DMF and allowed to react with 0.002 mole of the mixed anhydride of N^{α}-carbobenzoxy-L-arginine hydrochloride. The reaction mixture was worked up and purified as described earlier in this preparation again using the base extraction, the Amberlite IR-45 column, and *n*-butyl alcohol–ether precipitation. The product was filtered and extracted in a Soxhlet apparatus with hot tetrahydrofuran for several hours. This trihydrochloride was then recrystallized again from *n*-butyl alcohol–ether as a highly electrostatically charged white solid, difficult to handle when wet, which could be handled and stored readily when dry. A sample (52 μg.) subjected to two-dimensional paper chromatography revealed only one spot, Sakaguchi positive; R_f^1 0.60; R_f^2 0.74.

LAP Digest of Decarbobenzoxylated XI.—Compound XI was hydrogenated over 10% palladium-on-charcoal catalyst in methyl alcohol. After removal of solvent and catalyst a solid of R_f^1 0.17 and R_f^2 0.46 was obtained by *n*-butyl alcohol–ether precipitation. This solid (2.0 mg.) was dissolved in 1.0 ml. of tris(hydroxymethyl)aminomethane (Tris) buffer (pH 8.5, 0.01 *M* Mg^{2+}), 0.2 ml. of a LAP solution (5 mg. of Worthington LAP in 1 ml. of water) was added, and the solution was maintained at 37° for 24 hr. This solution (30 μl.) was then spotted on Whatman No. 1 paper. Only one spot (R_f^1 0.21; R_f^2 0.30), corresponding to arginine hydrochloride, Sakaguchi and ninhydrin positive, was detected.

Carbobenzoxyglycylglycyl-L-arginine-2-naphthylamide Hydrochloride (XII).—This compound was prepared from carbobenzoxyglycylglycine[29] (13.32 g., 0.05 mole) and L-arginine-2-naphthylamide hydrochloride[13,20,22] (16.79 g., 0.05 mole) by the procedure described for I–IV. The residue obtained after removal of solvent was purified by dissolving in hot water, cooling, adding ether, and agitating. The flocculent solid obtained was washed with acetone–ether (1:1) and recrystallized from ethyl alcohol–ether. Two-dimensional chromatography showed a single spot, chlorine and Sakaguchi positive; R_f^1 0.83; R_f^2 0.84; R_f^3 0.71.

Acetylglycylglycyl-L-arginine-2-naphthylamide Hydrochloride (XIII).—This compound was prepared from acetylglycylglycine[20,30] (5.22 g., 0.03 mole) and L-arginine-2-naphthylamide hydrochloride[13,20,22] (10.07 g., 0.03 mole) by the procedure described for I–IV. The residue obtained after removal of solvent was dissolved in water and the solution was cooled to 0–5° and extracted at pH 10.6 with ether several times. The water layer, adjusted to a pH of 7, was concentrated to dryness at 40–45°. The residue obtained was dried by dissolving in ethyl alcohol several times and concentrating under reduced pressure to dryness. It was finally dissolved in *n*-butyl alcohol containing just enough ethyl alcohol to dissolve it. After standing overnight, sodium chloride was removed by filtration and the hygroscopic electrostatic solid was precipitated with dry ether. Two-dimensional chromatography showed a single spot positive to both the chlorine and Sakaguchi reagents; R_f^1 0.69; R_f^2 0.79; R_f^3 0.47.

Carbobenzoxyglycyl-L-arginyl-L-arginine-2-naphthylamide Dihydrochloride (XIV).—This compound was prepared from carbobenzoxyglycine[26] (1.04 g., 0.005 mole) and L-arginyl-L-arginine-2-naphthylamide dihydrochloride (2.64 g., 0.005 mole) by the procedure described for I-IV. Isolation of this hygroscopic electrostatic solid was effected by the procedure used for XIII. Two-dimensional chromatography showed a single spot positive to the chlorine and Sakaguchi reagents; R_f^1 0.80; R_f^2 0.87; R_f^3 0.39.

β-Carboxypropionylglycylglycyl-L-arginine-2-naphthylamide Hydrochloride (XV).—This compound was prepared from succinic anhydride (1.0 g., 0.01 mole) and glycylglycyl-L-arginine-2-naphthylamide hydrochloride[31] (3.30 g., 0.0075 mole) by the procedure described for V. The product was recrystallized from ethyl alcohol–ether. It exhibited only one spot positive to the chlorine and Sakaguchi reagents when subjected to two-dimensional chromatography; R_f^1 0.65; R_f^2 0.82; R_f^3 0.37.

Acknowledgment.—We wish to thank Mr. Michael Rokoff for preparing some samples of 1-arginine-2-naphthylamide hydrochloride and Mr. Stuart Lessans for help in the chromatographic studies.

(29) R_f^1 0.84; R_f^2 0.83; R_f^3 0.30.

(30) R_f^1 0.56; R_f^2 0.42; R_f^3 0.06.

(31) Obtained by catalytic hydrogenolysis of XII with 10% palladium on carbon in methanol. The crude solid obtained by removal of catalyst and solvent was used without further purification; R_f^1 0.65; R_f^2 0.72; R_f^3 0.59.

