role of the serine residue which is responsible for the loss of activity in anhydrochymotrypsin.

Thus, the definitive identification of the precise role of the serine residue still eludes us. The number of alternative roles, however, have been further narrowed. It is seen that the serine residue cannot play any major role in the binding of substrate to the protein. Its modification may affect the specificity somewhat but the binding properties of the protein are changed only slightly from those of the native enzyme. The change in the catalytic properties is dramatic and whatever its detailed role the serine hydroxyl group must be intimately involved with the catalytic power of the enzyme.

The formation of anhydrochymotrypsin is perhaps the forerunner of the production of other proteins produced in an analogous way, *i.e.*, by converting an essential catalytic residue to a smaller residue. Such proteins which presumably will have lost their catalytic activity without having lost their binding properties may be useful in exploring the specificity relationships of enzymes in the absence of catalysis. Moreover, as in the case of chymotrypsin, a conversion of a residue to a smaller group eliminates arguments of steric access which would be important in any enzyme-catalyzed reaction especially if the active site is in a cleft of the molecule (as indicated for lysozyme)[43] where space is limited. Horecker and co-workers have utilized an elimination reaction in an ingenious way to remove complications of SH residues in studies on aldolase.[44]

A particularly useful property of the anhydro enzyme is that it offers the possibility of adding other atoms, for example, H_2S, to produce new proteins in which the catalytic residue has been converted to residues of similar appearance but with different chemical properties. From such "chemical mutations" the precise role of the serine residue may emerge.

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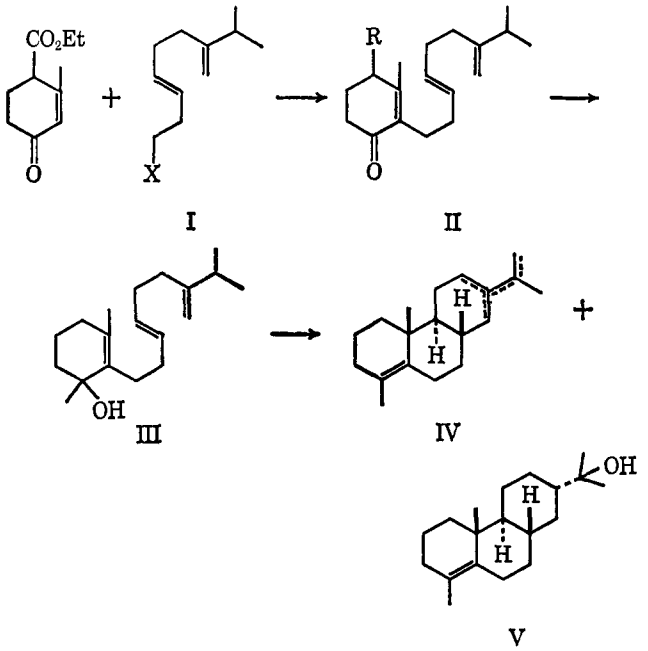
Communications to the Editor

An Efficient, Stereospecific Polyolefinic Cyclization. Total Synthesis of *dl*-Fichtelite

Sir:

In our search for polyolefinic systems that will undergo biogenetic-like polycyclization,[1] we have now extended previous ring-closure studies of butenylcyclohexenol systems[2] to include the cyclization of the trienol III. To our gratification we found, as described below, that this substrate undergoes stereospecific ring closure under mild conditions to give tricyclic material in very high yield. This finding has led to a facile total synthesis of *dl*-fichtelite (IX).



Following prior art[2b,c] we prepared the trienol III (*Anal.* Found: C, 82.2; H, 11.8) by alkylation of Hagemann's ester with the bromo diene I (X = Br) to produce II (R = CO_2Et). Hydrolysis and decarboxylation gave the unsaturated ketone II (R = H) which, on treatment with methyllithium,[2c] afforded III.

$$C_6H_5CH_2O(CH_2)_2C{\equiv}CCH_2X$$
VI

$$C_6H_5CH_2O(CH_2)_2C{\equiv}C(CH_2)_2COCH(CH_3)_2$$
VII

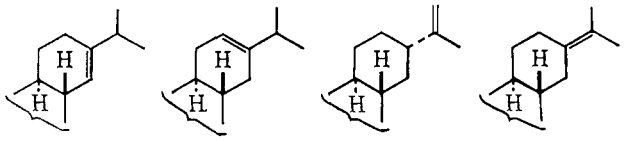
The bromide I (X = Br) was produced as follows. The product VI (X = OH) of reaction of the anion of the benzyl ether of 3-butyn-1-ol with formaldehyde was treated with phosphorus tribromide to give VI (X = Br). Reaction of VI (X = Br) with ethyl sodioisobutyrylacetate, followed by hydrolysis and decarboxylation, gave the ketone VII. Reaction of this ketone with methylenetriphenylphosphine, followed by treatment of the product with sodium in ammonia, gave the alcohol I (X = OH). The tosylate I (X = OTs), on

(1) W. S. Johnson, *Pure Appl. Chem.*, **7**, 317 (1963).

(2) (a) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Am. Chem. Soc.*, **86**, 1972 (1964); (b) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *ibid.*, **87**, 5148 (1965); (c) J. A. Marshall and N. Cohen, *ibid.*, **87**, 2773 (1965).

treatment with lithium bromide, afforded I (X = Br) (*Anal.* Found: C, 57.4; H, 8.4; Br, 34.6).

