equal acidities enables us to obtain some measure of the relative effects of alkyl groups on electron affinities of amino radicals. The N–H bond strength in methylamine[5a] is reported to be 92 kcal/mol; that for dimethylamine[5a] is reported to be 86 kcal/mol. If, again by analogy, this 6-kcal/mol difference holds for all primary and secondary amines, it follows that the electron affinity of the *t*-butylamino radical is about 6 kcal/mol greater than that of the dimethylamino radical. The size of this effect is consistent with our previous suggestion[1b] that polarizable groups are effective in stabilizing charge by an ion–induced dipole interaction. A simple calculation[6] making use of bond polarizabilities which estimates the energy gained by placing a negative charge adjacent to various alkyl groups gives stabilization differences of this order of magnitude. Because we ignore polarization through bonds[7] and cannot evaluate the effective permittivity, this is a drastic oversimplification. Nevertheless, it does suggest that the explanation has some validity.

It is relatively difficult to compare acidities of amines in the gas phase with those in solution. Solution acidities are virtually unknown, and measurements may be expected to be complicated in any case by factors such as ion pairing. For example, in cyclohexylamine solvent, cesium cyclohexylamide is significantly more basic than lithium cyclohexylamide toward triphenylmethane.[8] It is reasonable, however, to expect that solution acidities of primary amines will parallel those of alcohols. That is, bulky primary amide ions will be more basic than small ones, owing to the effects of solvation. It should be noted that amide ions in solution appear to be significantly more basic than hydroxide or alkoxide ions.[9] This may be a consequence of poorer hydrogen bonding to amide ions, among other things.

Our results provide the first direct gas-phase measurement of the relative acidities of water and ammonia, water being more acidic. A simple analysis based on reported values of bond strengths[5] and electron affinities[10] indicates that water is slightly more acidic, but a more refined analysis, including zero-point energy corrections, suggests the opposite.[11] However, it appears that the acidities are close, and small experimental errors in bond strengths and electron affinities would account for a wrong order. The fact that the acidity of water lies between that of diethylamine and ammonia indicates that there may be sufficient overlap in the acidities of water, alcohols, and amines for us to have a reasonable expectation of evaluating fairly small effects on electron affinities in alcohols and amines in the future.

Acknowledgment. We thank Professor J. D. Baldeschwieler for helpful discussions and J. V. Garcia for technical assistance. We gratefully acknowledge support from the National Science Foundation (GP-4924-X; GP-6736), the National Institutes of Health (GM-145752-02), the donors of the Petroleum Research Fund administered by the American Chemical Society (2917-A4), the National Aeronautics and Space Administration (NGR-05-020-250), and the Center for Materials Research, Stanford University.

(6) M. Davies, "The Electrical and Optical Aspects of Molecular Behavior," Pergamon Press Inc., New York, N. Y., 1965, p 160.
(7) W. M. Schubert, R. B. Murphy, and J. Robins, *Tetrahedron*, **17**, 199 (1962).
(8) A. Streitwieser, Jr., and J. I. Brauman, *J. Amer. Chem. Soc.*, **85**, 2633 (1963); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *ibid.*, **89**, 63 (1967).
(9) W. L. Jolly, *J. Chem. Educ.*, **44**, 304 (1967).
(10) Electron affinity of OH: A. F. Gaines and F. M. Page, *Trans. Faraday Soc.*, **62**, 3086 (1966); electron affinity of NH_2: F. M. Page, *ibid.*, **57**, 1254 (1961).
(11) C. D. Ritchie and H. F. King, *J. Amer. Chem. Soc.*, **90**, 838 (1968).

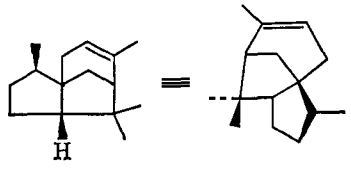
(12) Alfred P. Sloan Fellow, 1968–1970.
(13) National Science Foundation Predoctoral Fellow, 1966–present.

