2-Hydroxycyclohexylhydrazines. II.[1] Reaction with Nitrous Acid

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DL-2-Hydroxycyclohexylhydrazines (I) were treated with sodium nitrite in aqueous acetic acid solution. When one equivalent of sodium nitrite was used, *trans*-I gave DL-*trans*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*trans*-II) and cyclopentanecarboxaldehyde (III), while *cis*-I gave *cis*-II, III, DL-*cis*-2-cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine (*cis*-IV), and cyclohexanone (V). On the other hand, when two or more equivalents were used, *trans*-I afforded only III and *cis*-I afforded III and V, the products and their formation ratio being closely similar to those from the same treatment of DL-2-aminocyclohexanols (VI). This close similarity, which seemed unacceptable on the stereochemical basis, was explained by presuming that the reaction occurred through degradation to the nitrosated VI. The explanation was experimentally supported by the observation that the 1-nitrosated I blocked with a carbonyl compound, *trans*-II or *cis*-IV, was converted to *trans*-VI·HCl or *cis*-VI·HCl, respectively, by acidic hydrolysis.

There have been several reports dealing with the action of nitrous acid on simple alkyl[2] and aryl hydrazines,[3] but, to our knowledge, an analogous study on 2-hydroxyalkyl hydrazines has not been reported. On the other hand, the deamination reactions of DL-2-aminocyclohexanols (VI) by means of nitrous acid were examined by McCasland[4] from a stereochemical standpoint. He clearly revealed that the reactions were governed by conformations of VI to yield III from the *trans* isomer (*trans*-VI) and III and V from the *cis* isomer (*cis*-VI), as outlined in Chart I.

In this context it was of interest to examine the reaction of the diastereomeric DL-2-hydroxycyclohexylhydrazines (I) with nitrous acid. Thus, *trans*- and *cis*-I were treated with sodium nitrite in 10% aqueous acetic acid in the present study. Authentic samples of hitherto unknown compounds used for identifications of products were synthesized by methods described below. In the reaction of *trans*-I, use of one equivalent of sodium nitrite gave rise to DL-*trans*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*trans*-II) and cyclopentanecarboxaldehyde (III), while use of two or more equivalents gave only III (Chart I).

On the other hand, in the case of *cis*-I, use of one equivalent of sodium nitrite gave rise to DL-*cis*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine (*cis*-II), DL-*cis*-2-cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*cis*-IV), cyclopentanecarboxaldehyde (III), and cyclohexanone (V), while use of two or more equivalents afforded III and V (see Chart I). With respect to products formed, the diazotization of VI was closely similar to the reaction of I with two or more equivalents of nitrous acid. It is quite acceptable that *trans*-I gave only III on elimination of the hydrazino group, because of the preferred diequatorial conformation in *trans*-I. But in the reaction of *cis*-I where the hydrazino group, because it is bulkier, might preferentially exist in an equatorial position, the predominance of V over III in a ratio of about 4:1 seemed incomprehensible, for such a steric situation would favor the reverse predominance. This suggests the hypothesis that reaction of I is initiated by the loss of one nitrogen to give the nitrosated VI which is further deaminated to give the end products, the deamination reactions of I and VI proceeding by a common path.

To test this hypothesis, the mononitrosated compounds blocked with a carbonyl compound, *trans*-II and *cis*-IV, were submitted to hydrolysis in 20% ethanolic hydrochloric acid solution. The experiments resulted in the formation of DL-*trans*-2-aminocyclohexanol hydrochloride (*trans*-VI·HCl) and its *cis* isomer (*cis*-VI·HCl), respectively, splitting off the carbonyl compound, III or V (see Chart II). This presented evidence for the proposed hypothesis.

The preceding discussion also serves to explain the results from I on treatment with one equivalent of nitrous acid. *trans*-I consumed two moles of nitrous acid per mole to afford cyclopentanecarboxaldehyde (III). The remaining *trans*-I was converted to *trans*-II by condensation with product III, followed by nitrosation, or vice versa. The absence of *trans*-VI in the reaction mixture is explained by the fact that its precursor, 1-nitrosated *trans*-I, is stabilized by condensation with III to give *trans*-II. As stated above, when the 1-nitrosated *trans*-I was regenerated from *trans*-II by hydrolysis, it was converted immediately to *trans*-VI. The analogous explanation is applied to the formation of products from *cis*-I on the same treatment.

