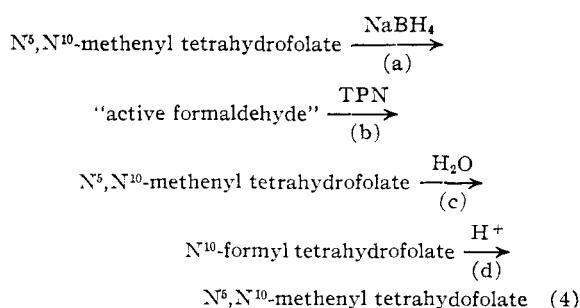


hydrofolic dehydrogenase system. This latter point is also demonstrated in Fig. 5. When the borohydride reduction product (curve 2) was treated with TPN and hydroxymethyl tetrahydrofolic dehydrogenase (containing cyclohydrolase²²), the absorption spectrum changed to that of curve 3. The decrease in light absorption at 300 m μ and the increase in the region of 260 m μ are indicative of N¹⁰-formyl tetrahydrofolate⁴⁶ formation, although the spectrum is obscured by the contribution due to the unreacted "active formaldehyde." Only 50% of the "active formaldehyde" would be reactive, due to the asymmetric carbon atom at the C⁶-position. The appearance of the absorption band at 355 m μ , characteristic of N⁵,N¹⁰-methenyl tetrahydrofolate, after acidification of the cell contents (curve 4), confirmed that the product of the *enzymic* oxidation was N¹⁰-formyl tetrahydrofolate. The above sequence of reactions is summarized in equation 4: steps (a) and (d) are non-enzymic, while (b) and (c) are enzymic.

The product of the borohydride reduction of N⁵,N¹⁰-methenyl tetrahydrofolate was more conclusively identified as "active formaldehyde" by a detailed examination of its reactivity in the hydroxymethyl tetrahydrofolic dehydrogenase system at pH 9.5. As shown in Fig. 6, synthetic "active formaldehyde" was an effective substrate for TPN reduction, and the amount of TPNH produced (0.35 μ mole) was equal to the theoretical maximum, *i.e.*, 50% of the "active formaldehyde"

(46) At the pH employed, the cyclohydrolase-catalyzed equilibrium of N⁵,N¹⁰-methenyl tetrahydrofolate and N¹⁰-formyl tetrahydrofolate lies far in the direction of the latter compound (see ref. 22).



added (0.70 μ mole). Under the same conditions, the borohydride reduction product was also quantitatively oxidized by TPN: 0.17 μ mole of TPNH were formed after the addition of 0.35 μ mole of borohydride-treated N⁵,N¹⁰-methenyl tetrahydrofolate to the reaction mixture, and the addition of a second, equal increment of the borohydride product led to the formation of a second equal increment of TPNH. A mixture of tetrahydrofolate and formaldehyde was, however, almost completely inactive, since the rate of adduct formation is low at this pH. It could be concluded, therefore, that "active formaldehyde" was formed *quantitatively* by the chemical reduction of N⁵,N¹⁰-methenyl tetrahydrofolate. Since NaBH₄ reduction was specific for N⁵,N¹⁰-methenyl tetrahydrofolate, additional evidence is provided for the contention that the N⁵,N¹⁰-bridge structure is retained during reduction to the formaldehyde level. A hydride-ion mechanism has been presented recently⁴² for the enzymic or chemical interconversion of "active formaldehyde" and "active formate."

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

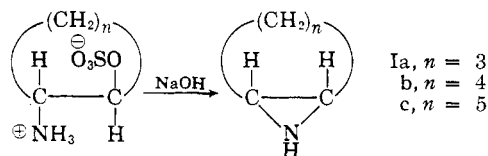
Chemistry of Ethylenimine. VII. Cyclooctenimine or 9-Azabicyclo[6.1.0]nonane¹

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Reaction of *trans*-2-aminocyclooctyl hydrogen sulfate with aqueous sodium hydroxide gives a mixture of cyclooctanone and the expected *cis*-cyclooctenimine. Formation of the two products is rationalized in terms of two alternative, energetically nearly equivalent transition states analogous to those proposed for the Hofmann elimination of cyclooctyltrimethylammonium hydroxide. Pyrolysis of N-(*p*-nitrobenzoyl)-cyclooctenimine (IIc) in toluene yields *cis*-N-(*p*-nitrobenzoyl)-3-cyclooctenylamine (V) and an isomeric oxazoline (VII). Formation of V from IIc is sterically and mechanistically analogous to the formation of *cis*-cyclooctene by the pyrolysis of cyclooctyldimethylamine oxide.

