Studies on Terpenes. III.[1] The Synthesis of *dl*-12-Oxo-6,9-ethano-*cis*-$\Delta^{1,2}$-octalin, a Potentially Useful Intermediate for the Total Synthesis of the Diterpene Alkaloid, Atisine[2]

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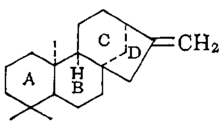
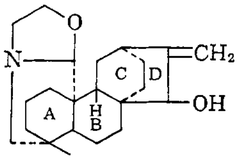
A stereoselective synthesis of *dl*-12-oxo-6,9-ethano-*cis*-$\Delta^{1,2}$-octalin (**17**) in ten steps beginning with ethyl *p*-hydroxybenzoate is described. This unsaturated tricyclic ketone comprises the BCD ring system of the diterpene alkaloid, atisine (**2**) and possesses functionality which makes it potentially suitable for eventual conversion to the alkaloid itself.

The hydrocarbon (−)-kaurene (**1**)[4-7] is representative of a class of diterpenes incorporating a bicyclo[3.2.1]octane ring system.[8] Another group of diterpenes represented by atisine (**2**),[9-11] are related to kaurene by virtue of the *trans,anti,cis* fusion of rings ABC, but differ in the possession of a bicyclo[2.2.2]-octane moiety. Extensive synthetic studies which culminated in partial[12] and total syntheses[13,14] of atisine have been recently and succinctly summarized by Girotra and Zalkow.[15] Our own studies have been concerned with the construction of CD ring systems of both types, and the present paper recounts the preparation of an intermediate containing a bicyclo[2.2.2]-octane grouping. Almost without exception, other workers have made use of synthetic schemes which involve the closure of ring D to an intact hydrophenanthrene (rings ABC) precurser. We, however, envisioned an approach to molecules of both the kaurene and atisine types which comprises the ring construction sequence C–B–D–A. We argued that this order would result in greater stereochemical flexibility which would be of particular value when faced by the variety of naturally occurring stereoisomeric bicyclo[3.2.1]-octane derivatives.[16]



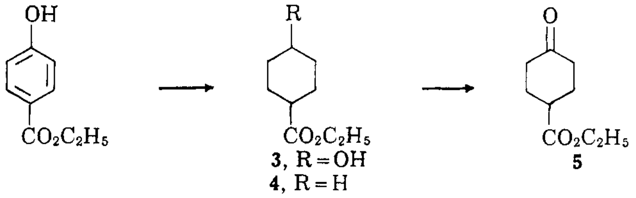
(−)-kaurene (**1**)



atisine (**2**)

The starting material employed in the work at hand, 4-carbethoxycyclohexanone (**5**), was conveniently prepared by chromic acid oxidation of the corresponding alcohol **3**, in turn produced by catalytic reduction of commercially available ethyl *p*-hydroxybenzoate. (Scheme I). When the reduction was carried out as described in the literature,[17] making use of platinum oxide in glacial acetic acid, the alcohol **3** is accompanied by a considerable quantity of the hydrogenolysis product, **4**, and could be obtained in only 30–40% yield. A number of variations in the hydrogenation procedure failed to improve this yield until, prompted by the timely report of Kay and Matthews,[18] rhodium on alumina was used as catalyst, resulting in an 87% yield of **3**. Oxidation was then effected in 83% yield by means of the two-phase system described by Brown and Garg.[19]

Scheme I



Condensation of methyl vinyl ketone with the pyrrolidine enamine[20] derivative of **5**, followed by hydrolysis, provided in good yield a mixture [$\lambda_{\max}^{\text{MeOH}}$ 238 mμ (ϵ 13,800)] of the isomeric octalones **6**, **7**, and **8** (Scheme II). One of the isomers [$\lambda_{\max}^{\text{MeOH}}$ 238 mμ (ϵ 16,700)] could preferentially be obtained by crystallization from an ether–isohexane solution at −70° and was assigned structure **6** on the following basis. Gas

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[1] Previous paper in this series: R. A. Finnegan, *J. Org. Chem.*, **26**, 3057 (1961).

[2] This work was supported in part by Research Grants GM-11412 and RG-8004 from the Division of General Medical Sciences, National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Preliminary announcement of this work has been made before the Organic Division at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965; Abstracts, p. 25S.

[3] Public Health Service Predoctoral Fellow, 1962–1965. This paper is based on a portion of a thesis submitted by P. L. Bachman to the Department of Chemistry, The Ohio State University, in partial fulfillment of the requirements for the Doctor of Philosophy degree, June 1965.

[4] L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, P. S. Rutledge, and J. K. Wilmshurst, *J. Chem. Soc.*, 1345 (1963).

[5] C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

[6] R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962).

[7] S. Masamune, *J. Am. Chem. Soc.*, **86**, 289 (1964).

[8] This class, which may be considered to include various stereoisomers of **1** and a number of oxygenated derivatives as well as certain of the *Garrya* alkaloids,[9] now comprises over 30 individuals.

[9] K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturstoffe*, **16**, 26 (1958).

[10] S. W. Pelletier and P. C. Parthasarathy, *J. Am. Chem. Soc.*, **87**, 777 (1965).

[11] D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **42**, 137 (1964).

[12] S. W. Pelletier and P. S. Parthasarathy, *Tetrahedron Letters*, 205 (1963).

[13] W. Nagata, T. Sugasawa, M. Narisuda, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

[14] S. Masumune, *ibid.*, **86**, 291 (1964).

[15] N. N. Girotra and L. H. Zalkow, *Tetrahedron*, **21**, 101 (1965). See also P. L. Bachman, Ph.D. Thesis, The Ohio State University, 1965.

