. On warming to 180°, decomposition of the hydrazone began with visible gas evolution. The mixture was heated under reflux (bath temperature 190–200°) for 4 hr. After cooling, the mixture was diluted with 20 ml of water and extracted twice with pentane. The pentane extract was washed with 0.1 *N* hydrochloric acid and water, and chromatographed on alumina. Elution with pentane gave 94 mg (72%) of **13** as a colorless oil, identical with norbourbonane prepared by methods A and B.

Attempted Wolff–Kishner Reduction of 11. Hydrazone 14. A mixture of 271 mg (1.32 mmol) of **11** and 2 ml of 85% hydrazine hydrate in 2 ml of diethylene glycol was heated under reflux for 10 min. After cooling, the mixture was diluted with water and extracted with pentane. The pentane extract was washed with saturated brine and chromatographed on neutral (activity II) alumina. Elution with benzene gave 256 mg (89%) of virtually pure hydrazone **14** as a colorless oil, ir 3400, 3200, and 1650 cm^{-1}. The hydrazone was unstable on storage at 0° over several days.

A mixture of 256 mg (1.16 mmol) of **14** and 715 mg of potassium hydroxide in 3 ml of diethylene glycol was heated at 185–190° for 1 hr. The cooled reaction mixture was diluted with water and extracted with pentane. The pentane extract, after washing with 0.1 *N* hydrochloric acid and water, was concentrated to give a colorless oil which appeared, on the basis of ir analysis, to be mainly unreacted **14**. Chromatography on alumina and elution with pentane failed to give a hydrocarbon fraction.

Alcohol 19. To a stirred solution of 1.24 g (6.01 mmol) of **11** and 0.23 g of sodium hydroxide in 20 ml of methanol at 0° was added 0.15 g (4.0 mmol) of sodium borohydride. The mixture was stirred at 0° for 4 hr and acidified with 2 *N* hydrochloric acid. Saturated ammonium sulfate solution was added and the mixture was extracted continuously with ether. Removal of the solvent, followed by chromatography on alumina and elution with benzene, gave 1.23 g (99%) of **19** as a colorless oil, which was homogeneous by glpc analysis: ir 3400 cm^{-1}; nmr, δ 4.25 (1 H, quartet, J = 8 Hz, C*H*OH), 2.45 (1 H, singlet, O*H*), 1.27 (3 H, doublet, J = 1.5 Hz, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$).

A mixture of 150 mg (0.60 mmol) of 3,5-dinitrobenzoyl chloride in 2 ml of dry benzene was added to 57 mg (0.27 mmol) of **19** in 0.5 ml of dry pyridine, and the mixture was warmed on the steam bath for 10 min. Water was added and the precipitated solid was taken up into ether. The ether solution was washed with 0.1 *N* hydrochloric acid (twice), saturated sodium carbonate solution, and water. The oily residue remaining after removal of solvent crystallized slowly from aqueous ethanol and was recrystallized from ethanol to give 83 mg (75%) of the 3,5-dinitrobenzoate ester of **19** as pale yellow plates: mp 131–135°; ir (mull) 3100, 1720, 1630, 1540, and 1335 cm^{-1}; mass spectrum, *m/e* 402 (molecular ion).

Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.60; H, 6.52; N, 7.02.

Nitrite Ester 20. Nitrosyl chloride was passed through a stirred solution of 256 mg (1.23 mmol) of **19** in 10 ml of dry pyridine at −25° for 15 min. The yellowish brown solution was allowed to warm to room temperature and diluted with 50 ml of ether. The precipitated pyridine hydrochloride was filtered off, and the filtrate was washed with water several times to decompose dissolved nitrosyl chloride (evolution of gas). The ether extract was dried and solvent removed *in vacuo* below 30° to give **20** as a pale yellow oil: ir 1645 and 1600 cm^{-1}; nmr, δ 5.67 (1 H, quartet, J = 8 Hz, C*H*ONO), 1.07 (3 H, doublet, J = 1.5 Hz, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$). Thin layer chromatography of crude **20** showed a pair of poorly resolved spots, presumably corresponding to *syn* and *anti* isomers, and a trace of ketone **11**. Attempts to purify **20** by distillation or column chromatography led to extensive decomposition; in the latter case about 55% of ketone **11** was recovered upon elution of a neutral (activity II) alumina column with benzene containing 25% ether.