Olefinic Cyclizations. VII. Formolysis of *cis*- and *trans*-5,9-Decadienyl *p*-Nitrobenzenesulfonate and of Some Isomeric Monocyclic Esters*,[1,2]

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Received November 13, 1964

Solvolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulfonate in 100% formic acid containing sodium formate yields, among other products, the formates of the *trans* monocyclic alcohol II and the *trans*-2-decalols III and IV. Solvolysis of the *cis* isomer VIII (R = $SO_2C_6H_4NO_2$) gave a very similar product distribution except that the cyclic products belonged exclusively to the *cis* series, *i.e.*, IX, X, and XI. The stereospecificity of these processes has interesting mechanistic implications which are given consideration. The formolysis of the *p*-nitrobenzenesulfonates of the monocyclic alcohols II, VI, and IX has been examined. These reactions are not stereospecific, and the mechanistic implications are discussed. It was discovered that butenylcyclohexene (VII), as well as the tertiary alcohol V, on treatment with 100% formic acid containing sodium formate undergoes stereospecific cyclization to give *cis-syn*-2-decalol (XI) in over 20% yield.

The solvolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulfonate (I, R = $SO_2C_6H_4NO_2$) in 80% formic acid containing sodium formate has been examined.[3] The most striking feature of this reaction was the fact that the products of ring closure were formed highly stereoselectively, perhaps even stereospecifically. Thus *trans*-2-(Δ³-butenyl)cyclohexanol (II) was produced (as the formate) to the exclusion of the *cis* isomer, and the decalols that formed were exclusively those with *trans*-fused rings, namely III and IV. As previously noted,[3,4] this stereoselective *trans* addition to the internal olefinic bond is in accord with the concepts advanced by Stork[5] and Eschenmoser[6] regarding the biogenesis of natural polycycloisoprenoids. There is, however, an alternative rationalization which must be considered, namely that the solvolysis proceeds to give

* To Professor Louis F. Fieser.

(1) Part VI: W. S. Johnson and R. Owyang, *J. Am. Chem. Soc.*, **86**, 5593 (1964).

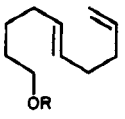
(2) A portion of this work has been disclosed in a preliminary communication, W. S. Johnson and J. K. Crandall, *ibid.*, **86**, 2085 (1964).

(3) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *ibid.*, **86**, 1959 (1964).

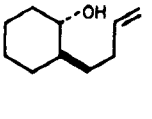
(4) W. S. Johnson, *Pure Appl. Chem.*, **7**, 317 (1963).

(5) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955).

(6) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).



I



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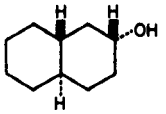
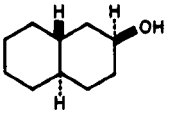
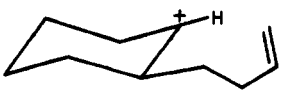


III



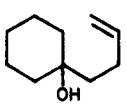
IV

what is essentially the intermediary cation A which reacts by selective equatorial nucleophilic attack either by the solvent or by the terminal olefinic bond. The plausibility of this concept and its bearing on the biological process have already been discussed.[4,7] This hypothesis has now been put to test by examining the formolysis of *cis*-5,9-decadienyl *p*-nitrobenzenesulfonate (VIII, R = $SO_2C_6H_4NO_2$). If this reaction, as well as that of the *trans* isomer, were to proceed *via* the cation A, both isomeric sulfonate esters would yield the same cyclic products.[8] The present paper constitutes a detailed report of this study.

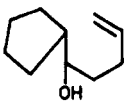


A

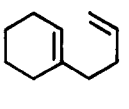
5,9-Decadiynol,[3] on selective hydrogenation over Lindlar catalyst, was transformed into the desired *cis*-5,9-decadienol (VIII, R = H) which was purified by preparative vapor phase chromatography. Treatment of the dienol with *p*-nitrobenzenesulfonyl chloride in pyridine afforded *cis*-5,9-decadienyl *p*-nitrobenzenesulfonate (VIII, R = $SO_2C_6H_4NO_2$), m.p. 26.5–27°.



V

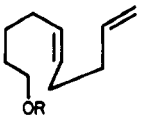


VI

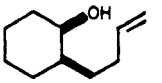


VII

The solvolyses of both the *cis* sulfonate ester VIII (R = $SO_2C_6H_4NO_2$) and the *trans* isomer I (R = $SO_2C_6H_4NO_2$) were examined under identical conditions, *i.e.*, 0.02 *M* solution of sulfonate ester in 100% formic acid containing pyridine (0.04 *M*) at 75° for 1 hr. The reactions were shown, by ultraviolet spectroscopy,[3] to have proceeded to the extent of 90% in the case of the *cis* and 95% in the case of the *trans* isomer. The products were treated with lithium aluminum hydride in order to cleave the formate esters and then analyzed, as previously described,[3] by vapor phase chromatography. The results in the *trans* series were quite similar to those previously obtained in 80% formic acid.[3] The total yield of alcohols was 62% and the composition of the mixture was 3% of V, 10% of VI, 57% of II, 8% of I (R = H), 5% of IV, 14% of III, and 3% of several minor unidentified components. There were no detectable amounts of the *cis*-2-decalols X and XI or of the *cis*-monocyclic alcohol IX. The yield of hydrocarbons was 13%. This fraction was a complex eight-component mixture of which 1-(Δ^3-butenyl)cyclohexene (VII) represented 50%. There were only trace quantities of materials having retention times in the region of the *cis*-octalins XII and XIII which, if present at all, were probably formed from acid-catalyzed cyclization of the diene VII (see below).