John I. Brauman,[12] Larry K. Blair[13]
Department of Chemistry, Stanford University
Stanford, California 94305
Received January 13, 1969

A Biogenetic-Type Synthesis of Cedrene[1]

Sir:

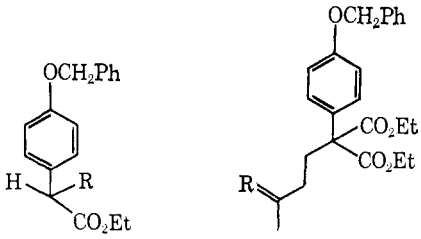
Cedrene, a tricyclic sesquiterpene found in *Juniperus* oil, has been shown to have structure **1** by chemical degradation[2] and synthesis.[3] We wish to describe an alternate synthesis of this natural product by a process utilizing a unique stereoselective dehydrohalogenation and culminating in a step which duplicates the presumed biogenesis.[4,5]



1

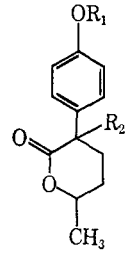
Ethyl benzyloxyphenylacetate (**2**), on treatment with sodium hydride in diethyl carbonate,[6] was carbethoxylated to yield malonic ester **3** (mp 67–68, 72%)[7] which, in the presence of potassium *t*-butoxide, underwent Michael addition to methyl vinyl ketone. The resulting keto diester **4** (mp 57–57.5, 63%), after sodium borohydride reduction to alcohol **5**, was saponified with alcoholic potassium hydroxide to the lactone acid **6** (formed on acidification of the reaction mixture). On distillation (280° (0.1 mm)) **6** was decarboxylated to afford lactone **7**[7] [mp 140–141°; 66% over-all from **4**; $\nu_{max}^{CHCl_3}$ 1725 cm^{-1}; δ_{CDCl_3} 1.40 (d, CH_3), 3.68 (m, benzylic methine H), 5.02 ppm (s, CH_2Ph)]. The benzyl protecting group of **7** was removed *via* hydrogenolysis with palladium on carbon (ethanol) yielding the phenol lactone **8**[7] which on standing for 3 days in anhydrous ethanol–hydrogen bromide[8] was converted to diastereomeric bromo esters **9** [oil, 71% from **7**; $\nu_{max}^{CHCl_3}$ 3615, 3390, 1720 cm^{-1}; δ_{CDCl_3} 1.20 (t) and 4.10 (q) (OCH_2CH_3), 1.63 ppm (d, CH_3)]. Cyclization *via*

(1) This research was supported in part by funds from Eli Lilly and Co. and Monsanto Chemical Co.
(2) G. Stork and R. Breslow, *J. Amer. Chem. Soc.*, **75**, 3219 (1953).
(3) G. Stork and F. H. Clarke, Jr., (a) *ibid.*, **77**, 1072 (1955); (b) *ibid.*, **83**, 3114 (1961).
(4) Professor E. J. Corey has reported (Ernest Guenther Award Lecture, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968) a synthesis of cedrene which, though parallel to our synthesis in design, utilizes a substantially different pathway.
(5) W. Parker, R. Ramage, and J. S. Roberts, *Quart. Rev.* (London), **21**, 331 (1967).
(6) F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 1352 (1950).
(7) Satisfactory elemental analyses were obtained for all fully characterized compounds.
(8) E. E. Van Tamelen, P. E. Aldrich, and T. J. Katz, *J. Amer. Chem. Soc.*, **79**, 6426 (1957).



