

studies on the rates of acylation and deacylation reactions of α -chymotrypsin and find them consistent with possible participation of a general acid species of pK_a above 13.9.¹⁷ While no claim is intended here for the presence of a catechol group in the active site of any enzyme, these observations do suggest the involvement of a general acid species.

No catalysis of ethyl acetate hydrolysis by catechol anion was observed under the conditions of this work.

(17) M. L. Bender, *J. Am. Chem. Soc.*, **84**, 2582 (1962).

This may indicate that the action of the catalyst is essentially nucleophilic, since ethyl acetate is not sensitive to nucleophilic agents.¹⁸ It does mean that catechol anion cannot compare favorably with chymotrypsin for increasing the rate of an "unactivated" ester hydrolysis reaction.

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(18) W. P. Jencks and J. Carriolo, *ibid.*, **83**, 1743 (1961).

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Proximity Effects. XXXIII. Solvolysis of *trans*-Bicyclo[6.1.0]nonane^{1,2}

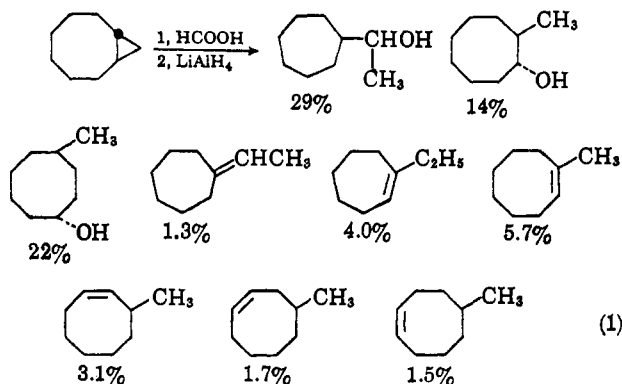
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trans-Bicyclo[6.1.0]nonane has been synthesized stereospecifically from *trans*-cyclooctene. Its solvolysis in formic acid resulted in several transannular reactions.

The stereospecific formation of *trans*-cyclooctene oxide from *trans*-cyclooctene has led us to investigate the possibility of preparing *trans*-bicyclo[6.1.0]nonane, which has the interesting structural feature of a *trans*-fused cyclopropane ring. The method of choice was irradiation of the pyrazoline formed by reaction of *trans*-cyclooctene with diazomethane. The over-all yield of *trans*-bicyclo[6.1.0]nonane was 23%.⁴ The structure was proved by elemental analysis and by spectral evidence.

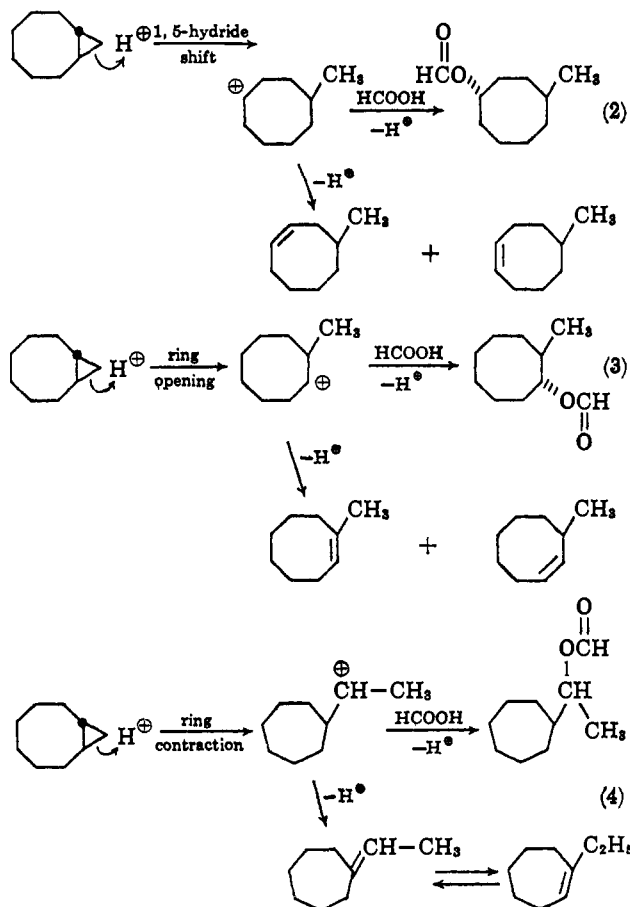
The cyclopropane ring was cleaved by shaking *trans*-bicyclo[6.1.0]nonane with formic acid at room temperature for one week. Lithium aluminum hydride reduction of the product mixture gave a mixture of alcohols and olefins in 85% yield. The products, identified by comparison of their infrared spectra and gas chromatographic retention times with those of authentic samples, are shown in eq. 1. A small portion (2–3%) of the products was unidentified.