VIII



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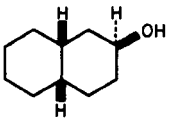
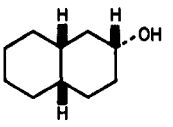
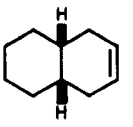


X



XI



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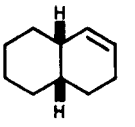
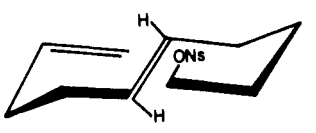
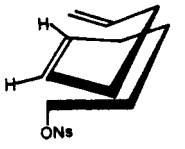


XIII

The solvolysis product of the *cis* sulfonate ester VIII (R = $SO_2C_6H_4NO_2$) afforded an alcohol fraction in 68% yield composed of 3% of V, 8% of VI, 56% of IX, 16% of VIII (R = H), 13% of an unresolved mixture of X and XI, and 4% of several minor unidentified products, none of which corresponded in retention time to either of the *trans*-2-decalols III or IV. There was a trace (<3%) of a component with the same retention time as authentic II. Vapor phase chromatography peak-enhancement experiments were employed for identification of these products in the *cis* series and, in addition, the components were separated by preparative vapor phase chromatography and identified by infrared spectroscopic comparison with authentic samples. The olefinic fraction, amounting to a 12% yield, consisted of 40% of VII and 60% of the mixture of octalins XII and XIII. The octalins were identified only by peak-enhancement experiments with an authentic mixture of the hydrocarbons produced by dehydration of *cis-syn*-2-decalol (XI).



B



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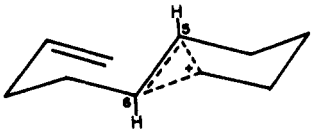

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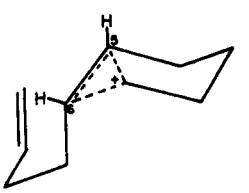

E

Since the cyclizations of the two isomeric sulfonate esters I and VIII (R = $SO_2C_6H_4NO_2$) proceed in exactly the opposite stereochemical sense, a common cationic

(7) W. S. Johnson, S. L. Gray, J. K. Crandall, and D. M. Bailey, *J. Am. Chem. Soc.*, **86**, 1966 (1964).

(8) Models suggest that the carbonium ion that would be formed first in the *cis* series would be the relatively unstable, flipped form of A with the butenyl side chain in the axial conformation. Implicit in the argument at hand is the assumption that the activation energy for the conversion of this cation into the equatorial form A is low compared with the activation energy for reaction of these ions with a nucleophile. Unfortunately this assumption appears to be completely open to question, and the consequences of its invalidity are taken into account in the discussion below.

intermediate cannot possibly be involved in both processes. If the solvolyses of both sulfonate esters proceed by the same basic mechanism—which is a reasonable assumption, particularly in view of the strikingly similar type of product distribution—then it follows that the cyclizations must either be concerted processes or involve cationic intermediates which retain the stereochemical integrity of the respective substrates. A decision between these latter two mechanisms is not possible, but the considerations set forth below have led us to a preference. It is reasonable (but not necessarily correct) to assume that the geometry of the transition states for the concerted bicyclization processes resembles more closely that of the ground-state conformations of the substrates in which all reacting centers are approximately within bond-forming distance, *i.e.*, formula B for the *trans* and C for the *cis* isomer, rather than the geometry of the respective bicyclic products. If this assumption is correct, then it is to be expected that the ratio of bicyclic to monocyclic product would be significantly lower in the *cis* than in the *trans* series, because molecular models show that there are very serious nonbonded interactions in the form C relative to B, which would render the former a high-energy species compared with the latter. These yield ratios, however, were in fact about 1.5:3.5 and 1.2:3.5, respectively.

The foregoing argument cannot be taken as unequivocal proof against the concerted process because of the assumptions involved. However, since the assumptions are reasonable, we are inclined to favor the alternative hypothesis, namely that intermediary species resembling the bridged cations D and E are involved in the solvolyses.[9] The activation energies for the reactions of the bridged cations (see below) would be expected to be comparable in the *cis* and *trans* series. Nucleophilic attack by the terminal olefinic bond of the cation D at C-5 on the side opposite the bridge yields *trans*-decalin derivatives, while similar attack by solvent yields the *trans*-butenylcyclohexanol (II). Attack by solvent at C-6 affords the butenylcyclopentylcarbinol VI. The butenylcyclohexene VII is envisaged as arising from collapse of the bridged ion to the secondary cation A followed by deprotonation. The tertiary alcohol V could be formed from cation A as the result of the thermodynamically favored hydride shift to give the tertiary cation, followed by attack of solvent. Similar arguments applied to the cation E account for the observed products in the *cis* series.

(9) It should be noted that we cannot rigorously exclude the possibility of the involvement, instead, of classical carbonium ions that react with nucleophiles much faster than they attain conformational equilibrium (see ref. 8). However, we prefer the bridged-ion hypothesis (see below, particularly footnote 10) which provides a satisfying rationalization of the stereospecificity of the cyclizations as well as a unifying treatment for explaining all of the products formed.