Photolysis of 20. A solution of 175 mg (0.74 mmol) of **20** in 120 ml of hexane (Fisher Spectranalyzed) was purged with nitrogen and irradiated with a Hanovia Type L 450-W lamp through Pyrex glass. At the end of 30 min a small amount of a colorless, polymeric solid had deposited, and infrared analysis of the solution indicated that all of the nitrite ester had decomposed. The photolysis mixture was filtered and the solvent removed yielding a gummy residue, which was chromatographed on alumina to give 99 mg (65%) of ketone **11**, identified by ir and glpc comparison with **11** prepared as described above, and 24 mg (14%) of **21**: ir 3400, 1635, 1555, and 930 cm^{-1}; nmr, δ 13.6 (1 H, broad singlet, O*H*), 1.27 (3 H, singlet, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$); mass spectrum, *m/e* 237 (molecular ion).

Resolution of Norbourbonone (10). Norbourbonone 2,3-Butylene Ketals (22 and 23). A solution of 400 mg (1.94 mmol) of **10** and 200 mg (2.22 mmol) of (*R*)-(−)-2,3-butanediol ([α]^{25}D −12.9°) in 10 ml of dry benzene containing a trace of *p*-toluenesulfonic acid was heated under reflux for 2 hr in a Dean–Stark water separator. Solvent was removed and the residue chromatographed on alumina. Elution with light petroleum gave 450 mg (83%) of a mixture of diastereomeric ketals which were separated by passage through a 0.25 in. × 20 ft column of 10% silicon rubber (Hewlett-Packard SE-30) on 60–80 mesh Diatoport S, maintained at 175°. Collection of the separate components gave first **23**: retention time 22.0 min; nmr, δ 3.52 (2 H, multiplet, C*H*OR), 1.21 (6 H, doublet, J = 5.5 Hz, OCHCH_3), and 0.8–1.0 ppm (9 H, singlet at 0.94 (CCH_3) overlying a multiplet (CH(CH_3)$_2$)); mass spectrum, *m/e* 278 (molecular ion). The ir spectra of **22** and **23** both showed peaks at 1200, 1180, 1140, and 1100 cm^{-1}.

A mixture of 41 mg (0.15 mmol) of **23** and 0.25 ml of 2 *N* hydrochloric acid in 1 ml of ethanol was heated under reflux for 30 min. The mixture was diluted with water and extracted with pentane. The pentane extract was chromatographed on alumina to give 20 mg (66%) of norbourbonone, [α]^{25}D +205° (*c* 0.83, chloroform), homogeneous by glpc. Similar hydrolysis of ketal **22** gave norbourbonone, [α]^{25}D −143° (*c* 0.28, chloroform). Norbourbonone derived from natural β-bourbonene[6] had [α]^{25}D −181° (*c* 0.46, chloroform).

Bourbonol (24) and Epibourbonol (25). A solution of methylmagnesium iodide in ether was prepared from 59 mg (2.46 mmol) of magnesium turnings and 540 mg (3.83 mmol) of methyl iodide in 10 ml of ether. To the stirred solution of Grignard reagent was added 422 mg (2.04 mmol) of **10** in 10 ml of ether. The mixture was stirred at room temperature for 6 hr and treated with saturated ammonium chloride solution. The ether layer was separated, washed with water, and concentrated. Chromatography of the residue on alumina, eluting with hexane–benzene mixtures, gave 215 mg (48%) of **24**: ir 3450 cm^{-1}; nmr, δ 1.70 (singlet overlying broad multiplet, O*H*), 1.20 (3 H, singlet, CH_3COH), 0.98 (singlet overlying multiplet, CCH_3) and 0.9 ppm (multiplet, CH(CH_3)$_2$). Further elution with benzene gave 54 mg (13%) of **25**, ir 3450 cm^{-1}. On glpc, the mixture of **24** and **25** gave separate peaks with retention times 17.6 and 19.0 min, respectively (column temperature 135°, flow rate 70 ml/min).