α -Methylcycloheptanemethanol was synthesized by lithium aluminum hydride reduction of cycloheptyl methyl ketone, formed by the reaction of cycloheptanecarboxylic acid with methyllithium. Ethylidenecycloheptane was synthesized from cycloheptanone and triphenylphosphinethylidene. 1-Ethylcycloheptene was the major product of dehydration of the 1-ethylcyclo-

heptanol formed from cycloheptanone and ethylmagnesium iodide. The remaining products will be described in the next paper of this series.⁵

Initial cleavage of the cyclopropane ring followed by ring contraction or hydride shifts could lead to the observed products as shown in eq. 2, 3 and 4.



The formates of *trans*-2-methylcyclooctanol and *trans*-4-methylcyclooctanol could most likely arise from attack by formic acid concerted with a 1,3- or 1,5-hydride shift, respectively.

Experimental⁶

trans-Bicyclo[6.1.0]nonane.—A solution of diazomethane in ether was prepared by addition of a solution of 70 g. of sodium

(1) Supported by a research grant (NSF-G5055) of the National Science Foundation.

(2) Paper XXX11: A. C. Cope and J. K. Hecht, *J. Am. Chem. Soc.*, **84**, 4872 (1962).

(3) Procter and Gamble Fellow, 1961–1962; National Science Foundation Summer Fellow, 1962.

(4) Reaction of *trans*-cyclooctene with methylene iodide–zinc–copper couple gave 80% of *cis*-bicyclo[6.1.0]nonane and 20% of the *trans* isomer.

(5) A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.*, in press.

hydroxide in 105 ml. of water to a suspension of 17.5 g. of bis-*N*-methyl-*N*-nitrosterephthalamide (du Pont EXR-101) in 500 ml. of ether followed by distillation. *trans*-Cyclooctene (1.56 g.) was added and the mixture was allowed to stand at room temperature for 24 hr. The ether and excess diazomethane were removed in a stream of nitrogen to a volume of 100 ml. Filtration and concentration afforded 2.12 g. (98%) of the crude light yellow pyrazoline, n_D^{25} 1.5005.

A 1.60-g. sample of the pyrazoline was dissolved in 80 ml. of ether and irradiated for 3 hr. with a quartz-contained mercury arc (Labortouchelampe S 81'', Quartzlampengesellschaft Hanau). The entire apparatus was immersed in a constant-temperature bath at 21°. After removal of the ether, collection on a silicone oil column at 100° gave 0.32 g. (24%) of *trans*-bicyclo[6.1.0]nonane, n_D^{25} 1.4665. The n.m.r. spectrum of *trans*-bicyclo[6.1.0]nonane showed a multiplet (4H) at 9.75 τ (cyclopropane) and a multiplet (12H) at 8.29 τ (methylene) and no vinyl protons. The infrared spectrum of this compound had bands at 3040, 2960 and 1020 cm^{-1} (cyclopropane).

Anal. Calcd. for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 86.82; H, 13.11.

Reaction of *trans*-Bicyclo[6.1.0]nonane with Formic Acid.—*trans*-Bicyclo[6.1.0]nonane (0.32 g.) was shaken with 2.0 ml. of 98–100% formic acid for 160 hr. at room temperature. Ether (40 ml.) was added and this solution was washed with three 30-ml. portions of saturated sodium bicarbonate solution. The aqueous layer was extracted with 20 ml. of ether. The combined ether extracts were dried over magnesium sulfate and added to a suspension of 0.40 g. of lithium aluminum hydride in 40 ml. of ether. The reaction mixture was allowed to stand for 2 hr. at room temperature, and the excess hydride was decomposed with water and 10% sulfuric acid. The ether layer was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated. The mixture of products (0.33 g.) was chromatographed over 15 g. of neutral activity I alumina. Elution with 100 ml. of pentane gave 0.06 g. (19%) of hydrocarbons. Subsequent elution with 10% methanol in ether gave 0.25 g. (66%) of alcohols. The alcohols were separated on a TCEP column⁸ at 135° and were identified by comparison of their infrared spectra and retention times with those of authentic samples as α -methylcycloheptanemethanol (29%), *trans*-2-methylcyclooctanol (14%) and *trans*-4-methylcyclooctanol (22%). The alcohol fraction contained several minor components (totaling 1–2%) which were separated poorly on TCEP and were not identified. The hydrocarbons were separated by gas chromatography on an NMPN column⁹ at 35° and on a silver nitrate-tetraethylene glycol column at 52°. They were identified by comparison of their infrared spectra with those of authentic samples as 1-methylcyclooctene (5.7%), 3-methylcyclooctene (3.1%), 4-methylcyclooctene (1.7%), 5-methylcyclooctene (1.5%), 1-ethylcycloheptene (4.0%) and ethylidenecycloheptane (1.3%). There was in addition an unidentified hydrocarbon fraction (1.7%).