(10) S. Winstein and N. J. Holness [*J. Am. Chem. Soc.*, **77**, 5562 (1955)] have shown that the product of substitution formed on formolysis of *trans*-4-*t*-butylcyclohexyl *p*-toluenesulfonate was almost exclusively that resulting from inversion, namely the *cis* alcohol. In our case, in contrast, the substitution product in the *trans* series consisted predominantly of *trans* alcohol, suggesting the intermediacy of solvent-separated ion pairs or dissociated ions. Moreover, since the ratios of the alcohols II and IX produced in the solvolysis of the two cyclic sulfonate esters were comparable (3:1 and 2:1), it is reasonable to assume that the major pathway for their formation involves a common intermediate, namely the carbonium ion A. If this is the case, then attack of this ion by solvent is not stereospecific, and the case for a bridged ion intermediate in the solvolysis of the acyclic sulfonate esters finds support.

In an attempt to shed light on the fate of a carbonium ion such as A, we next turned our attention to the solvolysis of the *p*-nitrobenzenesulfonates of the butenylcyclohexanols II and IX. The *trans* alcohol II was prepared by the reaction of cyclohexene oxide with di-(Δ^3-butenyl)magnesium, and the product was converted into the *p*-nitrobenzenesulfonate, m.p. 37.5–39.5°. An authentic specimen of the *cis* alcohol IX was obtained by repeated preparative vapor phase chromatographic separation of the minor component produced on reduction of 2-(Δ^3-butenyl)cyclohexanone with tri-*t*-butoxyaluminum hydride. For preparative purposes the *cis* alcohol was produced from the aforementioned *trans* alcohol II by treating its tosylate with lithium acetate in dimethylformamide followed by reductive (lithium aluminum hydride) cleavage of the resulting acetate. The over-all yield of IX was low (17%) due to eliminative formation of diene VII which competed with the displacement reaction. Moreover, the product was contaminated with about 13% of the *trans* isomer II which was presumably formed either from a competing SN1 displacement reaction or by epimerization at the tosylate stage by internal return from an ion-pair intermediate. In any case this impure specimen of the *cis* alcohol IX was satisfactory for preparation of the *p*-nitrobenzenesulfonate which, after purification by recrystallization, melted at 54–56°.

The sulfonate esters of II and IX were essentially completely solvolyzed in formic acid buffered with pyridine by heating at 50° for 1 hr. In the *trans* series this treatment gave a 40% yield of diene VII and 36% of a mixture of alcohols having the following composition: 22% of V, 4% of VI, 12% of IX, 37% of II, 2% of III, and 8% of X and/or XI. The remaining 16% of alcohols was accounted for as unidentified materials corresponding to three peaks in the vapor phase chromatogram. The *cis* series gave 64% of diene VII and 31% of alcohol mixture composed of 86% of V, 4% of IX, 7% of II, and 2% of X and/or XI. Thus elimination to form diene VII and its hydration product V was the major process in the *trans* series and the almost exclusive reaction in the *cis* series. The very small yield (*ca.* 0.5%) of *cis*-decalols obtained in the *cis* series could well have arisen from the cyclization of VII (and V), a reaction which is known to be promoted by acetic–sulfuric acid.[7] In order to test this hypothesis, the behavior of the diene VII and carbinol V was examined under the solvolysis conditions. The *cis-syn*-2-decalol (XI) was indeed formed, and under conditions involving prolonged heating at 75° it was possible to realize yields of 21% from the diene VII and 25% from the carbinol V. These yields are very much higher than previously obtained by the sulfuric acid method,[7] and it is noteworthy that no trace of *trans*-decalin derivatives could be detected. (In view of these results, it seems probable that, despite the experiment to the contrary which should certainly be re-examined, the *cis*-decalols formed after a 6-hr. solvolysis of the *trans* sulfonate ester[3] were derived from V and VII.)

The results of the solvolysis of the sulfonate ester of the *trans* alcohol II suggest that the reaction proceeds, at least in part, *via* the cation A[10] which gives rise to, among other things, the *trans* alcohol II by

equatorial nucleophilic attack of solvent, and to the decalol III by similar intramolecular attack of the olefinic bond. Not more than one-fourth of the *cis*-decalols (X and/or XI) could have been formed from VII and V (see *cis* series above); therefore the remaining three-fourths presumably was the result either of some participation of the olefinic bond in the solvolysis and/or a competing *cis* cyclization of the cation A, which could result either from an axial attack of the olefinic bond on the cationic center or by equatorial ring closure of A in its flipped modification with the butenyl side chain in the axial conformation. The absence of any detectable *trans*-decalol among the products of the solvolysis in the ester of the *cis* alcohol IX suggests that considerably less, if any, of cation A is formed in this compared with the epimeric series.

The foregoing results suggest that the cyclization of the cation A does give *trans*-decalol, but it has not been possible to ascertain if this is the exclusive stereochemical course of the reaction. In any case it is clear that the solvolysis of cyclic sulfonate esters of alcohols like II and IX does not proceed with appreciable participation of the olefinic bond, and this observation rules out the synthetic use of such systems for the formation of bicyclic systems. The possibility remains, of course, that similar systems with poorer leaving groups than sulfonate esters may solvolyze with more participation of the olefinic bond.