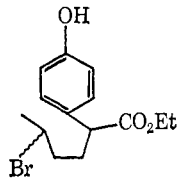
2, R = H
3, R = CO_2Et

4, R = O
5, R = H, OH

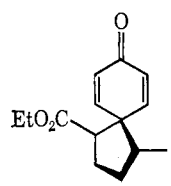


6, $R_1 = CH_2Ph$; $R_2 = CO_2H$
7, $R_1 = CH_2Ph$; $R_2 = H$
8, $R_1 = R_2 = H$

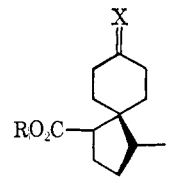
Ar_1-5 participation[9] with potassium *t*-butoxide in *t*-butyl alcohol afforded a product having spectral properties ($\nu_{max}^{CHCl_3}$ 1725, 1665, 1620 cm^{-1}; λ_{max}^{EtOH} 242 mμ) in accordance with structure **10**. Purification of the sensitive spiro dienone was not attempted. The crude product was hydrogenated over palladium on carbon (ethanol) with the observed uptake of 2 mol of hydrogen leading to the saturated spiro keto ester **11**. Column chromatography (silicic acid) yielded **11** as a clear liquid[7] [36% over-all yield from lactone **8**; $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (broad); δ_{CCl_4} 1.02 (d, CH_3), 1.23 (t) and 4.05 ppm (q) (OCH_2CH_3)] which proved to be a single isomer by vpc[10] and nmr analysis. Attempted epimerization with potassium *t*-butoxide failed to alter the spectral properties of the keto ester **11**, providing further proof for the presence of a single isomer. Assignment of the *trans* configuration to **10** and **11** is based on the assumption that the *cis* isomer, which would contain three



9



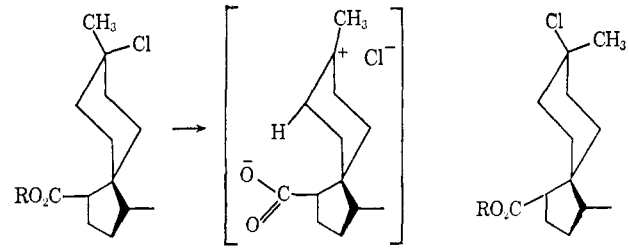
10



11, X = O; R = Et
12, X = CH_2; R = Et
13, X = CH_2; R = H
14, X = CH_3, Cl; R = H

contiguous groups on the same side of the cyclopentyl ring, would be the least likely to form due to an unfavorable activation energy in the Ar_1-5 cyclization reaction.[11]

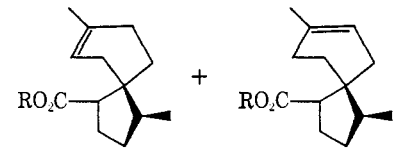
Keto ester **11** was caused to react with methylenetriphenylphosphorane in dimethyl sulfoxide at 25° for 12 hr.[12] The Wittig product **12**[7] [ν_{max}^{neat} 1730, 1655 cm^{-1}; δ_{CCl_4} 0.83 (d, CH_3), 1.20 (t) and 4.02 (q) (OCH_2CH_3), 4.48 ppm (s, $C{=}CH_2$)], isolated in 50% yield, was converted to acid **13** with refluxing 10% alcoholic potassium hydroxide (24 hr), and then to the chloro acid **14** by hydrochlorination with hydrogen chloride in anhydrous ether.[13] The chloro acid derived from this process was obtained as a 60:40 mixture of isomers, **15a** and **16a** (each representing one of two conformations) [δ_{CCl_4} 0.93 (d, $CHCH_3$), 0.87 (d, $CHCH_3$), 1.58 (s, $CClCH_3$), and 1.55 ppm (s, $CClCH_3$)]. This mixture was titrated at 35° with sodium methoxide in methanol[14] and the thymol blue end point maintained by adding additional base over 24 hr. The resulting carboxylate anion of **15a** is suitably disposed in the depicted conformation to act as an internal base to stereoselectively abstract hydrogen from intermediate **17**, which is formed