Previous papers in this series have described the preparation of cyclopentenimine (Ia),³ cyclohexenimine (Ib)⁴ and cycloheptenimine (Ic)⁵ by the treatment of the corresponding *trans*-2-aminocycloalkyl hydrogen sulfates with aqueous sodium hydroxide. Since these small carbocycles cannot accommodate a three-membered ring fused *trans*, the imines were assigned the *cis* configuration and the closure of the aziridine ring therefore must have occurred in each instance with inversion at the substituted carbon atom.



In contrast to the formation of cycloheptenimine, which occurred in 78% yield, we have now found that the reaction of *trans*-2-aminocyclooctyl hydrogen sulfate with aqueous sodium hydroxide gives a crude, volatile reaction product from which cyclooctenimine was isolated in only 33% yield, accompanied by 14% of cyclooctanone.

An analogous difference in the mode of an elimination reaction on going from the seven- to the eight-membered ring was reported by Cope,⁶ who

(6) A. C. Cope, R. A. Pike and C. F. Spencer, *THIS JOURNAL*, **75**, 3212 (1953).

(1) This research was supported by National Science Foundation Grant NSF-G6220 which provided a postdoctoral stipend for D. V. Kachelikar.

(2) To whom inquiries regarding this paper should be sent.

(3) P. E. Fanta, *J. Chem. Soc.*, 1441 (1957).

(4) O. E. Paris and P. E. Fanta, *THIS JOURNAL*, **74**, 3007 (1951).

(5) P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 555 (1959).

found that the pyrolysis of cycloheptyltrimethylammonium hydroxide gave an 87% yield of *cis*-cycloheptene, whereas cyclooctyltrimethylammonium hydroxide gave a mixture of olefins containing 60% of *trans*-cyclooctene and 40% of *cis*-cyclooctene. Since the Hofmann elimination is a concerted reaction requiring a backside attack on the carbon atom bearing the trimethylamino group,⁷ it was concluded that the two conformations of the transition state which place either a *cis*-hydrogen or a *trans*-hydrogen in the same plane as the departing trimethylamino group have similar energies.⁸ Thus the cyclooctane ring is sufficiently flexible to permit elimination of both *cis* and *trans* substituents on adjacent carbon atoms with backside attack.

In a similar way, the reaction of *trans*-2-amino-cyclooctyl sulfate ion with base may proceed via transition state A in which the attack of the hydroxide ion on the amino group is concerted with the approach of the nitrogen atom to the backside of the carbon-oxygen bond, which ultimately yields the *cis*-imine IIa. Alternatively, in transition state B the electron pair of the *cis*-hydrogen accomplishes the displacement by backside attack at the carbon-oxygen bond, giving the vinylamine III which is hydrolyzed to cyclooctanone⁹ under the conditions of the reaction.¹⁰ It was also demonstrated in a separate experiment that under similar reaction conditions, cyclooctanone is not formed from cyclooctenimine.¹¹

It is noteworthy that a third conceivable transition state C does not participate in the elimination reaction, since the allylamine IV is not found in the products. This may be explained on the grounds that the carbanion corresponding to transition state B is electrostatically stabilized by the polarization of the adjacent C-N bond, whereas no such stabilization is possible for the carbanion corresponding to transition state C.¹²

Cyclooctenimine was characterized further by the preparation of a picrate, the *N*-phenylthiocarbonyl derivative IIb and the *N*-*p*-nitrobenzoyl derivative IIc. Although IIc was recovered unchanged after refluxing for twenty-four hours in toluene solution, pyrolysis in toluene solution at 170–180° gave two products, both of which were found by elemental analyses to be isomeric with IIc.

The higher melting, less soluble isomer had an infrared spectrum with bands characteristic of the NH bond, amide C=O and *cis*-CH=CH-. Acid hydrolysis yielded an amine which was hydrogenated