In the hope of producing the bridged ions D and E by an alternative method, we examined the solvolysis of the *p*-nitrobenzenesulfonate, m.p. 35–37°, of Δ^3-butenylcyclopentylcarbinol (VI). The alcohol VI was prepared by the reaction of cyclohexene oxide with Δ^3-butenylmagnesium bromide, which in contrast to the dialkylmagnesium (see above), leads to the rearranged product.[11] The solvolysis product was given only cursory examination which was sufficient to show, however, that decalol formation was negligible. The alcoholic fraction had the following composition: 6% of V, 22% of VI, 3% of IX, 18% of II, a trace of X and/or XI, and 50% of an unidentified component. It is clear from these preliminary results that the intermediates in this reaction are not the same as those involved in the solvolysis of the acyclic sulfonates described above. The secondary nature of the sulfonate ester of VI probably minimizes the need for neighboring-group assistance in its ionization; hence we are probably dealing with simple cationic or S_N2 processes.

Experimental[12]

Preparation of Materials. ***cis*-5,9-Decadienol (VIII, R = H).**—A solution of 1.00 g. of freshly distilled 5,9-decadiynol[3] and 44 mg. of pyridine in 25 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 98 mg. of Lindlar catalyst.[13] After 13.7 mm. (corrected to STP) of gas was absorbed, the hydrogenation was interrupted. The reaction mixture was filtered, and the filtrate was concentrated at 80° (0.5 mm.) to give 0.82 g. of a colorless oily residue which was shown by gas chromatography to be a 4:1 mixture of two components. The major component was separated by preparative gas chromatography on a Carbowax column and was shown to be the dienol, λ_{max}^{film} 3.00, 6.09, 10.04, and 10.96 μ. Evaporative distillation at 70° (0.03 mm.) gave a colorless oil, $n^{20}D$ 1.4637, which on gas chromatography on a TCEP column at 145° showed a single peak with a significantly different retention time from that of the *trans* isomer.[3]

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.9; H, 11.8.

***cis*-5,9-Decadienyl *p*-Nitrobenzenesulfonate (VIII, R = $SO_2C_6H_4NO_2$).**—To a solution of 692 mg. of the aforementioned *cis*-dienol in 4 ml. of dry pyridine at −15° was added 1.00 g. of *p*-nitrobenzenesulfonyl chloride. The mixture was shaken to dissolve the acid chloride and was then allowed to stand at −15° for 3 hr. It was then poured into 50 ml. of ice–water containing 4 ml. of concentrated hydrochloric acid, and the resulting mixture was extracted with ether. The combined extracts were washed with water, saturated sodium bicarbonate, followed by saturated brine, and then dried over anhydrous magnesium sulfate. The crude oily residue obtained on removal of the solvent at reduced pressure was dissolved in ether–petroleum ether (b.p. 60–68)° and filtered through a short column of Florisil to give 1.25 g. (82%) yield of pale yellow oily sulfonate ester. Low-temperature recrystallization of this material twice from pentane gave 0.25 g. of pale yellow plates, m.p. 26.5–27°.

Anal. Calcd. for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.5; H, 6.4; N, 4.4.

***trans*-2-(Δ^3-Butenyl)cyclohexanol (II).**—To the Grignard reagent from 1.6 g. of magnesium turnings and 10.0 g. of 4-bromo-1-butene[14] in 75 ml. of anhydrous ether was added dropwise 7 ml. of anhydrous dioxane over a 0.5-hr. period. The resulting slurry was stirred overnight; then a solution of 3.0 g. of cyclohexene oxide in 5 ml. of ether was added dropwise to the stirred reaction mixture at 0° over a 30-min. period. After 4 hr. (stirring) the reaction mixture was poured into 300 ml. of cold saturated ammonium chloride solution, and the aqueous layer was extracted with ether. The combined organic layers were washed with 15% potassium hydroxide solution, then with water, followed by saturated brine, and finally dried over anhydrous magnesium sulfate. The residue obtained on removal of the solvent under reduced pressure was distilled through a 5-in. Vigreux column to give 2.09 g. (44% yield) of colorless liquid, b.p. 106–111° (20 mm.). The infrared spectrum of this material was identical in every respect with that of authentic II.[3] Gas chromatography indicated a purity of 97%.

The ***p*-nitrobenzenesulfonate** was prepared by adding 490 mg. of *p*-nitrobenzenesulfonyl chloride to an ice-cold solution of 338 mg. of the alcohol II in 5 ml. of pyridine. The mixture was allowed to stand in the refrigerator at 5° overnight; then the product was isolated as described above (including the Florisil treatment) for the decadienyl sulfonate ester. Crystallization of the crude oily product from pentane gave 397 mg. (53% yield) of pale yellow needles, m.p. 38–39°. Two recrystallizations raised the melting point to 37.5–39.5°.

Anal. Calcd. for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24. Found: C, 56.8; H, 6.4.

***cis*-2-(Δ^3-Butenyl)cyclohexanol (IX). A. From 2-(Δ^3-Butenyl)cyclohexanone.**—A solution of 1.00 g. of this ketone[15] in 10 ml. of anhydrous ether was added to a stirred slurry of 5.0 g. of lithium tri-*t*-butoxyaluminum hydride in 60 ml. of ether at −78°. Stirring was continued as the reaction mixture was allowed to come to room temperature. After a total of 8 hr., 2 ml. of water was added dropwise, followed by a small amount of anhydrous magnesium sulfate. The mixture was stirred for a short while, then filtered, and the insoluble salts were washed several times with ether. The combined filtrate and washings were concentrated at reduced pressure to give a colorless oil. Gas chromatographic analysis on a TCEP column indicated a 33:67 ratio of the *cis* to *trans* alcohols, respectively. The minor

(11) *Cf.* N. G. Gaylord and E. I. Becker, *Chem. Rev.*, **49**, 413 (1951).