15a, R = H
b, R = CH_3

17

16a, R = H
b, R = CH_3



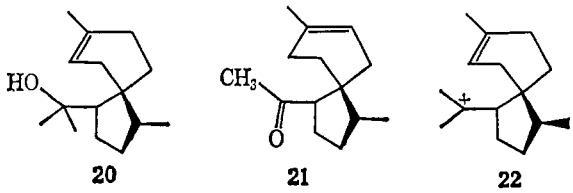
18a, R = H
b, R = CH_3

19a, R = H
b, R = CH_3

solvolytically. The crude acid product (**18a**, **19a**, unreacted **16a**) was esterified with diazomethane to afford a mixture of methyl esters **18b** and **19b**, obtained after preparative vpc. The mixture showed two O-methyl singlets in the nmr at δ 3.48 and 3.57 ppm in the ratio of 3:1. The major peak was assigned to O-methyl in **18b** on the basis of its appearance at higher field (shielding effect by the double bond). Thermal dehydrochlorination of the mixture of chloro esters **15b** and **16b** yielded a 1.1:1 mixture of esters **18b** and **19b**, indicating that a significant degree of the anticipated stereoselectivity was observed in the base-promoted dehydrochlorination. Stereoselective formation of unsaturated acid **18a** requires that conformer **17** contribute significantly to the conformational equilibrium, or that the alternate conformation of **17** be long-lived enough to allow inversion to the indicated conformation.

Addition of 2 equiv of methylmagnesium chloride to the mixture of esters in tetrahydrofuran led to alcohol **20**, contaminated with a small amount of a ketone, possibly **21**.[15] Alcohol **20** should be a suitable precursor for the formation of cedrene *via* a biogenetic-type

(9) R. Baird and S. Winstein, *J. Amer. Chem Soc.*, **84**, 788 (1962).
(10) All gas chromatographic work was performed with a 5-ft silicon column (20% SE 30) on a Varian Aerograph instrument, Model No. 90-P.
(11) For a similar argument, see S. Masamune, *J. Amer. Chem. Soc.*, **86**, 288 (1964).
(12) A. Maercker, *Org. Reactions*, **14**, 395 (1965).
(13) H. C. Brown and M. Rei, *J. Org. Chem.*, 31, 1090 (1966).
(14) R. K. Maurmeyer, M. Margosis, and T. S. Ma, *Mikrochim. Acta*, 177 (1959).
(15) This ketone is more sterically hindered than the one formed from ester **18b**, and for this reason Grignard addition may stop at the ketone stage for this isomer. Retreatment of the reaction product with excess methylmagnesium chloride (2 hr, reflux) failed to alter the amount of ketonic product.



20 21 22

cyclization[16] involving carbonium ion **22**. Dissolution of this alcohol in 88% formic acid at 25° resulted in the instantaneous separation of an oily layer (estimated 80% yield), identified as cedrene by comparison of its nmr, ir, and behavior on vpc with natural cedrene.

(16) The defining characteristics of biogenetic-type syntheses are described in; E. E. van Tamelen, *Fortschr. Chem. Org. Naturstoffe*, **19**, 245 (1961).

Terry G. Crandall, Richard G. Lawton
Department of Chemistry, University of Michigan
Ann Arbor, Michigan 48104
Received December 19, 1968

A Detailed Stereochemical Analysis of Electron Impact Induced 1,3 Elimination in Cyclohexanol and Cyclohexyl Chloride

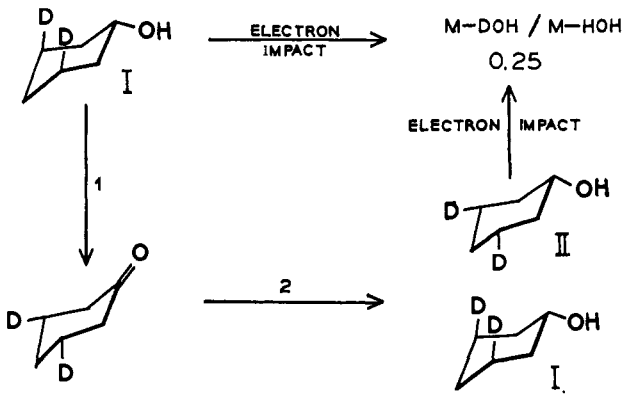
Sir:

Various studies have documented the position of hydrogen abstraction in the electron impact induced elimination reactions of alcohols and chlorides (1). In acyclic hydrocarbon chains, in which the competing hydrogens are all secondary, the loss of water (X = OH in eq 1) involves a highly specific 1,4 elimination[1] while the corresponding chlorides (X = Cl) show a less specifically favored 1,3 elimination.[2] While it has been noted[2,3] that these results point to a dominant heteroatom role in the choice of abstraction site, the similar site selectivities in cyclohexyl chloride[4] and cyclohexanol[4,5] are (*ca.* 70:30, 1,4:1,3 statistically corrected) suggest on the contrary that the structure of the hydrocarbon moiety can be the determining factor. We now report that the 1,3 elimination in cyclohexanol takes place by a rearrangement reaction which is precluded in acyclic alcohols, while the on the surface similar loss of hydrogen chloride from cyclohexyl chloride occurs from an intact molecular ion.

$$(C_nH_qX)\cdot^+ \longrightarrow (C_nH_{q-1})\cdot^+ + HX \qquad (1)$$

Two equivalents of *p*-toluenesulfonyl chloride in pyridine was added slowly to *cis*-1,3,5-trihydroxycyclohexane[6] in cold pyridine. The derived tosylate was treated with lithium aluminum deuteride in ethyl ether to produce, by stereospecific reaction,[7] *cis*-3,5-dideuterio-*trans*-cyclohexanol (I).[8] Oxidation of I with Jones reagent[9] gives rise to *cis*-3,5-dideuteriocyclohexanone which on subsequent reduction with lithium aluminum hydride must give an essentially equal mixture of I and its epimer, *cis*-3,5-dideuterio-*cis*-cyclohexanol (II). Scheme I summarizes these transformations and presents the results of mass spectral analysis of water elimination from I and the mixture of I and II.

Scheme I[a,b]



[a] The mass spectral data were taken near threshold (nominal 9 eV). [b] The ratios for (M − DOH)/(M − HOH) were indistinguishable for I and for the mixture of I and II. The ratio was different (0.40) but still indistinguishable at 70 eV.

If the tosylate displacement leading to I were stereospecific, the results would require that the end result of steps 1 and 2 (Scheme I) be stereochemically equivalent to the impact of 9-V electrons. The following experiment provides unequivocal evidence that this conclusion is correct.

Treatment of I and the mixture of I and II with phosphorus pentachloride in cold chloroform leads, by inversion of configuration,[10] to the respective chlorides[8] III and an equal mixture of III and IV. Scheme II presents these transformations as well as the mass spectral results for the loss of hydrogen chloride from the derived chlorides.

It follows from the divergent results on the loss of hydrogen chloride from III and from the mixture of III and IV that the displacement leading to I is stereospecific. Indeed, the decreased loss of deuterium chloride from the mixture of III and IV points out the necessary *cis* relationship between the abstracted hydrogens and the chlorine in the 1,3 elimination in cyclohexyl chloride. Further, the quantitative ratios for DCl/HCl loss allow the assignment of a lower limit of 84% stereospecificity to the displacement producing I as well as in the *cis* elimination in the derived cyclohexyl chloride molecular ion. These results require that the 1,3 elimination of water in cyclohexanol be

(1) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964); S. Meyerson and L. C. Leitch, *ibid.*, **86**, 2555 (1964), and references therein.

(2) A. M. Duffield, S. D. Sample, and C. Djerassi, *Chem. Commun.*, 193 (1966).

(3) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, p 132.

(4) M. M. Green and J. Schwab, *Tetrahedron Lett.*, 2955 (1968).

(5) C. G. MacDonald, J. S. Shannon, and G. Sugowdz, *ibid.*, 807 (1963); H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 158 (1964).

(6) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **85**, 451 (1952).

(7) G. K. Helmkamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

(8) All deuterated materials were found to be identical with authentic protium materials by vapor phase chromatography. In addition, we have oxidized (hot nitric acid) I to adipic acid. The nmr spectrum of the derived dimethyl ester shows multiplets at δ 1.6 (3 H) and 2.3 (3 H) and a singlet at 3.6 (6 H), as required for deuterium incorporation at C-3 and C-5 in the parent cyclohexanol.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 142.

(10) For a general discussion and leading references see: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 91, 92.