A mixture of 250 mg (1.13 mmol) of **24** and 288 mg (1.25 mmol) of 3,5-dinitrobenzoyl chloride in 5 ml of dry pyridine was heated at 110° for 1 hr. The mixture was poured into water and extracted with ether. The ether extract was washed with 0.1 *N* hydrochloric acid, concentrated, and chromatographed on alumina. Elution with a hexane–benzene (4:1) mixture gave a viscous oil which was crystallized from hexane–ethanol to furnish 265 mg (53%) of bourbonol 3,5-dinitrobenzoate: mp 122–123°; ir (mull) 3150, 1720, 1620, 1535, and 1335 cm^{-1}; nmr, δ 9.19 (3 H, multiplet, aromatic *H*), 1.58 (singlet overlying broad multiplet, OCCH_3), 1.04 (3 H, singlet, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$).

Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73. Found: C, 63.73; H, 7.13; N, 6.98.

β-Bourbonene (2). A solution of triphenylmethylenephosphorane in ether was prepared by addition of 3 ml of a 1 *N* solution of phenyllithium in ether to a stirred suspension of 900 mg (2.48 mmol) of triphenylmethylphosphonium bromide in ether. To the solution of Wittig reagent was added 250 mg (1.2 mmol) of **10** in 2 ml of ether. The mixture was allowed to stand for 10 hr and was then diluted with water and extracted with pentane. The residue, obtained after a removal of the solvent, was chromatographed on alumina. Elution with petroleum ether gave 169 mg (68%) of synthetic **2** as a colorless oil: ir 3080, 1662, 1388, 1376, and 888 cm^{-1}; nmr, δ 4.71 (2 H, multiplet, C=C*H*$_2$), 1.00 (3 H, singlet, CCH_3), and 0.85 ppm (6 H, unsymmetrical doublet, CH(CH_3)$_2$); mass spectrum, *m/e* 204 (molecular ion). Synthetic **2** was homogeneous by glpc on a $^3/_8$ in. × 10 ft column packed with 20% FFAP (Wilkens) on 60–80 mesh Chromosorb W at 150°, and was indistinguishable from natural β-bourbonene in retention time and by comparison of ir, nmr, and mass spectra.

α-Bourbonene (1). A. Dehydration of Bourbonol (24) and Epibourbonol (25). A solution containing 200 mg (0.45 mmol) of the mixture of **24** and **25** and 1 ml of phosphorus oxychloride in 10 ml of dry pyridine was heated under a nitrogen atmosphere at 110° for 2 hr. The mixture was poured over crushed ice and

extracted with ether. The ether extract was washed with 0.1 *N* hydrochloric acid and saturated sodium bisulfite solution. The residue after removal of solvent was chromatographed on alumina. Elution with light petroleum gave 120 mg (65%) of a mixture of **1** and **2** in the ratio 84:16, respectively. Glpc separation ($^3/_8$ in. × 10 ft column packed with 20% FFAP on Chromosorb W, 150°) gave **1** as a colorless oil: ir 3060, 1650, 1370, 1358, and 805 cm^{-1}; nmr, δ 5.25 (1 H, multiplet, =C*H*), 1.70 (doublet overlying multiplet, J = 2 Hz, =CCH_3), 1.02 (3 H, singlet, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$).

B. Acid-Catalyzed Isomerization of β-Bourbonene (2). A mixture of 130 mg (0.64 mmol) of synthetic **2** in 10 ml of 95% ethanol containing 2 drops of 10% hydrochloric acid was heated under reflux for 1 hr. The solution was made alkaline with 10% sodium bicarbonate solution and extracted with ether. The light brown, oily residue after removal of solvent was chromatographed on alumina, and elution with light petroleum gave 90 mg (69%) of virtually pure **1**. Glpc purification as described above gave synthetic **1**, identical with material prepared by method A. An exactly analogous reaction with natural **2** produced **1**, identical by ir, nmr, and mass spectra and glpc retention time with synthetic **1**, prepared by the two methods described above.