[16] A (CB)–D–A order of ring synthesis has been successfully applied by Masamune,[7] attempted unprofitably by R. B. Turner, R. E. Lee, Jr., and E. G. Hildenbrand [*J. Org. Chem.*, **26**, 4800 (1961)], and, more recently, intimated by G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi [*J. Am. Chem. Soc.*, **87**, 1148 (1965)].

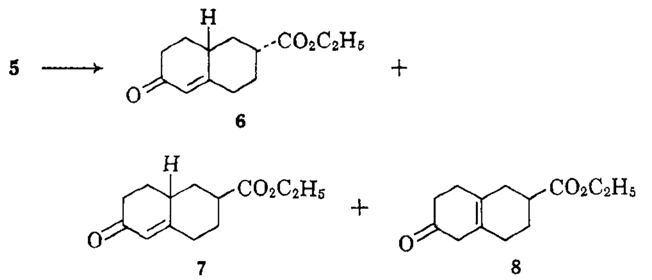
[17] D. E. Applequist and J. P. Klieman, *J. Org. Chem.*, **26**, 2178 (1961).

[18] I. A. Kay and R. S. Matthews, *ibid.*, **28**, 325 (1963). See also A. W. Burgstahler and Z. J. Bithos, *Org. Syn.*, **42**, 62 (1962).

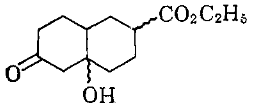
[19] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).

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

SCHEME II



chromatographic analysis of the mixture showed the three components to be present in the ratio 18:48:34, in the order of their elution from the column; the isomer obtained by low-temperature crystallization corresponding to the third peak. When the original mixture was submitted to acid-catalyzed equilibration conditions, the composition ratio changed to 22:35:43. Similar treatment of the purified isomer, as well as the mixture remaining after the removal of this isomer, provided mixtures with nearly the identical composition ratios. The third component was therefore assigned structure **6**, since the conjugated octalone bearing an equatorial carbethoxy group is expected to predominate under equilibrium conditions. The difference between the extinction coefficient of the original mixture (13,800) and that of purified **6** (16,700)[21] indicates the presence of 17% of the nonconjugated ketone **8** which agrees well with the gas chromatographic estimate (18%) for the component of shortest retention time. No attempt was made to purify ketones **7** and **8**; the mixture remaining after the obtention of **6** was simply re-equilibrated in order to produce additional crops of **6**, which was further characterized by the formation of a sharply melting dinitrophenylhydrazone derivative, as well as by the preparation of a crystalline carboxylic acid (**6a**) by hydrolysis. From the residue remaining after distillation of the crude mixture of octalone esters was isolated in about 1% yield a crystalline ketol ester which was formulated as **9** in view of the results obtained on microanalysis as well as its ready dehydration to a mixture of **6**, **7**, and **8**.



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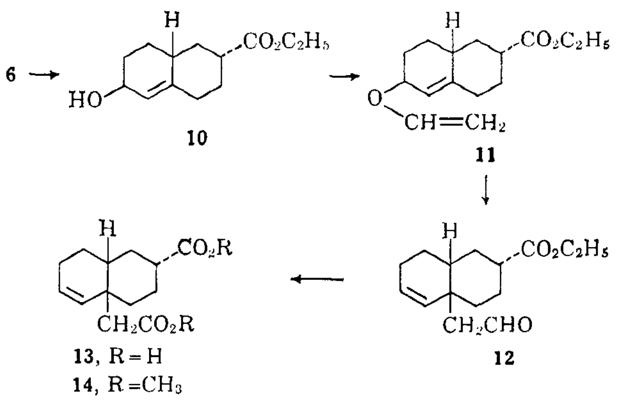
Since the octalone **6** was destined to serve as rings B and C in the projected atisine intermediate, the second phase of the synthesis was planned to effect the establishment of the *cis* ring fusion as well as the introduction of an angular substituent which would permit the construction of ring D. Reduction of **6** with lithium tri-*t*-butoxyaluminum produced in very high yield an allylic alcohol which, on the basis of numerous[22-25] close analogies, was confidently assigned the quasi-equatorial configuration **10** (see Scheme III).

SCHEME III



Confirmation of this assignment was forthcoming from an examination of the p.m.r. spectrum of **10**. Dauben and Ashcraft[24] observed that in a similarly constituted octalol, the vinyl proton appeared as a doublet (5.37 p.p.m.) with a coupling constant of 1.3 c.p.s. in the quasi-equatorial alcohol, and as a doublet (5.52 p.p.m.) with a coupling constant of 4.5 c.p.s. in the quasi-axial alcohol. In agreement with this data, the pertinent signal in the spectrum of **10** (5.45 p.p.m.) appeared to be only very weakly split (J = 1–2 c.p.s.).

Transetherification[26] of **10** readily afforded the vinyl ether **11** in 66% yield after chromatography. Without further purification, the ether was rearranged[27] by pyrolysis to the aldehyde **12** in 46% yield after chromatography on fluorisil.[28,29] The structure of the aldehyde followed from its infrared spectrum, microanalytical data, and the formation of a crystalline semicarbazone derivative, while its purity was evident by its appearance as a single, uniformly symmetrical peak on gas chromatography. Oxidation of **12** with silver oxide was accompanied by simultaneous saponification of the ester group, providing the crystalline diacid **13** which, with diazomethane, was converted to the corresponding dimethyl ester **14**. The stereochemical integrity of this sequence insures that the diester **14** is a derivative member of the desired *cis*-decalin family.