The trienol III, on mixing with formic acid, underwent immediate dehydration to the sparingly soluble tetraene. On shaking the reaction mixture for 11 min at room temperature, the tetraene completely disappeared. Chromatography gave a 67% yield of hydrocarbon fraction and 28% of an alcohol. As shown below, the former fraction proved to be the olefin mixture IV, and the latter mainly the alcohol V. Vapor phase chromatography (Carbowax) of the hydrocarbon fraction showed the presence of four olefins, A, B, C, and D (in order of increasing retention time), in a ratio of 23:45:2:30. The four components were separated by preparative vpc. Each of these substances showed high-field three-proton singlet absorption for the angular methyl group at δ = 0.93–0.96 ppm relative to tetramethylsilane in the nmr spectra and three-proton singlet absorption at 1.57–1.59 for the vinyl methyl group at C-4 (steroid numbering). The spectra of olefins A and B were similar, showing typical six-proton doublet (J = 7 cps) absorption for the isopropyl group centered at 0.96 ppm and absorption for only one vinylic proton. The widths at half-height of the vinylic proton signals were 3 cps for A at 5.10 ppm and 7 cps for B at 5.33 ppm. These data are consistent with the structures IVa and IVb, respectively. The spectrum of olefin

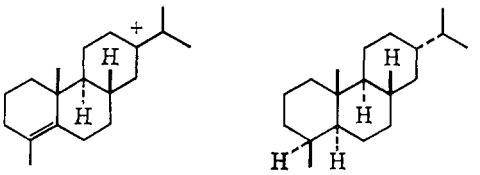


IVa IVb IVc IVd

C showed typical absorption for $CH_2{=}C(CH_3)$–, namely a two-proton "singlet" at 4.59 and a three-proton triplet (J = 1 cps) at 1.67 ppm, and therefore corresponds to IVc. The terminal methylene structure was confirmed by the bands at 6.08 and 11.25 μ in the infrared spectrum. The nmr spectrum of olefin D showed no absorption for vinylic protons and nine-proton absorption in the 1.58–1.65 ppm region (CH_3-C=C), corresponding to structure IVd.

Each of the olefins, on shaking with formic acid, was converted into mixtures of the four. This fact provides strong evidence that these substances differ only in the position of the double bond in ring C and that they all possess the same configuration at the ring junctures.[3]

The alcohol fraction, which appeared to be essentially homogeneous on thin layer chromatography, showed in the nmr spectrum no absorption for vinylic protons and six-proton singlet absorption at 1.07 ppm, which is consistent with the *t*-dimethylcarbinol structure V. In accord with this formulation, dehydration with phosphorus oxychloride and pyridine gave, in 68% yield, a mixture of olefins consisting almost entirely of IVc and IVd, predominantly the former. On shaking with formic acid, the alcohol was partially converted to the mixture of olefins A–D. Therefore the alcohol clearly belongs to the same stereochemical series as the hydrocarbons. If, as seems probable, all these products are produced from the expected primary product of cyclization, namely the cation VIII, in an equilibration process involving conventional carbonium ion transformations, then the configuration of the group at C-13 in substance IVc and in V should be mainly in the more stable α (equatorial) form.



VIII IX

Conclusive proof of the tricyclic nature of the reaction products described above was afforded by conversion of the olefin mixture, on hydrogenation over platinum oxide in acetic acid, into a mixture of approximately equal amounts of two saturated hydrocarbons, which were separated by preparative vpc. The higher retention time material was shown to be *dl*-fichtelite (IX) by infrared, high temperature mass, and nmr spectral comparison with the natural product,[4] which is known[5] to have the configuration shown in formula IX. Hydrogenation of each of the olefins A–D, over platinum oxide in ethanol, effected selective reduction of the bond in ring C. Each of these dihydro compounds, on further hydrogenation in acetic acid, afforded *dl*-fichtelite as described above. These experiments establish that the olefins have the same configuration at C-8, 9, and 10.

Thus the cyclization of the trienol III appears to proceed essentially quantitatively and stereospecifically (with respect to bridgehead configurations) *via* the tricyclic cation VIII. For reasons which will be set forth in a definitive paper, we believe that the formation of this cation does not involve the intermediacy of an isolable bicyclic substance. Hence the process either is synchronous or involves cationic intermediates that do not deprotonate prior to further cyclization. In any case the mechanism appears to differ from the stepwise process that is involved in the acid-catalyzed cyclization of desmethylfarnesic ester,[6] which proceeds stereospecifically in 60–70% yield. The present case appears to be the most efficient nonenzymic cyclization of its kind recorded to date. We are currently examining the possibility of producing higher polycyclic systems by this method.

Acknowledgment. We thank the U. S. Public Health Service, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(3) It is assumed that extensive hydride shifts do not occur to any appreciable extent so as to involve the C-8 position, because in this event the C-9 proton would have been lost, giving a significant amount of the thermodynamically preferred Δ^8 isomer; *cf.*, *inter alia*, E. E. Royals, W. C. Bailey, and R. W. Kennedy, *J. Org. Chem.*, **23**, 151 (1958).

(4) We are indebted to Professor R. E. Ireland for supplying us with this specimen which originally came from Professor O. Jeger, whom we also wish to thank.

(5) A. W. Burgstahler and J. N. Marx, *Tetrahedon Letters*, No. 45, 3333 (1964).

(6) A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Connor, Ed., J. and A. Churchill, Ltd., London 1959, p 217; W. S. Johnson, S. L. Gray, J. K. Crandall, and D. M. Bailey, *J. Am. Chem. Soc.*, 86, 1966 (1964).

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