Many years ago Thiele[2] proposed two possible pathways, A and B, which are outlined in Chart III for the reaction of an alkyl hydrazine with nitrous acid with elimination of the hydrazino group. In either case, the reaction leads to the alkyl nitrosamine. More recently Clusius[3b] by the use of N^{15} has confirmed the intramolecular nature of the nitroso migration in the case of phenylhydrazine. In accordance with pathway B proposed by Thiele, this work might picture the nitrosation process of a 2-hydroxyalkyl hydrazine to the 2-hydroxyalkyl nitrosamine as well as the case of an alkyl hydrazine. But the reaction course of a 2-hydroxyalkyl hydrazine, as indicated above, probably involves the temporary condensation with carbonyl compounds which are formed in the final reaction. This may be a feature differing from the case of a simple alkyl hydrazine.

Authentic compounds used for the identification of the reaction products, II and IV, were prepared as follows. The condensation of *trans*-I with cyclopentanecarboxaldehyde (III) afforded DL-*trans*-2-cyclopentylmethylene-1-(2-hydroxycyclohexyl)hydrazine which, then, was nitrosated with sodium nitrite in aqueous acetic acid furnishing *trans*-II. *cis*-II, *trans*-

(1) Studies in Stereochemistry. XXXII.
(2) J. Thiele, *Ann.*, **376**, 239 (1910).
(3) (a) K. Clusius and H. R. Weisser, *Helv. Chim. Acta*, **35**, 1548 (1952); (b) K. Clusius and K. Schwarzenbach, *ibid.*, **42**, 739 (1959).
(4) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2293 (1951).