The final stage of the present synthesis invoked Dieckmann cyclization of the diester as a method for closing the bridge constituting ring D. Although unsatisfactory results of numerous attempts (see Experimental Section) at cyclization were disappointing, they were not entirely unexpected. It is clear that, in order for the cyclization to proceed, the diester **14** must first undergo isomerization to **15** (see Scheme IV) in which the ester groups are disposed *cis* to one another. Furthermore, the potential ring C (see **2**) must assume a boat conformation as an additional requirement for ring closure. Although the intermediates resulting from these events would be present in only small concentration, we reasoned that conversion

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[21] 3-Keto-Δ^4 steroids have ϵ 16,600: L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 19.

[22] O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

[23] R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, No. **17**, 1 (1960).

[24] W. G. Dauben and A. C. Ashcraft, *J. Am. Chem. Soc.*, **85**, 3673 (1963).

[25] A. Ogiso and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 820 (1964).

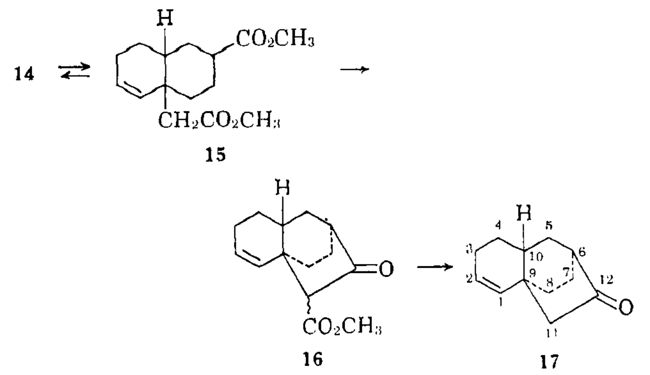
[26] W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

[27] A. W. Burgstahler and I. C. Nordin, *ibid.*, **83**, 198 (1961).

[28] The aldehyde **12** was accompanied by a comparable amount of by-product, presumed to be a mixture of dienes resulting from the elimination of acetaldehyde (see Experimental Section). The suppression of this damaging side reaction might be facilitated by a more rigorous purification of the starting vinyl ether.

[29] Passage of the aldehyde **12** through a column of basic alumina resulted in the formation of the corresponding primary alcohol **18** (see Experimental Section) in 32% yield.

SCHEME IV



to the β-keto ester **16** and its removal from the equilibrating mixture by formation of a stable enolate salt would provide sufficient thermodynamic driving force for the reaction.[30] Several more drastic attempts at cyclization with sodium methoxide in refluxing xylene resulted in the formation of the diacid **13** as the major product[31] which led to the recovery, after remethylation, of 61% of the starting diester. In addition to the diacid, however, a 10% yield of a neutral oil was obtained whose infrared spectrum and positive ferric chloride test indicated that some formation of **16** had indeed occurred. A compromise between the reaction conditions which led mainly to recovered starting material (refluxing benzene)[32] and those which effected mainly demethylation (refluxing xylene) was next carried out with gratifying results. Sodium methoxide in refluxing toluene afforded in 46% yield the keto ester **16**. The structure of this substance, which provided satisfactory microanalytical data, was substantiated by the formation of a deep green color with ferric chloride and the presence of infrared maxima at 1748 and 1721 cm.$^{-1}$.[12,33]

Hydrolysis and decarboxylation was smoothly effected by submitting the β-keto ester to the action of refluxing aqueous dioxane containing a little hydrochloric acid. dl-12-Oxo-6,9-ethano-cis-$\Delta^{1,2}$-octalin (**17**, see Scheme IV) was thus obtained in 77% yield as a colorless oil ($\nu_{\max}^{\mathrm{CHCl_3}}$ 1721 cm.$^{-1}$) possessing a camphor-like odor.[34] The purity of the product was established by gas chromatography on four different columns and the microanalytical data for **17**, as well as for the derived dinitrophenyl hydrazone (m.p. 153.5–155°) and semicarbazone (m.p. 197–198°), were in accord with theory. Finally, the p.m.r. spectrum, including its integral, was in complete agreement with structure **17**. In addition to the unresolved methylene signals between 1.0 and 2.3 p.p.m., the two protons on the keto bridge appeared as a sharp singlet at 2.1 p.p.m. and the two vinyl protons appeared as a multiplet at 5.3–5.8 p.p.m. Analysis of this latter region (Figure 1) shows the vinyl hydrogens as an AB quartet (J = 10 c.p.s.) with the low-field doublet (A) further split into a pair of triplets (J = 3 c.p.s.) by the allylic hydrogens (X) at C-3. A Dreiding model of **17** shows that the unsaturated ring may assume a half-chair conformation in which the proton at C-2 (A) bisects the angle formed by the C-3 protons (X) thus giving rise to the AX_2 pattern. The incompletely resolved splitting of the B lines can be attributed to long-range coupling, also with the allylic hydrogens. It is of consequence to point out that this spectrum can not be interpreted on the basis of any other double-bond isomer, thus precluding the possibility that any untoward double-bond migration had occurred.

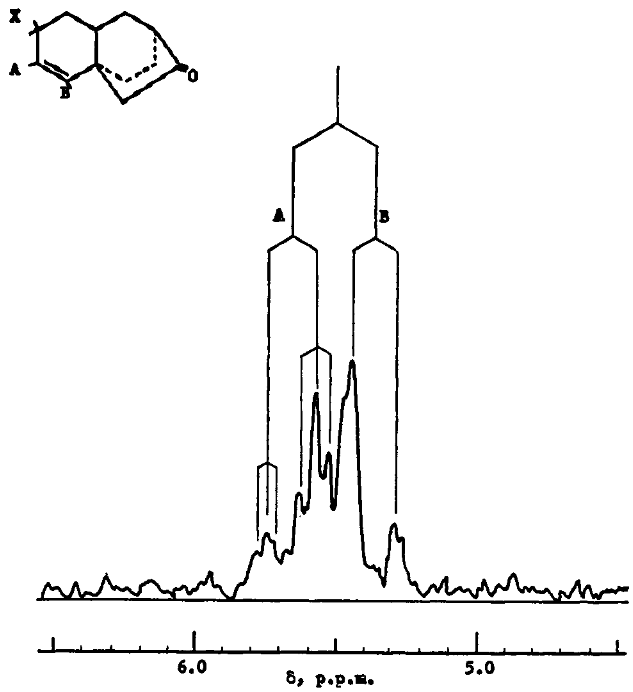


Figure 1.—The p.m.r. spectrum of 12-oxo-6,9-ethano-cis-$\Delta^{1,2}$-octalin; vinyl proton region.