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Syntheses of *dl*-Lupinine and the Hydrolulolidine and Hydrojulolidine Ring Systems[1a]

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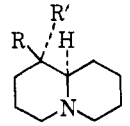
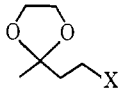
Abstract: A method of quinolizidine and indolizidine synthesis is outlined. It is based on the acid-induced interaction of the α carbon of ketal functions of N-alkyl side chains of 3-acyl-2-piperideines with the piperideine α carbon. The syntheses of lupinine and related, but more complex, tricyclic alkaloid models by this method are developed.

During recent years we have been engaged in the development of a two-step synthesis of quinolizidines and indolizidines and its exploitation in the indole alkaloid field.[2] It is based on the conversion of 1-alkyl-3-acylpyridinium salts into 1-alkyl-3-acyl-2-piperideines on hydrogenation and acid-induced cyclization of the products.[3] The crucial second step depends on the presence of a nucleophilic moiety on the side chain radiating from the nitrogen site of the ring system and its intramolecular reaction with the nuclear aminocarbonium ion created by the action of acid. Since heretofore the nucleophilic units had been exclusively indole groups, it now became of interest to vary these substituents and thus to broaden the scope of alkaloid synthesis. Transient enols or enol ethers were chosen as possible nucleophilic alternates. A description of their employment in the preparation of the alkaloid lupinine (Ia) and hydrojulolidine and hydrolulolidine derivatives is presented herewith.



Ia, R = CH_2OH; R′ = H
b, R = H; R′ = CH_2OH



IIa, X = OH
b, X = OTs
c, X = $CH(CO_2Me)_2$
d, X = Br

Lupinine (Ia). The structural features of this simple alkaloid are ideally suited for construction by the aforementioned method of synthesis.[4] The spatial relationship of the oxygenated side chain to the nitrogen site suggests derivation of the substituted ring from a nicotinic acid system and the remaining four-carbon unit from a N-alkyl chain. The following reactions were modeled on this argument. Treatment of 4-hydroxy-2-butanone ethylene ketal (IIa)[5] with *p*-toluenesulfonyl chloride yielded labile sulfonate IIb whose alkylation of methyl nicotinate produced the salt IIIa.[6] Hydrogenation of the latter over palladium–charcoal[7] afforded the tetrahydropyridine IVa.

While it was predictable that IVa could be induced to form a bicyclic compound by ketal hydrolysis and intramolecular Mannich reaction, the concomitant liberation of a ketone group was an undesirable feature in connection with further chemical operations. Hence, it was important to transform IVa into a quinolizidine

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(2) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Amer. Chem. Soc.*, **90**, 5251 (1968), and references therein.

(3) For a general discussion of this method of synthesis, see E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

(4) For previous syntheses of *dl*-lupinine see (a) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937); (b) K. Winterfeld and H. von Cosel, *Arch. Pharm.*, **278**, 70 (1940); (c) V. Boekelheide and J. P. Lodge, Jr., *J. Amer. Chem. Soc.*, **73**, 3681 (1951); (d) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *ibid.*, **75**, 3243 (1953); (e) J. Ratusky and F. Šorm, *Collect. Czech. Chem. Commun.*, **19**, 340 (1954); (f) H. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 313 (1956); (g) E. E. van Tamelen and R. L. Foltz, *J. Amer. Chem. Soc.*, **82**, 502 (1960); (h) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).

(5) L. Willimann and H. Schinz, *Helv. Chim. Acta*, **32**, 2151 (1949).

(6) The sulfonic ester IIb is an interesting variant of methyl vinyl ketone as a reactive intermediate in organochemical synthesis and can be used for C-alkylation. The preparation of IIc by the alkylation of dimethyl malonate is described in the Experimental Section. Recently the ketal bromide IId[5] was utilized in related fashion [G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964); G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964)].

(7) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).