CHART I

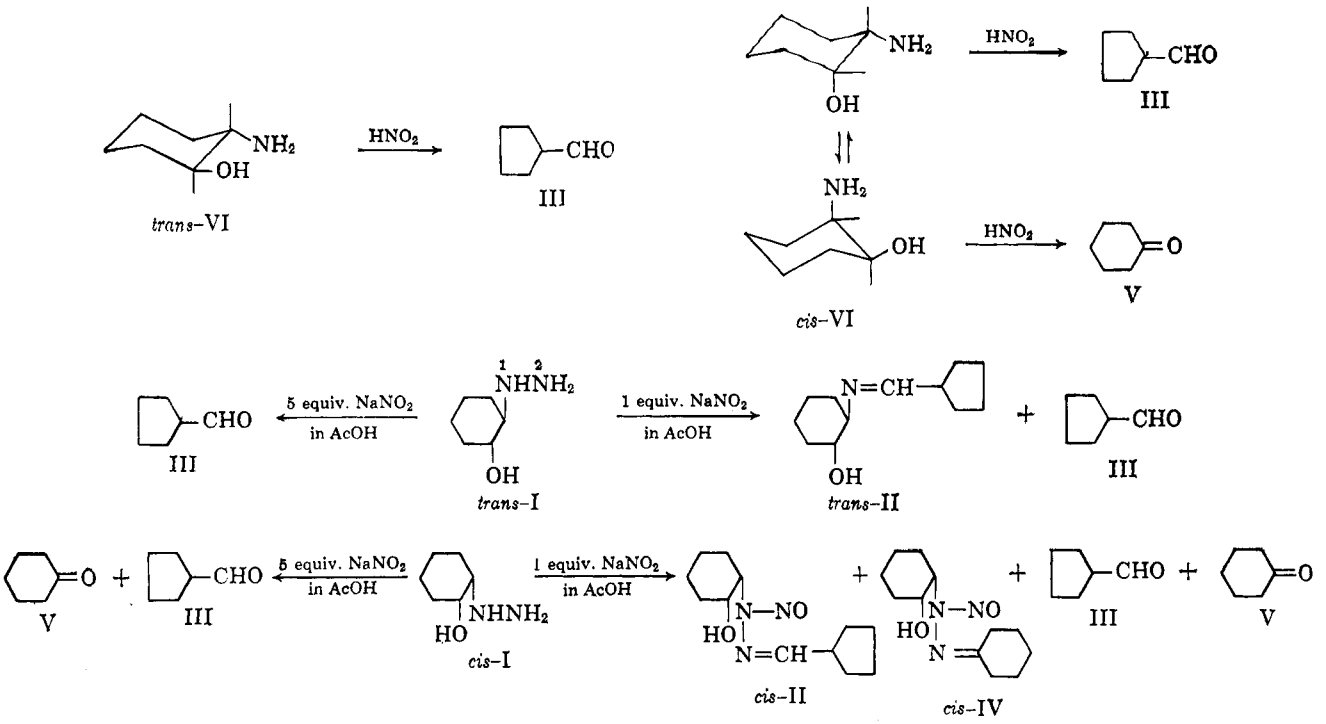


CHART II

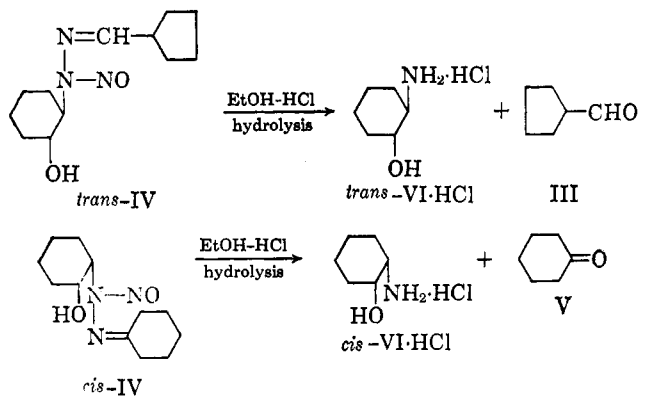


CHART III

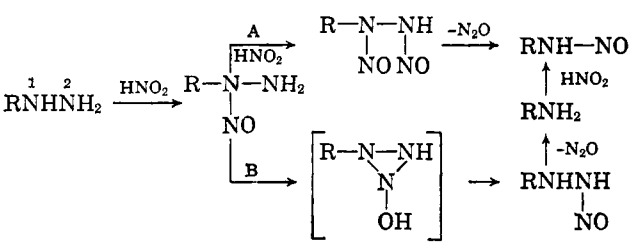
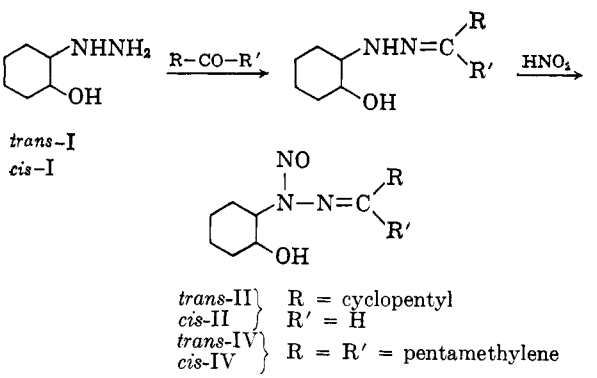


CHART IV



IV, and *cis*-IV were also prepared in the similar way (see Chart IV).

Experimental[5]

DL-*trans*-**2-Cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**II**).—An ethanolic solution (2 ml.) of *trans*-I (1.03 g.) and cyclopentanecarboxaldehyde (III, 0.85 g.) was refluxed for 4 hr. and evaporated to dryness. To the residue was added ethanol and it was evaporated. The treatment was repeated until the aldehyde (III) was not detected in the distillate by the 2,4-dinitrophenylhydrazone formation test. The residue, an oil, was washed with ether to yield 1.60 g. (96%). To a 10% aqueous acetic acid solution (10 ml.) containing 1.2 g. (5.7 mmoles) of the oil was added dropwise 5.7 ml. of 1 *N* aqueous sodium nitrite (5.7 mmoles) at 5–10° and the charge was allowed to stand for 30 min. with stirring. The resulting precipitate was filtered and recrystallized from benzene as colorless needles, m.p. 70–71° dec., 0.94 g. (69%) yield.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 59.91; H, 8.96; N, 17.70.

DL-*trans*-**2-Cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**IV**).—An ethanolic solution (2 ml.) of *trans*-I (5.71 g.) and cyclohexanone (V, 4.30 g.) was refluxed for 3 hr. Evaporation of ethanol left crystals, m.p. 56–58° dec., 5.50 g. (60%) yield, which were hygroscopic and slowly decomposed in contact with air. Nitrosation of the crystals was carried out just like the preparation of *trans*-II, furnishing *trans*-IV, 86% yield, colorless needles, m.p. 119–119.5° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 59.91; H, 8.75; N, 17.33.