The utility of **17** as an intermediate in a total synthesis of, for example, atisine (**2**), is already established in part by the transformation of similarly constituted D-ring ketones to the requisite allylic alcohol moiety in several laboratories.[13,35,36] Remaining, then, is the elaboration of an appropriately substituted ring A, and the value of **17** in this regard will be measured by the success of various presently planned devices for the activation of the hydrogens at C-4.

Experimental Section

The infrared spectra were measured on the Perkin-Elmer Model 237 spectrophotometer and the ultraviolet spectra were taken on the Perkin-Elmer Model 202 spectrophotometer. The p.m.r. spectra were made on the Varian Associates A-60 spectrometer Chemical shifts are measured in parts per million (p.p.m.) using deuteriochloroform or carbon tetrachloride as solvent and con-

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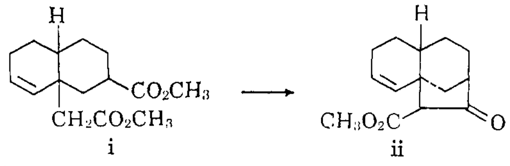
[30] We noted, however, that, in a somewhat more complicated case, a diester in which the ester groups were already *cis* was converted by sodium in refluxing xylene to the corresponding bicyclo[2.2.2]octanone in only 30% yield.[12]

[31] Compare the alkyl-oxygen fission reactions reported by F. C. Chang and N. F. Wood, *Tetrodedron Letters*, 2969 (1964).

[32] By way of contrast, it may be pointed out that the isomeric *cis* diester i, on treatment with sodium methoxide in refluxing benzene, afforded the keto ester ii in 62% yield. R. A. Finnegan and P. L. Bachman, to be published.



[33] S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

[34] Similar treatment of ii (see footnote 32) provided the corresponding bicyclo[3.2.1]octanone in 85% yield.

[35] S. Masamune, *J. Am. Chem. Soc.*, **86**, 290 (1964).

[36] R. A. Bell and R. E. Ireland, *Tetrahedron Letters*, 269 (1963).

taining tetramethylsilane as an internal reference standard. Analyses were performed by Dr. A. Bernhardt, Mülheim, Germany. Melting points were observed on a Fisher-Johns melting point block and are uncorrected. Gas chromatography was carried out using a Wilkens Aerograph instrument, with helium as carrier gas, and equipped with a 5 ft. × 0.25 in. column packed with 20% SF-95 silicone on firebrick, and using a 60-cc./min. flow rate, unless otherwise stated. Retention times were measured from the air peak.

All solvents and liquid reagents were distilled before use. Solid reagents were generally analytical grade and were used without further purification.

Ethyl vinyl ether was Eastman practical grade, and was washed free of stabilizer with cold 2 *N* hydrochloric acid and then with cold 2 *N* sodium hydroxide followed by water until neutral. It was dried over anhydrous potassium carbonate and distilled from sodium just before use.

The mercuric acetate was Baker Analyzed reagent and it was recrystallized from absolute ethanol, vacuum dried thoroughly, and stored in the dark.

Ethyl 4-Hydroxycyclohexanecarboxylate (3).—A solution of 83 g. of ethyl *p*-hydroxybenzoate and 250 ml. of 95% ethanol containing 1 g. of 5% rhodium on alumina was shaken with hydrogen in a Parr hydrogenation apparatus at room temperature. At pressures of from 60 to 30 p.s.i., the theoretical uptake of hydrogen (132 p.s.i.) was realized in less than 24 hr. The solution was filtered through Supercel and the ethanol was then removed under pressure to give a colorless oil. The oil was diluted with cold water and extracted with ether. The organic layer was washed with cold aqueous sodium hydroxide (10%), dilute hydrochloric acid, then with aqueous sodium bicarbonate. After being dried (Drierite), the solvent was removed under reduced pressure to give 73 g. (87%) of ethyl 4-hydroxycyclohexanecarboxylate. Since gas chromatographic anaylsis indicated only traces of ethyl cyclohexanecarboxylate (**4**), the oil was not distilled but was oxidized directly to the ketone.

4-Carbethoxycyclohexanone (5).—To a 1-l. three-necked flask equipped with mechanical stirrer, reflux condenser, and addition funnel was added 69 g. of ethyl 4-hydroxycyclohexanecarboxylate dissolved in 200 ml. of ether. Chromic acid solution, prepared by dissolving 41 g. of sodium dichromate dihydrate in 53 g. of concentrated sulfuric acid and diluting to 200 ml. with water, was then added during 1 hr. with vigorous stirring while maintaining the temperature below 20° with an ice bath. Stirring was then continued for 4 hr. at room temperature after which the phases were separated. The aqueous phase was extracted with three portions of ether which were combined with the organic phase, washed with saturated sodium bicarbonate solution, and dried over Drierite. The ether was then removed under reduced pressure to give 61 g. of colorless oil, which was distilled to give 56 g. (83%) of 4-carbethoxycyclohexanone (**5**), b.p. 62–64° (0.15 mm.), 70° (0.5 mm.) [lit.[37] 158° (40 mm.)]. A 2,4-dinitrophenylhydrazone was obtained as yellow needles, m.p. 126° (lit.[38] m.p. 125–126°).