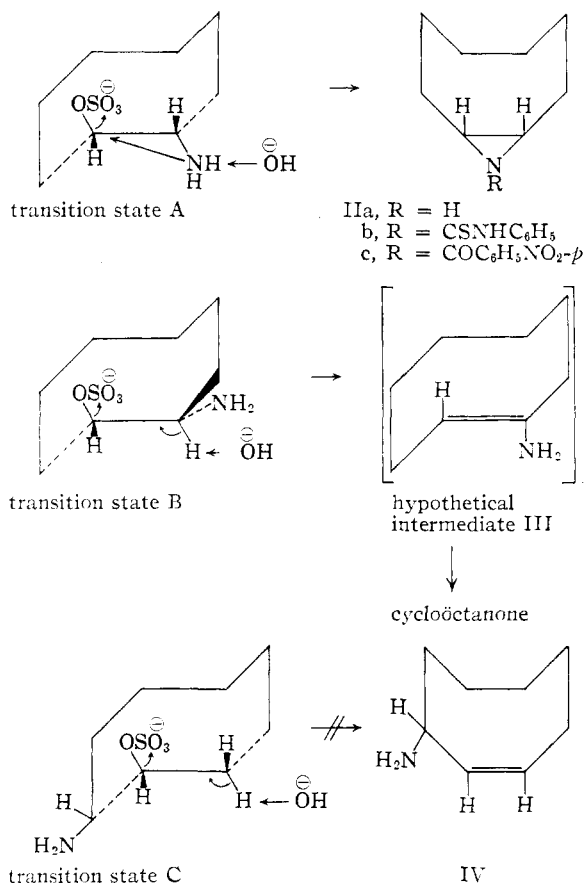
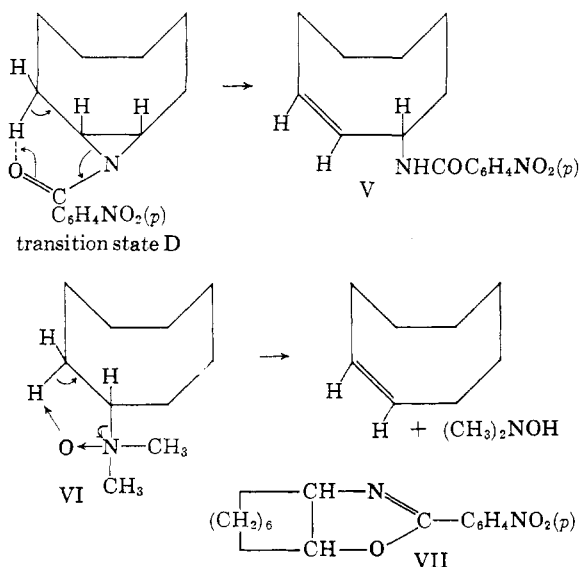


Fig. 1.—Alternative transition states for the reaction of *trans*-2-amino-cyclooctyl sulfate ion with hydroxide ion.

to give cyclooctylamine. On the basis of these data, and in analogy with the previously observed rearrangements of *N*-acylaziridine derivatives to give unsaturated amides,¹³ this product is assigned the structure *cis*-*N*-(*p*-nitrobenzoyl)-3-cyclooctenylamine (V). The formation of V may be re-



(7) D. Y. Curtin, R. D. Stolow and W. Maya, *THIS JOURNAL*, **81**, 3330 (1959).

(8) A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955), give perspective drawings of the ball-and-stick models of the two conformations. This statement is somewhat ambiguous, and it would therefore be more precise to say that in certain cyclooctane derivatives, both *cis* and *trans* substituents on adjacent carbon atoms may assume the anti-parallel arrangement in the formation of a transition state involved in a concerted elimination reaction; cf. V. Prelog in "Perspectives in Organic Chemistry," ed. by A. Todd, Interscience Publishers, Inc., New York, N. Y., 1956.

(9) An analogous vinylamine intermediate has been proposed to account for the formation of cyclohexanone from the reaction of *cis*-2-chlorocyclohexylamine with aqueous sodium hydroxide, ref. 4.

(10) Transition states A and B may be demonstrated with Fisher-Hirschfelder scale atom models.

(11) This experiment was suggested by a referee.

(12) This explanation was suggested by Dr. S. I. Miller.

(13) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958); P. B. Talukdar and P. E. Fanta, *ibid.*, **24**, 526 (1959).

sonably pictured as occurring by means of an intramolecular rearrangement *via* transition state D, which results in a *cis* elimination sterically and mechanistically analogous to the observed formation of *cis*-cyclooctene in 90% yield by the pyrolysis of the tertiary amine oxide VI.⁶

The lower-melting, more soluble isomer obtained from the pyrolysis of IVb had a characteristic C=N band and no NH band in the infrared absorption spectrum, and was sufficiently basic to form a picrate. On the basis of these data it is assigned the oxazoline structure VII, although it is not established whether the rings are fused *cis* or *trans*.¹⁴

Cyclooctenimine also differs from cycloheptenimine in being much more resistant to acid-catalyzed hydrolytic ring opening, since it was recovered unchanged after refluxing for one hour with dilute, aqueous perchloric acid.

