cally and analyzed for acid and residual oxidant. After 4.7 days, 5.85 moles of oxidant had been consumed and 2.76 moles of acid formed; after 11 days, 5.99 moles of oxidant had been consumed while 2.95 moles of acid had been formed. Analysis of the remaining oxidation mixture, using dimedone according to the procedure of Fleury and Lange,[16] showed the presence of 1.86 moles of formaldehyde.

1,4-Anhydro-D-galactitol Tetrabenzoate.—1,4-Anhydro-D-galactitol (0.30 g.) was benzoylated in pyridine (5 ml.) with benzoyl chloride (1.5 ml.) in the usual manner to give from methanol solution 0.92 g. (87%) of crystals melting at 87–92°. After recrystallization from a variety of solvents this material was obtained as a mixture of prisms and needles which still showed a wide melting point range although chromatography on alumina indicated that it was chemically homogeneous. A wholly independent preparation (involving benzoylation of very impure, sirupy 1,4-anhydro-D-galactitol) later furnished seeds of higher melting material and thereafter the product was obtained only as clear tetragonal prisms melting at 99–101° and showing in chloroform +41.7° (*c*, 1.03). In order to ensure that no alteration had taken place in the structure of the substance, a sample was debenzoylated with barium methylate in methanol to give (in 93% yield), 1,4-anhydro-D-galactitol, identified by melting point and mixed melting point.

Anal. Calcd. for $C_{34}H_{28}O_9$: C, 70.33; H, 4.86. Found: C, 70.29; H, 4.99.

Acknowledgment.—The authors wish to thank Mrs. Evelyn G. Peake, Miss Paula M. Parisius and Dr. William C. Alford of this Laboratory for analytical determinations incident to this research.

(16) P. Fleury and J. Lange, *J. pharm. chim.*, **17**, 196 (1933).

BETHESDA, MARYLAND RECEIVED MARCH 16, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

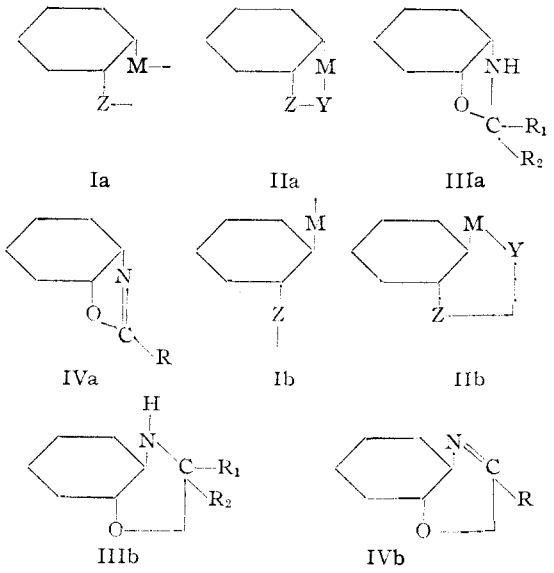
Heterocyclization of Epimeric Aminocyclanols. I. Oxazolines[1,2]

BY G. E. McCASLAND AND E. CLYDE HORSWILL

The conversion of aminocyclanols to bicyclic (heterocyclic) derivatives has been investigated with regard to its possible utility as an indicator of diastereomeric configuration. The formation of oxazolines by reaction of aminocyclanol free base with ethyl iminobenzoate free base in homogeneous solution in ethylene dichloride was studied. The *trans* epimers of 2-aminocyclohexanol and -pentanol each yielded a large precipitate found to consist of the N-(2-hydroxycycloalkyl)-benzamidine hydrochloride. The *cis* epimers gave negligible amounts of precipitate. Both *cis*- and *trans*-2-aminocyclohexanols readily formed oxazolines. The conversion of *cis*-2-aminocyclopentanol to oxazoline was also easy, but formation of a *trans*-cyclopentanoöxazoline has thus far not been found possible.