6-Carbethoxy-$\Delta^{1,9}$-octalin-2-one (6).—A solution of 50.3 g. (0.294 mole) of 4-carbethoxycyclohexanone (**5**), 40 ml. of pyrolidine, and 250 ml. of benzene, in a 1-l. round-bottomed flask equipped with a Dean–Stark water separator, was refluxed overnight under a nitrogen atmosphere during which time 6.2 ml. (0.34 mole) of water was removed. The solvent and excess pyrolidine were removed under reduced pressure and the remaining orange oil was cooled to room temperature and dissolved in 75 ml. of dry, thiophene-free benzene. Freshly distilled methyl vinyl ketone (21 g., 0.3 mole) dissolved in 55 ml. of benzene was added with stirring during 0.5 hr. and the resulting solution was then refluxed overnight under a nitrogen atmosphere. A solution of 15 g. of sodium acetate, 30 ml. of acetic acid, and 30 ml. of water was then added and the mixture was refluxed for an additional 4 hr. The mixture was then diluted with 300 ml. of water, and the phases were separated. The aqueous phase was extracted with four 100-ml. portions of ether which were combined with the organic phase and washed with two 50-ml. portions of dilute hydrochloric acid followed by water until neutral. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure to yield 67.2 g. of deep red oil. The oil was flash distilled under reduced pressure to afford 38.6 g. (59%) of mixed isomers (**6**, **7**, and **8**) as a pale yellow oil: b.p. 130–144° (0.08 mm.); $\nu_{\max}^{\text{film}}$ 1724, 1667, 1618 cm.$^{-1}$; $\lambda_{\max}^{\text{MeOH}}$ 238 mμ (ϵ 13,800). The oil was dissolved in 100 ml. of dry ether and was diluted with 40–70 ml. of isohexane. The solution was then cooled in a Dry Ice–acetone bath (*ca.* −70°) and additional isohexane was added in portions (to avoid oiling) to effect complete crystallization. When crystallization was complete, the mixture was rapidly filtered through a fritted-glass filter which was precooled to −70°. The purity of the crystallized isomer was checked by gas chromatographic analysis at 210–225°. Two more recrystallizations afforded 21.4 g. of nearly colorless **6**. The remaining 17.2 g. of uncrystallized ester was dissolved in 50 ml. of absolute ethanol in a 100-ml. round-bottomed flask, and 0.44 g. of dry hydrogen chloride was then added. The flask was tightly stoppered, and the solution was allowed to stand for 19 hr. at room temperature. An excess of saturated sodium bicarbonate solution was then added, and the resulting mixture was diluted with 100 ml. of water and extracted with ether. The ether extract was washed with several portions of saturated bicarbonate solution and then dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure gave a dark orange oil which was rapidly distilled to furnish 14.6 g. of yellow oil. The oil was crystallized twice from an ether–isohexane solution at −70° to afford an additional 6.3 g. of **6** for a total of 23.5 g. (36%): $\nu_{\max}^{\text{film}}$ 1724, 1667, 1618 cm.$^{-1}$; $\lambda_{\max}^{\text{MeOH}}$ 238 mμ (ϵ 16,700). A portion of the oil was distilled twice for analysis.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; O, 21.59; mol. wt., 222. Found: C, 70.54, 70.45; H, 8.34, 8.42; O, 21.02, 21.11; mol. wt., 227.

A 2,4-dinitrophenylhydrazone was obtained as lustrous, deep red plates, m.p. 192.5–193.0°.

Anal. Calcd. for $C_{19}H_{22}N_4O_6$: C, 56.71; H, 5.51; N, 13.92. Found: C, 57.23, 56.51; H, 5.71, 5.47; N, 13.89.

$\Delta^{1,9}$-Octalin-2-one-6-carboxylic Acid (6a).—A solution of 1.00 g. of purified keto ester **6**, 25 ml. of methanol, 15 ml. of water, and 2 g. of anhydrous potassium carbonate was refluxed under a nitrogen atmosphere overnight. The methanol was then removed under reduced pressure, and the resulting clear solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether (150 ml.) was extracted with three portions of sodium bicarbonate solution (10%) totaling 20 ml. The bicarbonate extract was acidified with concentrated hydrochloric acid and extracted with three portions of ether (20 ml.) which were combined, washed with water until neutral, and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure gave 0.73 g. of buff-colored solid, m.p. 141–143°. Several recrystallizations from benzene afforded crystals, m.p. 147–149°, which were sublimed (95° at 0.02 mm.) to give an analytical sample with m.p. 143–144°; $\nu_{\max}^{\text{Nujol}}$ 1724, 1645, 1613 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.02; H, 7.31.

Isolation and Identification of Alcohol 9.—The dark red pot residue (*ca.* 28 g.) from the distillation of the mixed octalone ester, **6**, **7**, and **8**, solidified on cooling to room temperature. The residue was triturated with 50–100 ml. of ether, cooled to −20°, and filtered to give 1 g. (*ca.* 1%) of colorless crystals, m.p. 156–159°. Several recrystallizations from a chloroform–isohexane solution gave an analytical sample: m.p. 159.8–160.2°; ν^{KBr} 3356, 1721 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; O, 26.63; mol. wt., 240. Found: C, 65.07; H, 8.48; O, 26.69; mol. wt., 233.

A solution of 0.99 g. of the solid (m.p. 152–157°), 0.083 g. of *p*-toluenesulfonic acid, and 15 ml. of dry benzene, in a 25-ml. round-bottomed flask equipped with a Dean–Stark water separator, was refluxed for 7 hr. The resulting deep yellow solution was diluted to 30 ml. with benzene, washed with two 15-ml. portions of saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The benzene was removed under reduced pressure to give 0.90 g. of deep yellow oil which was distilled (bulb to bulb, air bath), b.p. 115° (0.025 mm.), to furnish 0.71 g. of nearly colorless oil. Its infrared spectrum and gas chromatogram were identical with those of the mixed octalone esters.