Experimental¹⁵

(±)-*trans*-2-Aminocyclooctanol.—*cis*-Cyclooctene oxide¹⁶ (10.5 g.) and 100 ml. of 28% aqueous ammonia were heated in a rocking steel bomb at 145° for 22 hr. The brown solution was boiled to remove ammonia, decolorized with Norit and concentrated by heating on a steam-bath at about 20 mm. pressure. Two recrystallizations of the residue from benzene-petroleum ether gave 6.0 g. (50%) of amino alcohol, m.p. 71–72° with previous sintering (lit.¹⁷ 73–74°). Reaction of the amino alcohol with phenyl isothiocyanate gave the *N*-phenylthiocarbamyl derivative, m.p. 102–103° after recrystallization from ethanol.

Anal. Calcd. for C₈H₁₇N₂O₂S: C, 64.71; H, 7.97; N, 10.06. Found: C, 65.09; H, 7.85; N, 9.81.

(±)-*trans*-2-Aminocyclooctyl Hydrogen Sulfate.—The procedure described for the preparation of the homologous cycloheptyl compound was used.⁸ The yield of product once recrystallized from water was 79%, and the analytical sample was obtained by a second recrystallization from water; long, glistening white needles, dec. without melting at 270–275° (uncor.).

Anal. Calcd. for C₈H₁₇NO₄S: C, 43.03; H, 7.67; N, 6.27. Found: C, 42.73; H, 7.54; N, 6.02.

Cyclooctenimine (IIa).—A solution of 12.0 g. of the sulfate ester and 12 g. of sodium hydroxide in 75 ml. of water was heated in a distilling flask, and the volatile product was collected in a cooled receiver containing sodium hydroxide pellets and 100 ml. of ether. Whenever the residue in the flask started to crystallize, more water was added and distillation was continued until no further oily drops appeared in the condensate. The aqueous portion of the distillate was further extracted with four 50-ml. portions of ether, and the combined ether solution was dried over sodium hydroxide pellets and distilled, giving 4.43 g. (65%) of colorless oil, b.p. 87–90° (19 mm.). The presence of a ketone in this material was indicated by a strong band at 6.0 μ in the infrared absorption spectrum.

The crude product was taken up in 50 ml. of 2 *N* hydrochloric acid and extracted with three 25-ml. portions of ether. The combined ether solution was dried over anhydrous magnesium sulfate and distilled, leaving a residue of 0.94 g. (14%) of crystalline cyclooctanone. Identity was confirmed by comparison of the infrared absorption spectrum with an authentic sample and preparation of the semicarbazone, lustrous plates, m.p. 171–172° (lit. 170–171°).¹⁸

(14) *d,l-trans*-2-Phenyl-4,5-tetramethylene-2-oxazoline was obtained in 20% yield by the pyrolysis of *N*-benzoyl-*cis*-cyclohexenimine; F. Winteritz, M. Mousseron and R. Dennilauler, *Bull. soc. chim. France*, 382 (1956).

(15) Melting points are corrected, unless otherwise stated. Infrared absorption spectra were determined with the Perkin-Elmer Infracord spectrophotometer, using sodium chloride disks. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

(16) A. C. Cope, S. W. Fenton and C. F. Spencer, *THIS JOURNAL*, **74**, 5884 (1952).

(17) Obtained by a similar procedure, J. Sicher and M. Svoboda, *Collection Czechoslov. Chem. Commun.*, **23**, 1252 (1958).

The hydrochloric acid solution from this extraction was cooled and added to 50 ml. of cold 4 *N* aqueous sodium hydroxide covered with 50 ml. of ether. The aqueous portion was further extracted with three 25-ml. portions of ether and the combined ether solution was dried over sodium hydroxide pellets and distilled, giving 2.21 g. (33%) of colorless *cis*-cyclooctenimine (IIa), which had the characteristic odor of an ethylenimine derivative, b.p. 94–97° (25 mm.), *n*_D²⁰ 1.4949, *λ*_{max} 3.1 μ (N—H band).

Anal. Calcd. for C₈H₁₃N: C, 76.73; H, 12.08; N, 11.19. Found: C, 76.90; H, 12.20; N, 10.98.

The picrate formed yellow needles from ethanol, m.p. 190–195° dec.

Anal. Calcd. for C₁₄H₁₅N₃O₇: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.51; H, 5.24; N, 15.38.