DL-*cis*-**2-Cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-**II**).—Condensation of *cis*-I with III followed by nitrosation was carried out like the preparation of *trans*-II. The condensation product, DL-*cis*-2-cyclopentylmethylene-1-(2-hydroxycyclohexyl)hydrazine crystallized to yield 82.4% as colorless needles, m.p. 109–110° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.34; H, 10.48; N, 13.41.

Nitrosation of the condensation product, followed by recrystallization from ethanol, gave colorless needles, m.p. 90–90.5° dec., 87% yield. It was recommended that, prior to

(5) All melting points are uncorrected.

nitrosation, a small volume of 2% aqueous hydrochloric acid be added to the acetic acid solution to dissolve the condensation product completely.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 60.39; H, 8.80; N, 17.74.

DL-*cis*-**2-Cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine** (*cis*-**IV**).—Condensation of *cis*-I with V followed by nitrosation was carried out exactly like the preparation of *trans*-II. The condensation product, DL-*cis*-2-cyclohexylidene-1-(2-hydroxycyclohexyl)hydrazine, was recrystallized from benzene, m.p. 102–104° dec., 90% yield.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.44; H, 10.48; N, 13.24.

The nitrosated product, *cis*-IV, was recrystallized from ethanol as colorless plates, m.p. 120–121° dec., 83% yield.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 59.81; H, 9.04; N, 17.56.

Acidic Hydrolysis of *trans*-II. The Formation of DL-*trans*-**2-Aminocyclohexanol Hydrochloride** (*trans*-**VI·HCl**).—A suspension of *trans*-II (0.58 g.) in 20% ethanolic hydrochloric acid solution (2 ml.) went slowly into clear solution while standing at room temperature. After 3 hr., ethanol (10 ml.) was added to the solution, and the solution was distilled. The treatment was repeated until cyclopentanecarboxaldehyde (III) was not found in the distillate. The oily residue crystallized with ice cooling to yield 0.065 g. (20%) of colorless needles, m.p. 172–173° after recrystallization from ethanol–ether. The product was identified as *trans*-VI·HCl by a mixture melting point and infrared spectrum determinations.

Acidic Hydrolysis of *cis*-IV. The Formation of DL-*cis*-**2-Aminocyclohexanol Hydrochloride** (*cis*-**VI·HCl**).—After work-up just like the foregoing item, 1.60 g. of *cis*-IV was converted to 0.06 g. (7%) of *cis*-VI·HCl, which was recrystallized from ether–ethanol as colorless needles, m.p. 181–182°. The identification depended upon a mixture melting point and infrared spectrum determinations.

Reaction of DL-*trans*-**2-Hydroxycyclohexylhydrazine** (*trans*-**I**) **with Nitrous Acid. (1). The Simultaneous Formation of *trans*-II and III.**—To 11 ml. of 10% aqueous acetic acid solution containing 0.73 g. (5.6 mmoles) of *trans*-I was added dropwise 5.6 ml. of 1 *N* aqueous sodium nitrite (5.6 mmoles) at 5–10° while stirring. The solution was stirred for 30 or more minutes causing the precipitation of crystals. Filtration followed by recrystallization from benzene gave colorless needles, 0.15 g. (22.4%) yield, m.p. 70–71° dec. alone and on admixture with authentic *trans*-II. The infrared spectrum was completely superimposed on that of *trans*-II. The filtrate was neutralized with sodium carbonate, and sodium chloride was added. The solution was extracted with ether, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was converted by the usual method to the 2,4-dinitrophenylhydrazone which was recrystallized from ethanol furnishing pale yellow scales, 0.08 g. (5%) yield, m.p. 152–154° dec. alone and on admixture with authentic III 2,4-dinitrophenylhydrazone.