(12) Melting points were determined on a Kofler hot-stage microscope. Analytical gas chromatographic determinations were performed on Aerograph Hy-Fi gas chromatographs (Models A-600B and A-600C) equipped with hydrogen flame ionization detectors. Relative peak areas were determined with a disk chart integrator. The following 0.125-in.-diameter columns were used: a 5-ft. column of 15% Carbowax 20M (Carbowax), a 5-ft. column of 15% Craig succinate ester (Craig), and a 5-ft. column of 15% 1,2,3-tris-(2-cyanoethoxy)propane (TCEP). An Aerograph Autoprep (Model A-700) chromatograph was used for the preparative separations. The following 20 ft. × 0.375 in. columns were used: 20% Carbowax 20M (Carbowax), 15% polyethylene glycol succinate (PEGS), and 20% phenyldiethanolamine succinate (PDEAS).

(13) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(14) This halide was prepared from the corresponding alcohol according to the procedure of F. B. LaForge, N. Green, and W. A. Gersdorff [*J. Am. Chem. Soc.*, **70**, 3707 (1948)] for the preparation of 5-bromo-1-pentene.

(15) See footnote 21 of ref. 3

component was isolated by two passes through a PDEAS preparative gas chromatography column. Rapid short-path distillation at 100° (0.1 mm.) gave a pure sample, $n^{20}D$ 1.4770. Analytical gas chromatography on a TCEP column indicated this to be a single substance free of the *trans* isomer.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.9; H, 11.8.

B. From *trans*-2-(Δ^3-Butenyl)cyclohexanol.—To an ice-cold solution of 2.09 g. of the *trans* alcohol II, prepared as described above, in 10 ml. of pyridine was added 2.60 g. of *p*-toluenesulfonyl chloride. After standing in the refrigerator for 24 hr., the reaction mixture was poured into ice–water containing 11 ml. of concentrated hydrochloric acid; it was then extracted with ether. The combined organic layers were washed with water, followed by saturated sodium bicarbonate solution, and then dried over anhydrous magnesium sulfate. The crude oily tosylate (3.77 g.) obtained on removal of the solvent under reduced pressure was dissolved in 50 ml. of dimethylformamide; then 4.0 g. of lithium acetate was added. The heterogeneous mixture was allowed to stand overnight at room temperature and then was warmed on a steam bath for 24 hr. The reaction mixture was diluted with water and extracted with pentane. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was dissolved in 100 ml. of ether, 1.0 g. of lithium aluminum hydride was added, and the mixture was stirred at room temperature for 1 hr. Four milliliters of water was added dropwise with cooling, and the resulting slurry was filtered. Removal of the solvent at reduced pressure gave a mobile, colorless oil which consisted to two major products. The bulk of the material was 1-(Δ^3-butenyl)cyclohexene as determined by preparative gas chromatography on a PEGS column and by infrared comparison. The alcohol fraction was also isolated, and it consisted of 352 mg. (17% yield) of an 87:13 mixture of *cis*- and *trans*-butenylcyclohexanol. This material was used to prepare the *p*-nitrobenzenesulfonate ester.

The ***p*-nitrobenzenesulfonate** was prepared from 194 mg. of the aforementioned crude alcohol according to the method described above. The reaction was conducted at −15° for 22 hr. Crystallization of the crude product from pentane gave 151 mg. (35% yield) of pale yellow crystals, m.p. 50–54°. Recrystallization afforded pale yellow rhombic crystals, m.p. 54–56°.

Anal. Calcd. for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24. Found: C, 56.8; H, 6.4.

Δ^3-Butenylcyclopentylcarbinol (VI).—To the Grignard reagent from 1.0 g. of magnesium turnings and 6.0 g. of 4-bromo-1-butene[14] in 40 ml. of ether was added dropwise a solution of 4.0 g. of cyclohexene epoxide in 10 ml. of ether with stirring and cooling (ice bath). The mixture was allowed to stir overnight at room temperature; then saturated ammonium chloride solution was added until the initially precipitated salts redissolved. The aqueous layer was extracted with ether. The combined organic layers were washed with water, then with saturated sodium bicarbonate solution, and finally dried over anhydrous magnesium sulfate. The residue obtained on removal of the solvent at reduced pressure was distilled through a 5-in. Vigreux column to give 1.78 g. (28% yield) of colorless liquid, b.p. 101–105° (15 mm.). Further purification was effected by preparative gas chromatography on a PEGS column. Gas chromatography showed that this material contained none of the butenylcyclohexanol. The infrared spectrum was identical with that of authentic butenylcyclopentylcarbinol (VI).[3]

The ***p*-nitrobenzenesulfonate** was prepared according to the procedure described above. The reaction was conducted at 5° overnight. The product crystallized from pentane in the form of pale yellow needles, m.p. 35–37°. It was an unstable substance, decomposing on storing at room temperature.

Anal. Calcd. for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24. Found: C, 57.0; H, 6.2.