Treatment of the imine with phenyl isothiocyanate gave the *N*-phenylthiocarbamyl derivative IIb, white plates from ethanol, m.p. 132–133°.

Anal. Calcd. for C₁₅H₂₀N₂S: C, 69.19; H, 7.74; N, 10.76. Found: C, 69.33; H, 7.81; N, 10.80.

N-(*p*-Nitrobenzoyl)-cyclooctenimine (IIc).—A suspension of 3.71 g. of *p*-nitrobenzoyl chloride in 75 ml. of benzene was added slowly with stirring and cooling to a solution of 2.37 g. of cyclooctenimine and 2.02 g. of triethylamine in 25 ml. of dry benzene. After 2 hours of stirring, the reaction mixture was filtered, and the filtrate was concentrated to a solid residue under reduced pressure. Recrystallization of the residue from 50 ml. of benzene gave 0.41 g. of a solid, m.p. 165–170°, which was not further identified. The benzene solution was again concentrated to a crystalline residue under reduced pressure, and the residue was recrystallized from hexane, giving 4.1 g. (79%) of IIc, m.p. 115–116°, *λ*_{max} 6.0 μ (amide C=O, no NH band).

Anal. Calcd. for C₁₅H₁₅N₂O₄: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.61; H, 6.65; N, 10.17.

Pyrolysis of *N*-(*p*-Nitrobenzoyl)-cyclooctenimine (IIc).—A solution of 1.74 g. of IIc in 60 ml. of toluene was heated in a steel bomb at 170–180° for 24 hours. The cold toluene then contained a crystalline solid which was removed by filtration and recrystallized from benzene (Norit), giving 0.65 g. (37%) of *cis*-*N*-(*p*-nitrobenzoyl)-3-cyclooctenylamine (V), fine, white needles, m.p. 195–196°, *λ*_{max} 3.1 μ (N—H band), 6.0 (amide C=O) and 11.2 μ (*cis*-CH=CH band). The latter band is also found in the spectrum of *cis*-cyclooctene.⁶

Anal. Calcd. for C₁₅H₁₅N₂O₄: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.98; H, 6.57; N, 10.44.

The toluene filtrate was concentrated to a solid residue which was recrystallized from methanol, giving 0.40 g. (23%) of 4,5-hexamethylene-2-(*p*-nitrophenyl)-2-oxazoline (VII), pale yellow, irregular crystals, m.p. 134–135°, *λ*_{max} 6.1 μ (C=N), no NH band.

Anal. Calcd. for C₁₅H₁₅N₂O₄: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.72; H, 6.42; N, 10.14.

The picrate of the oxazoline was prepared in ethyl acetate, yellow needles, m.p. 215.5–216.5°.

Anal. Calcd. for C₁₄H₂₁N₃O₁₀: C, 50.10; H, 4.21; N, 13.91. Found: C, 50.56; H, 4.64; N, 13.89.

Degradation of V to Cyclooctylamine.—Amide V (0.2 g.) was refluxed for 6 hours with 25 ml. of 5 *N* hydrochloric acid. Cooling gave a precipitate of *p*-nitrobenzoic acid, m.p. 240° (lit. 240°). The filtrate was made alkaline with sodium hydroxide, extracted with three 30-ml. portions of ether and the ethereal solution was dried and concentrated. The oily residue was taken up in absolute alcohol and shaken for 1 hour with a few mg. of platinum oxide catalyst under a hydrogen pressure of 1 atm. After removal of the catalyst, the solution was concentrated *in vacuo* to an oily residue, which on treatment with alcoholic picric acid gave a crystalline picrate, m.p. 192° (cyclooctylamine picrate reported¹⁹ m.p. is 193–194°).

Attempted Hydrolysis of Cyclooctenimine.—A solution of 0.6 g. of cyclooctenimine and 1.5 ml. of 70% perchloric acid in 10 ml. of water was refluxed for 1 hour, made alkaline with sodium hydroxide and extracted with four 25-ml. portions of chloroform. Drying and evaporation of the chloroform left

(18) A. T. Blomquist and L. H. Liu, *THIS JOURNAL*, **75**, 2153 (1953).

(19) V. Prelog, M. Fausy El-Newehy and O. Häfner, *Helv. Chim. Acta*, **33**, 365 (1950).

(5) D. J. Cram in "Steric Effects in Organic Chemistry," ed. by M. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 304. See also the comprehensive review of pyrolytic *cis*-eliminations, by C. H. DePuy and R. W. King, *Chem. Revs.*, in press.