(2). **The Formation of III.**—*trans*-I was treated essentially as in method 1, except 28.0 mmoles of sodium nitrite per 5.6 mmoles of the material was used. Consequently, the reaction furnished only a carbonyl compound which was converted to the 2,4-dinitrophenylhydrazone; the yield was 1.06 g. Recrystallization from ethanol gave pale yellow scales, 0.85 g. (53%) yield, m.p. 156–158° dec. alone and on admixture with authentic III 2,4-dinitrophenylhydrazone.

Reaction of DL-*cis*-**2-Hydroxycyclohexylhydrazine** (*cis*-**I**) **with Nitrous Acid. (1). The Simultaneous Formation of *cis*-II, III, *cis*-IV, and V.**—To 42 ml. of 10% aqueous acetic acid solution containing 3.0 g. (23 mmoles) of *cis*-I was added dropwise 23 ml. of 1 *N* aqueous sodium nitrite (23 mmoles) at 5–10° with good stirring. Stirring was continued for 30 or more minutes. An oily product which separated from the solution during the operation crystallized on standing. Filtration followed by repeated recrystallization from ethanol gave colorless plates, 0.56 g. (22%) yield, m.p. 120–121° dec. alone and on admixture with authentic *cis*-IV. Allowing the filtrate to stand for many hours caused the deposition of another crystalline product. Filtration followed by repeated recrystallization from ethanol gave colorless needles, 0.02 g. (0.7%) yield, m.p. 90–90.5° dec. alone and on admixture with authentic *cis*-II. Thereafter, the filtrate was treated as in 1 of the previous item to give a mixture of 2,4-dinitrophenylhydrazones. Fractional recrystallization gave pale yellow scales, m.p. 150–153° dec., 0.05 g. (0.71%) yield, and pale orange-yellow scales, m.p. 155–156° dec., 0.16 g. (2.4%) yield. The former and the latter scales were identical with III 2,4-dinitrophenylhydrazone and V 2,4-dinitrophenylhydrazone, respectively, by mixture melting point determinations.

(2). **The Simultaneous Formation of III and V.**—*cis*-I (11.5 mmoles) was treated with sodium nitrite (57.5 mmoles) in an aqueous acetic acid solution just like in 1 of this item. Only III and V were isolated as 2,4-dinitrophenylhydrazones from the reaction mixture to yield 0.16 g. (4.9%) and 0.61 g. (19%), respectively.

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The Light-Induced Reactions of Iodine Trichloride with Cyclohexane[1]

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Iodine trichloride and cyclohexane undergo a photochemically induced reaction. The products isolated are hydrogen chloride, chlorocyclohexane, iodocyclohexane, *trans*-1,2-dichlorocyclohexane, *trans*-1-chloro-2-iodocyclohexane, and molecular iodine. A free-radical chain sequence involving the $ICl_2\cdot$ radical is proposed to account for the formation of hydrogen chloride, chlorocyclohexane, and iodocyclohexane. Dehydrohalogenation of the halocyclohexanes produced in the chain sequence yields cyclohexene, the intermediate required for the formation of the 1,2-dihalocyclohexanes. Molecular iodine arises from reaction of hydrogen iodide with iodine trichloride.

A number of reports dealing with the halogenation of aromatic hydrocarbons by means of iodine trichloride have appeared in the literature.[3] Products were obtained in which both chlorine and iodine had been substituted on the aromatic ring, and the nature of the products indicated that the reaction proceeded by ionic mechanisms in the absence of illumination. The present paper is concerned with the light-induced reaction of iodine trichloride with the aliphatic hydrocarbon, cyclohexane. The results of our study are best interpreted in terms of a free-radical chain reaction involving the interhalogen radical $ICl_2\cdot$.

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(2) This paper was taken from a portion of a thesis submitted by W. W. H. in partial fulfillment of the requirements for the Ph.D. degree from the University of Kansas, 1963.

(3) (a) E. Campaigne and J. R. Leal, *J. Am. Chem. Soc.*, **75**, 230 (1953); (b) G. Calingaert, M. E. Griffing, E. R. Kerr, A. J. Kalka, and H. D. Orloff, *ibid.*, **73**, 5224 (1951); (c) V. Arrequine, Jr., and E. B. Garcia, *Anales asoc. quim. Arg.*, **9**, 121 (1921); (d) V. Thomas and P. Depuis, *Compt. rend.*, **143**, 282 (1906); (e) H. Muller, *J. Chem. Soc.*, **15**, 41 (1862).