6-Carbethoxy-$\Delta^{1,9}$-octalin-2-ol (10).—To a thoroughly dried 500-ml. round-bottomed flask, equipped with a magnetic stirrer, was added 250 ml. of dry tetrahydrofuran (freshly distilled from lithium aluminum hydride) and 18.5 g. (90 mmoles) of lithium tri-*t*-butoxyaluminum hydride. The resulting opaque solution

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[37] W. H. Perkin, *J. Chem. Soc.*, **85**, 427 (1904).

[38] A. S. Linsey, *ibid.*, 3224 (1958).

was cooled to 0° and a solution of 5.02 g. (22.5 mmoles) of keto ester **6** in 150 ml. of the same dry tetrahydrofuran was then added dropwise with stirring over a 15-min. period, under a nitrogen atmosphere. Stirring was continued for 0.5 hr. with cooling and then for 1 hr. while warming to room temperature. The reaction mixture was then poured into 500 ml. of cold water containing 32 ml. of concentrated hydrochloric acid. To the resulting solution was added 70 ml. of ether and the two resulting phases were separated. The aqueous phase was extracted with three 150-ml. portions of ether which were combined with the organic phase and washed with water until neutral. The combined aqueous washings were extracted with several smaller portions of ether which, in turn, were combined and washed with water until neutral. The entire ether extract was then combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to afford 4.94 g. (98%) of yellow oil. The oil was distilled (bulb to bulb, air bath) (b.p. 105° at 0.06 mm.) to give 4.6 g. (91%) of nearly colorless alcohol **10**: $\nu_{\max}^{\text{film}}$ 3380, 1730, 1665 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; O, 21.40. Found: C, 69.63, 69.53, H, 9.09, 9.15; O, 21.21, 21.17.

Vinyl Ether of 10.—To a dry, 100-ml. round-bottomed flask, equipped with a magnetic stirrer and reflux condenser, was added 3.30 g. (14.8 mmoles) of alcohol **10**, 60 ml. of destabilized, freshly distilled ethyl vinyl ether, and 0.70 g. of mercuric acetate. The solution was refluxed for 18 hr. under a nitrogen atmosphere, and approximately 100-mg. portions of mercuric acetate were added 2 and 4 hr. after refluxing began. The solution was then cooled, quickly washed twice with cold dilute sodium carbonate solution, and dried over anhydrous potassium carbonate. The ethyl vinyl ether was then removed on a steam bath under a stream of nitrogen to give 3.95 g. of yellow oil. The oil was rapidly chromatographed through a short column of Fisher A540 alumina with 1 l. of isohexane. Removal of the isohexane under reduced pressure then gave 2.42 g. (66%) of vinyl ether **11** as a yellow mobile oil: $\nu_{\max}^{\text{film}}$ 1730, 1634, 1170 cm.$^{-1}$.

The oil was immediately pyrolyzed, without further purification or characterization.

Pyrolysis of Vinyl Ether 11. The Aldehyde 12.—A sealed, heavy-walled Pyrex tube, containing 10.5 g. of vinyl ether **11** in a nitrogen atmosphere, was heated in a refluxing ethylene glycol bath at 196° for 4.5 hr. After cooling to room temperature, the oil was removed from the sealed tube and carefully chromatographed on a column of 123 g. of 100–200-mesh Fluorisil, measuring 1.5 × 13 in. Elution with 0.4 l. of isohexane afforded 3.3 g. of pale yellow oil: $\nu_{\max}^{\text{film}}$ 1736, 1637 (weak), 1610 cm.$^{-1}$ (weak); $\lambda_{\max}^{\text{MeOH}}$ 236, 244, 268 mμ (ϵ 8200, 5800, 1400, respectively). Gas chromatography showed the oil to be a mixture of two components in approximately equal amounts. The mixture was not investigated further.

Continued elution with 0.15 l. of isohexane and 1.5 l. of benzene then afforded a yellow oil which was distilled (bulb to bulb, air bath), b.p. 110° (0.10 mm.), to give 4.8 g. (46%) of the aldehyde **12** as a colorless, mobile oil: $\nu_{\max}^{\text{CCl}_4}$ 2725, 1727 cm.$^{-1}$; retention time (209°), 21 min.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17; mol. wt., 250. Found: C, 72.04; H, 8.87; O, 19.18; mol. wt., 241.

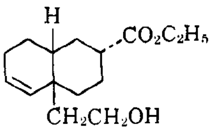
A semicarbazone was prepared as a white powder, m.p. 192–193° from 95% ethanol.

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.92; H, 8.32; N, 13.67.

A portion of the pyrolyzed vinyl ether (3.47 g.), the infrared spectrum of which showed no hydroxyl absorption, was transferred directly from the pyrolysis tube to a column of Fisher A540 alumina measuring 1 × 12 in. Elution with 0.5 l. of isohexane, 1.0 l. of benzene, and 0.5 l. of benzene–chloroform (1:1) afforded 0.72 g. of the mixed side products (see above). Continued elution with 0.5 l. of chloroform then gave 1.40 g. of a deep yellow oil. The oil was distilled (bulb to bulb, air bath), b.p. 115° (0.08 mm.), to give 1.1 g. (32%) of colorless hydroxy ester: $\nu_{\max}^{\text{film}}$ 3425, 1727 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02; mol. wt., 252. Found: C, 71.73; H, 9.20; O, 19.17; mol. wt., 240.