Chromic Acid Oxidation of the Alcohol Fraction.—A 70-mg. sample of the mixture of alcohols was dissolved in 1 ml. of acetone and titrated to an orange-brown end-point with an 8 *N* solution of chromic acid. Water (3 ml.) was added and the resulting mixture was extracted with three 2-ml. portions of ether. The combined ether extracts were washed with 1 ml. of water, 1 ml. of saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated, giving 30 mg. (45%) of ketones. The product was fractionated on a TCEP column⁸ at 135° and gave two peaks. The smaller one (31%) was identified as 4-methylcyclooctanone by comparison of its infrared spectrum and retention time with those of an authentic sample. The major

(8) Melting points are corrected and boiling points are uncorrected. Analyses were performed by Dr. S. M. Nagy and his associates. The equipment used for gas chromatography is described by A. C. Cope and P. E. Peterson, *J. Am. Chem. Soc.*, **81**, 1643 (1959), footnote 24.

(7) The product was shown by gas chromatography (silicone oil, 100°) to be free of the *cis* isomer.

peak (69%) was shown by comparison of infrared spectra to be a mixture of 2-methylcyclooctanone and cycloheptyl methyl ketone.

Cycloheptyl Methyl Ketone.⁸—A solution of 5.5 g. of methyl iodide in 20 ml. of ether was added to 0.79 g. of lithium wire in 20 ml. of ether at such a rate as to maintain mild refluxing, and the mixture was stirred for an additional hour. The resulting solution of methyllithium was filtered and added over a period of 0.5 hr. to a solution of 1.15 g. of cycloheptanecarboxylic acid in 20 ml. of ether. This mixture was stirred for 0.5 hr. and then poured over 40 g. of crushed ice. The product was isolated by extraction with 20 ml. of ether, dried over magnesium sulfate and concentrated. Distillation through a semimicro column gave 0.46 g. of cycloheptyl methyl ketone, b.p. 92–94° (37 mm.). The ketone formed a 2,4-dinitrophenylhydrazone, m.p. 115.5–116.4° (lit.¹⁰ m.p. 117–118°).

α -Methylcycloheptanemethanol.—A solution of 0.30 g. of cycloheptyl methyl ketone in 3 ml. of ether was added to a suspension of 0.30 g. of lithium aluminum hydride in 5 ml. of ether and the mixture was allowed to stand for 10 min. at room temperature. Water and 10% sulfuric acid were added and the product was extracted with 10 ml. of ether. The ether solution was washed with saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated, giving 0.29 g. (95%) of α -methylcycloheptanemethanol. A sample collected from a silicone grease column at 155° had n_D^{25} 1.4731.

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}$: C, 76.00; H, 12.75. Found: C, 75.71; H, 12.89.

The 3,5-dinitrobenzoate had m.p. 74.5–75.4° after two recrystallizations from pentane.

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_6$: C, 57.13; H, 5.99. Found: C, 56.92; H, 5.80.

Ethylidenecycloheptane.—To a suspension of 4.08 g. of ethyltriphenylphosphonium bromide in 55 ml. of ether was added 5.8 ml. of a 1.76 *M* solution of methyllithium in ether. The solution was stirred for 1 hr., after which 1.62 g. of cycloheptanone was added and the mixture was refluxed for 1 hr. The ether was distilled, 100 ml. of pentane was added, and the solution was filtered through 20 g. of neutral alumina (activity I). Concentration gave 0.97 g. (82%) of ethylidenecycloheptane. A sample collected from a silicone grease column at 140° had n_D^{25} 1.4685.

Anal. Calcd. for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 87.03; H, 13.06.

Reaction of Cycloheptanone with Ethylmagnesium Iodide.—A solution of 4.04 g. of cycloheptanone in 20 ml. of ether was added to the Grignard reagent prepared from 7.02 g. of ethyl iodide and 1.08 g. of magnesium in 40 ml. of ether. The mixture was stirred at room temperature for 0.5 hr. Water (10 ml.) and 5% sulfuric acid (20 ml.) were added and the ether layer was concentrated. Sodium bisulfate (8 g.) was added, and the resulting mass was heated at 100° for 0.5 hr. Distillation gave 2.71 g. (60%) of an olefin mixture, b.p. 152–156°. Gas chromatography on NMPN⁶ at 35° showed that it consisted of ethylidenecycloheptane (24%) and 1-ethylcycloheptene (76%).¹¹ A sample of 1-ethylcycloheptene collected by gas chromatography had n_D^{25} 1.4606.

Anal. Calcd. for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 86.75; H, 12.99.

Acknowledgment.—The authors are grateful to Dr. Thomas Van Auken for his help in the synthesis of *trans*-bicyclo[6.1.0]nonane.

(8) The procedure is similar to that of J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).

(9) The product contained water which presumably arose from dehydration of α,α -dimethylcycloheptanemethanol formed as a by-product.

(10) S. L. Friess and R. Pinson, Jr., *J. Am. Chem. Soc.*, **74**, 1302 (1952).

(11) Dehydration of the Grignard reaction product with iodine gave 67% of 1-ethylcycloheptene and 33% of ethylidenecycloheptane. Equilibration of ethylidenecycloheptane with formic acid gave 64% of 1-ethylcycloheptene.