Cyclization Studies. A. Formolysis of *cis*-5,9-Decadienyl *p*-Nitrobenzenesulfonate (VIII, R = $SO_2C_6H_4NO_2$).—To a stirred solution of 0.025 ml. of pyridine (0.04 *M*) in 7.5 ml. of formic acid[16] at 75 ± 2° was added 47 mg. (0.019 *M*) of the sulfonate ester, m.p. 26.5–27°. The solution was maintained at this temperature for 1 hr., cooled to 0°, and poured into 50 ml. of ice–water. The mixture was saturated with salt and extracted five times with pentane. The combined organic layers were washed with saturated sodium bicarbonate solution, then with saturated brine, and dried over anhydrous magnesium sulfate. Most of the solvent was removed by distillation through a 15-in. Vigreux column. The residue was diluted to 50 ml. with ether in a volumetric flask, and an aliquot was removed for ultraviolet spectroscopic analysis for unreacted starting material as previously described.[3] The reaction was shown in this way to have proceeded 90% to completion. The remaining solution was stirred with 0.2 g. of lithium aluminum hydride for 1 hr. Water was added dropwise with cooling to decompose the excess hydride, and then enough 10% sulfuric acid was added with cooling to dissolve the precipitated salts. The aqueous layer was extracted with four small portions of ether. The combined organic layers were washed with saturated sodium bicarbonate solution, then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation through a 15-in. Vigreux column, and the residue was diluted with ether to 5 ml. in a volumetric flask. Yield data were obtained by gas chromatographic analysis on a Carbowax column using column temperatures of *ca.* 150 and 80° for the alcoholic and olefinic products, respectively. Details on chromatographic behavior of the various components have already been reported.[3] The absolute yield of alcohols was determined, by the method already described,[3] to be 68%. A known solution of *cis-syn*-2-decalol was employed as an internal standard, and equivalent detector response was assumed for the isomeric alcohols. The individual alcohols were identified by peak enhancement with authentic materials,[3] and the proportions of these components were 3% of V, 8% of VI, 56% of IX, 16% of VIII (R = H), 13% of an inseparable mixture of X and XI, and several unidentified components comprising 4% of the mixture. The absolute yield of olefinic products was determined, by the method already described,[3] to be 12%. 1-(Δ^3-Butenyl)cyclohexene was used as a calibration standard, and equal detector response was assumed for the isomeric olefins. The chromatogram showed three peaks in the relative proportions of 40:32:28. The preponderant material was identified, by peak enhancement, as 1-(Δ^3-butenyl)-cyclohexene, while the other two are tentatively assigned *cis*-octalin structures since their retention times corresponded with those of the two olefins obtained by the potassium bisulfate dehydration of *cis-syn*-2-decalol (XI). There was no evidence for the presence of the *trans*-2-decalols, and only a trace (<3%) of IX was present.

In a larger scale experiment, a solution of 1.04 g. of the sulfonate ester and 0.47 ml. of pyridine in 150 ml. of formic acid was heated for 2 hr. at 75°. The mixture was processed, and the product was isolated and treated with lithium aluminum hydride in the manner described above, to yield 425 mg. of crude oily product. Gas chromatographic analysis (see above) indicated an 88% yield of the following alcohols in the proportions given: 9% of VI, 57% of IX, 13% of VIII, 15% of unresolved X and XI, and 7% of four unidentified components. No detectable quantities of III and IV were present, and only a trace of II was observed. These products were separated by preparative gas chromatography on a Carbowax column. The infrared spectra of the above-mentioned components were identical with those of the corresponding authentic specimens.[3] The infrared spectrum of the fraction composed of a mixture of the *cis*-decalols X and XI indicated them to be present in a ratio of approximately 3:1.

B. Formolysis of *trans*-5,9-Decadienyl *p*-Nitrobenzenesulfonate (I, R = $SO_2C_6H_4NO_2$).—A 49-mg. specimen of this ester, m.p. 40–41.5°, was solvolyzed in 7.5 ml. of anhydrous formic acid containing 0.025 ml. of pyridine exactly as described above for the *cis* isomer. After a 1-hr. reaction period the reaction was 95% complete. The absolute yield of alcohols was 62% and consisted, as shown by correspondence with previous gas chromatographic data,[3] of the following products in the relative proportions indicated: 3% of V, 10% of VI, 57% of II, 8% of I (R = H), 5% of IV, 14% of III, and a total of 3% of several unidentified components. There were no detectable amounts of IX or of the *cis*-2-decalols among the products. The olefinic products were present in 13% yield and showed eight peaks in the gas chromatogram. The major peak corresponded to VII which accounted for 50% of the olefins. Only a trace of *cis*-octalin product could possibly be present among the other peaks.

C. Formolysis of *trans*-2-(Δ^3-Butenyl)cyclohexyl *p*-Nitrobenzenesulfonate.—To a stirred solution of 0.025 ml. of pyridine in 7.5 ml. of anhydrous formic acid at 50 ± 2° was added 55 mg. of

(16) The anhydrous formic acid was prepared by distillation from boric anhydride; see H. I. Schlesinger and A. W. Martin, *J. Am. Chem. Soc.*, **36**, 1589 (1914).

the sulfonate ester, m.p. 37.5–39.5°. After 1 hr. at this temperature, the mixture was processed as described above under part A. The sulfonate ester was essentially completely consumed. Product analysis for the alcohols was performed on the TCEP column at about 150°, and the components were identified by their characteristic retention times. The absolute yield, determined as described above, of total alcohols was 36%, and consisted of the following proportions of individual components: 22% of V, 4% of VI, 12% of IX, 37% of II, 2% of III, 8% of X and/or XI, and 16% of three unidentified components. The olefin fraction was analyzed on Carbowax at about 90° and consisted of a single product (40% yield), namely the diene VII which was identified by its retention time.