Structure **18** was assigned to this product on the basis of its p.m.r. spectrum. In addition to a multiplet at 5.2–5.8 p.p.m. (two vinyl hydrogens), a triplet at 1.24 p.p.m., and a quartet at 4.12 p.p.m. (ethyl group, J = 7 c.p.s.), the spectrum showed a triplet at 3.73 p.p.m. (J = 7.5 c.p.s., two hydrogens) whose chemical shift and splitting corresponds to that expected for the protons on the hydroxyl bearing the methylene group.


18

Further elution of the column with chloroform–ethanol (4:1, 1:1) and ethanol gave only traces of additional material.

Oxidation of Aldehyde 12. The Diacid 13.—To a solution of 3.8 g. (15.4 mmoles) of aldehyde **12**, 95 ml. of ethanol, and 32 ml. (18 mmoles) of silver nitrate solution (3.72 g. dissolved in 39 ml. of water), was added 120 ml. (74 mmoles) of sodium hydroxide solution (3.72 g. dissolved in 150 ml. of water) in 30 min. with stirring, under an atmosphere of nitrogen. The mixture was stirred for 12.5 hr., then filtered and distilled under reduced pressure to remove the ethanol. The concentrated filtrate was washed with a little ether, acidified with concentrated hydrochloric acid, and extracted with four 50-ml. portions of ether, which were combined, washed with water until neutral, and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure afforded 3.30 g. (91%) of an amber-colored glass. The glass was dissolved in approximately 20 ml. of boiling acetonitrile and then cooled to −15° to give 1.70 g. of colorless diacid, m.p. 140–155°. A second crystallization afforded an additional 0.61 g., m.p. 135–155°, for a total of 2.31 g. (64%) which was esterified without further purification. Four additional recrystallizations from acetonitrile afforded an analytical sample of **13**, m.p. 158.0–158.5°, $\nu_{\max}^{\text{Nujol}}$ 1701 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; O, 26.86; mol. wt., 238; equiv. wt., 119. Found: C, 65.44; H, 7.59; O, 27.00; mol. wt., 249; equiv. wt., 126.

Esterification of Diacid 13. The Diester 14.—A solution of 88 mg. of diacid **13** in several milliliters of ether was treated with an excess of ethereal diazomethane and the excess diazomethane was then destroyed by the dropwise addition of glacial acetic acid. The solvent was removed under reduced pressure and the remaining oil was distilled (bulb to bulb, air bath), b.p. 105° (0.10 mm.), to give 91 mg. (92.5%) of the colorless diester **14**: $\nu_{\max}^{\text{CCl}_4}$ 3030, 1739 cm.$^{-1}$; retention time, 22 min. (210°).

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.34; H, 8.20.

Dieckmann Cyclization of Diester 14. 11-Carbomethoxy-12-oxo-6,9-ethano-*cis*-$\Delta^{1,2}$-octalin (16).—To a dry, 100-ml. round-bottomed flask containing 5–8 ml. of dry methanol (freshly distilled from sodium) was added 178 mg. (7.73 mg.-atoms) of reagent grade sodium cut into small pieces. When the sodium had all dissolved, the methanol was removed under high vacuum (0.10–0.05 mm.) while being heated on a steam bath. After 0.5 hr. the vacuum was released, the sides of the flask were scrapped quickly down, and 10 ml. of dry toluene was then distilled (from calcium hydride) directly into the flask. The slurry of sodium methoxide and toluene was heated on a steam bath for several minutes and then allowed to cool slightly. The toluene was carefully removed under high vacuum and the remaining sodium methoxide was kept under high vacuum for 1 hr. at the steam-bath temperature and then for 1.5 hr. at room temperature. The sides of the flask again were scraped quickly down, a dry magnetic stirring bar was added, and 15 ml. of dry toluene was distilled directly into the flask which was then flushed with dry nitrogen. To the stirred slurry of sodium methoxide in toluene was added during 25 min. a solution of 0.863 g. (3.26 mmoles) of diester **14** in 45 ml. of dry toluene. The mixture was stirred for 40 min. at room temperature and then brought to a gentle reflux (oil bath, 125°) for 80 hr. under a nitrogen atmosphere. After cooling to room temperature, the salmon-colored slurry was poured with rapid stirring into an ice-cold solution of 75 ml. of water and 5 ml. of glacial acetic acid, and when the color had been discharged, the phases were separated. The aqueous phase was saturated with sodium chloride and extracted with four 20-ml. portions of benzene, which were combined with the toluene phase and washed with five 20-ml. portions of water. The combined aqueous washings were washed with four 10-ml. portions of benzene which were combined with the rest of the organic phase and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 0.748 g. of viscous yellow oil which gave a brown color with ferric chloride.

The oil was then dissolved in 20 ml. of ether and washed with two 20-ml. portions of saturated aqueous sodium bicarbonate solution which were combined and washed with a little ether. The combined ether phase was dried over anhydrous magnesium sulfate, and the ether then was removed under reduced pressure to give 540 mg. of a yellow, mobile oil possessing a camphor-like odor. The oil was distilled (bulb to bulb, air bath), b.p. 85° (0.035 mm.), to afford 353 mg. (46%) of colorless β-keto ester **16**, which gave a deep green color with ferric chloride: $\nu_{\max}^{\mathrm{CHCl_3}}$ 1748, 1721 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.05; H, 7.95.

Additional attempts at cyclization may be summarized as follows. Sodium methoxide in refluxing benzene[39] gave only tar along with recovered starting material. Potassium *t*-butoxide in dimethyl sulfoxide (100°) and sodium hydride in dimethyl sulfoxide[40,41] (100°) also produced tar and recovered diester and, in addition, a quantity of the diacid **13**.[31] Potassium *t*-butoxide either in refluxing *t*-butyl alcohol or in a mixture of *t*-butyl alcohol and dimethyl sulfoxide at 100° also failed to effect ring closure. In addition to tar and starting diester, a mixture of resinous half-esters was obtained from which **14** could be reconstituted by methylation.