D. Formolysis of *cis*-2-(Δ^3-Butenyl)cyclohexyl *p*-Nitrobenzenesulfonate.—To a stirred solution of 0.025 ml. of pyridine in 7.5 ml. of anhydrous formic acid at 50 ± 2° was added 51 mg. of the sulfonate ester, m.p. 54–56°. After 1 hr. the product was processed as described above in section A. The reaction was essentially complete. The alcohols were analyzed as described above, section C, and the absolute yield of total alcohols was 31%, consisting of the following proportions of individual components: 86% of V, 4% of IX, 7% of II, and 2% of X and/or XI. Analysis for olefins on a Carbowax column at *ca.* 80° showed a single peak corresponding to a 64% yield of the diene VII. The identity of these products was based on retention time data.

E. Formolysis of Δ^3-Butenylcyclopentylcarbinyl *p*-Nitrobenzenesulfonate.—A solution of 49 mg. of the sulfonate ester, m.p. 35–37°, and 0.025 ml. of pyridine in 7.5 ml. of anhydrous formic acid was heated for 1 hr. at 50 ± 2°. The mixture was processed as described above, section A. Analysis of the alcohol fraction as described above, section C, showed the following relative proportions of products: 6% of V, 22% of VI, 3% of IX, 18% of II, a trace of X and/or XI, and 50% of an unidentified alcohol which was not one of the 2-decalols. The identities of these components were established by peak-enhancement experiments. The hydrocarbon fraction was not examined.

Treatment of 1-(Δ^3-Butenyl)cyclohexene (VII) with Formic Acid.—A solution of 286 mg. of the diene[3] and 0.025 ml. of pyridine in 16 ml. of anhydrous formic acid was heated to 75° for 11.5 hr. under a nitrogen atmosphere. The product was processed and analyzed as for a solvolysis reaction (see description above under section A of the formolysis studies). Analysis of the alcohols on the Craig column indicated a total yield of 42% consisting of the following components in the specified proportions: 5% of V, 15% of an unidentified alcohol, 20% of a second unidentified alcohol, and 50% of XI. The remaining 10% was accounted for as six minor peaks in the gas chromatogram. Detectable amounts of *trans*-2-decalols were not observed. Analysis for olefins on the Carbowax column indicated a total yield of 19%. About 50% of this fraction corresponded to starting material, and the remainder was accounted for as four peaks in the gas chromatogram. The alcohols were separated by preparative gas chromatography on the PEGS column and examined by infrared methods. The unidentified alcohols corresponded with those obtained previously in the sulfuric–acetic acid cyclization.[7] Compound XI was obtained as a crystalline solid, m.p. 96–101° (lit.[17] m.p. 104°).

When a shorter reaction time (3.5 hr.) was used, the area under the peak corresponding to the tertiary carbinol V increased while that of the other alcohol peaks decreased. The absolute yield of decalol XI was 7%.

Treatment of 1-(Δ^3-Butenyl)cyclohexanol (V) with Formic Acid.—A solution of 341 mg. of the carbinol[3] and 0.025 ml. of pyridine in 15 ml. of anhydrous formic acid was heated for 21 hr. at 75°. The mixture was processed and the product was analyzed as in the preceding experiment. The gas chromatographic pattern for the alcohols was very similar to that obtained in the preceding experiment. About 50% of the alcohol mixture corresponded to the decalol XI, and the absolute yield of this material was 25%. The major alcohols were identified by preparative gas chromatographic separation and infrared spectral examination.

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(17) See R. P. Linstead, A. B. L. Wang, J. H. Williams, and K. D. Errington, *J. Chem. Soc.*, 1136 (1937).

The Reformatsky Reaction. I. Zinc and Ethyl α-Bromoisobutyrate*

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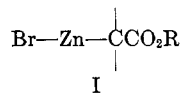
The behavior of the Reformatsky reagent prepared discretely from zinc and ethyl α-bromoisobutyrate in ether–benzene has been examined. Titration with a standard solution of fluorenone and vapor phase chromatography demonstrate that under normal conditions approximately 70% of active reagent is produced along with some 30% of a dimeric substance which affords ethyl isobutyrylisobutyrate on work-up. This dimeric product may be produced by zinc reduction of ethyl γ-bromoisobutyrylisobutyrate, whose presence in small amounts may be demonstrated on work-up, but it is shown that it can also be produced from the active reagent alone, with the elimination of the elements of ethoxyzinc bromide. The adduct formed from this reagent and 9-fluorenone in an instantaneous reaction is unusually prone to decompose into the ketone and ethyl isobutyrate on treatment with even weak bases. This suggests that the initial adduct has little ionic character in the β-oxido portion, and the infrared spectrum of a solution of the adduct implies a zinc chelate structure.

Two extreme views of the precise nature of Reformatsky reagent are possible: the older and more common view being that of an analog (I) of the classical Grignard reagent,[3] and a more recent view being that of the



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bromozinc enolate of an ester[4] (II). The latter view is implicit in arguments concerning the parallelism between the Reformatsky reaction and the Ivanov reaction[4] with which the paper cited deals explicitly.

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(2) Summer participant, National Science Foundation Grant 22898, 1963.

(3) R. L. Shriner in *Org. Reactions*, **1**, 1 (1942).

(4) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).