Decarboxylation of β-Keto Ester 16. 12-Oxo-6,9-ethano-*cis*-$\Delta^{1,2}$-octalin (17).—A solution of 214 mg. of β-keto ester **16**, 2.5 ml. of *p*-dioxane, 1 ml. of water, and 0.5 ml. of concentrated hydrochloric acid was refluxed under an atmosphere of nitrogen for 10 hr. The solution was cooled to room temperature, diluted with 40 ml. of water, and extracted repeatedly (*ca.* eight times) with small quantities of ether totaling 40 ml. The combined ether extract was washed with four small portions of dilute aqueous sodium carbonate solution followed by small portions of water until neutral. The combined carbonate and water washings were then washed with three portions of ether, totaling 20 ml., which were combined with the ether extract and dried over anhydrous magnesium sulfate. The ether was removed on a steam bath under a stream of nitrogen to give 175 mg. of dark oil which was distilled (bulb to bulb, air bath), b.p. 50° (0.015 mm.), to afford 125 mg. (77%) of colorless ketone which possesses a camphor-like odor: $\nu_{\max}^{\mathrm{CHCl_3}}$ 1721 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.16; H, 9.15.

Gas chromatography gave the following retention times: 13.2 min. (20% SF 96, 5 ft × 0.25 in., 173°); 11.1 min. (20% DEGS, 6 ft. × 0.25 in., 218°); 25 min. (20% NPGS, 6 ft × 0.25 in., 205°); 1.95 min. (0.35% silicone grease on glass beads, 6 ft. × 0.25 in., 183°).

A 2,4-dinitrophenylhydrazone was prepared as orange needles, m.p. 153.5–155.0°.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.37; H, 5.73; N, 15.78.

A semicarbazone was prepared, recrystallized twice from chloroform–isohexane solution, and sublimed (140–160° at 0.02 mm.), m.p. 197.0–198.0° dec.

Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21. Found: C, 66.93; H, 7.90.

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The α-Bromobenzyl Alkyl Ether as an Intermediate in the Reaction of Benzyl Alkyl Ethers with Free-Radical Reagents

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The yields of benzaldehyde (the major product) from the reaction of a series of benzyl alkyl ethers with N-bromosuccinimide, bromotrichloromethane, *t*-butyl hypobromite, and *t*-butyl peroxide in carbon tetrachloride have been determined. The yields are insensitive to changes in the alkyl group, R, and are not much affected by replacement of the free-radical halogenating agents by a nonhalogenated radical source (*t*-butyl peroxide). These results, while not definitive enough to allow extended comment on the reaction mechanism, are discussed briefly in terms of the nature of the intermediate steps involved in the formation of benzaldehyde from the benzyl ether radical ($C_6H_5\dot{C}HOR$). There is little change in the relative reactivities of the various benzyl alkyl ethers ($C_6H_5CH_2OR$) with changes in the hydrogen abstracting species ($Br\cdot$, $CCl_3\cdot$, *t*-BuO·) or with changes in R. Apparently, the stabilizing influence of the ether oxygen on the benzyl ether radical is not strongly dependent on the structure of the R group.

The major product of the reaction of *p*-benzhydrylbenzyl methyl ether (I) with N-bromosuccinimide has been identified as *p*-benzhydrylbenzaldehyde (II)

$$(C_6H_5)_2CHC_6H_4CH_2OCH_3\text{-}p \qquad\qquad (C_6H_5)_2CHC_6H_4CHO\text{-}p$$

I II

(60–65% yield).[1] Included among the products are *p*-methoxymethyltriphenylmethyl bromide (III) (6–7% yield) and an unidentified halogen-containing material. It has been suggested, because of its behavior in solvolytic processes, that this substance may be the α-bromo ether IV. On the basis of these ob-

$$(C_6H_5)_2CBrC_6H_4CH_2OCH_3\text{-}p \qquad\qquad (C_6H_5)_2CHC_6H_4CHBrOCH_3\text{-}p$$

III IV

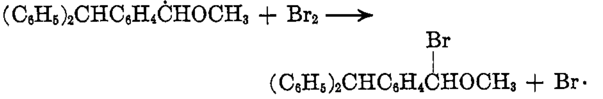
servations, two alternate paths have been proposed by which the radical V, presumed to be a precursor of the various products, may be consumed. This sequence of reactions is illustrated in eq. 1–3. The isolation of the material thought to be *p*-benzhydryl-α-bromobenzyl methyl ether (IV) has raised doubts about the suggestion made by previous investigators[2,3] that, in the reaction of benzyl alkyl ethers with free-radical halogenating agents, the α-bromo ether serves as an unstable intermediate in the formation of the benzaldehyde in the products.

$$(C_6H_5)_2CHC_6H_4\dot{C}HOCH_3$$

V

$$\mathrm{I} + Br\cdot \longrightarrow (C_6H_5)_2CHC_6H_4\dot{C}HOCH_3 + HBr \qquad (1)$$

$$(C_6H_5)_2CHC_6H_4\dot{C}HOCH_3 \longrightarrow (C_6H_5)_2CHC_6H_4CHO + CH_3\cdot \qquad (2)$$



$$(C_6H_5)_2CHC_6H_4\dot{C}HOCH_3 + Br_2 \longrightarrow (C_6H_5)_2CHC_6H_4\overset{\displaystyle Br}{\overset{|}{C}}HOCH_3 + Br\cdot \qquad (3)$$

The present investigation was initiated to explore this matter in more detail through study of the relationship between alkyl group structure and the relative yields of benzaldehyde in the reaction of a series

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