Introduction

One of the classical methods for determining the diastereomeric configuration of a disubstituted cycloalkane is to compare the ease of conversion of the two epimers (Ia, Ib) to bicyclic derivatives (IIa, IIb). The new ring is usually heterocyclic and the process may then be called *heterocyclization*. M and Z are the directly attached atoms of functional groups such as –OH, $-NH_2$, –COOH, and Y is a bridge containing zero, one, two or more atoms. The heterocyclization is presumed to occur with retention of configuration at C–M and C–Z.



The validity of the method depends on the sizes of both rings. When the cycloalkane ring contains two to five carbon atoms the expected sharp differences in proximity of M and Z for the two epimers often cause pronounced differences in the ease of ring formation. The more flexibile and non-coplanar cyclohexane ring may or may not show a significant *cis–trans* difference. Cycloheptane and higher rings are unsuitable for the heterocyclization method.

The heterocyclic ring to be formed should contain not more than four (possibly five) atoms for cyclohexanes; not more than five atoms for cyclopentanes,[3,4] and not more than six (possibly seven) atoms for cyclobutane and smaller rings. It should also be noted that three-membered heterocyclic ring formation is not useful due to the possibility of Walden inversion and that methods are rarely available for preparing four-atom rings with two adjacent hetero-atoms.

The above conclusions are based largely on reported work[5,6,7] with alicyclic diols, dicarboxylic

(1) We wish to thank the Research Council of Ontario for a generous grant in support of this work.

(2) For related publications see: (a) G. E. McCasland, THIS JOURNAL, **73**, 2295 (1951); (b) **73**, 2293 (1951); (c) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); (d) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949); (e) H. E. Carter, R. K. Clark, Jr., Betty Lytle and G. E. McCasland, *J. Biol. Chem.*, **175**, 683 (1948); (f) G. E. McCasland and D. A. Smith (to be submitted for publication).

(3) Bicyclic saturated hydrocarbons of the *trans* "five-five" type have been isolated by R. P. Linstead, *et al.*, *J. Chem. Soc.*, 436 (1935). A double bond should increase the ring-strain.

(4) R. P. Linstead and E. M. Meade, *ibid.*, 935 (1934).

(5) See C. S. Marvel, in Gilman, "Organic Chemistry: An Advanced Treatise," 2nd Edition, Wiley, New York, N. Y., 1943, pp. 447–453, 477–483.

(6) R. C. Fuson, *ibid.*, pp. 108–115.

(7) C. J. Maan, *Rec. trav. chim.*, **48**, 332 (1929); J. Böeseken, *Advances in Carbohydrate Chem.*, **IV**, 189 (1949); A. Windaus, *et al.*, *Ber.*, **56**, 91 (1923).

acids and hydroxy- or aminocarboxylic acids. We have now examined the possible extension of this general method to aminocyclanols, using compounds of known configuration. The only feasible derivative here seemed to be an oxazolidine IIIa–IIIb or oxazoline IVa–IVb (which may have such groups as alkyl, aryl, hydroxy, mercapto as substituents at position 2).

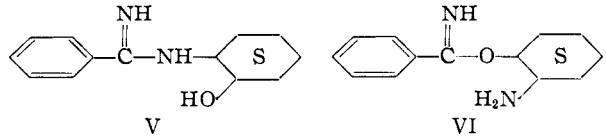
It should be noted that certain methods with the same basic principle (ease of cyclization) but not involving actual isolation of heterocyclic intermediates—*e.g.* acyl migration,[2a,8] lead tetraacetate oxidation[2f,9] and hydrogen bonding studies[10]—have previously been applied successfully to such compounds.

Reaction with an Imino-Ester

A number of the more common preparative methods for oxazolines were unsuitable here because of probable stereochemical inversion. The reaction of an imino-ester with an aminocyclanol hydrochloride,[11,12,13] however, presumably occurs with retention. Although on the basis of molecular geometry[2c] *cis*-2-aminocyclohexanol might be expected to cyclize more easily, nevertheless the *trans*-epimer does yield a stable (*trans*) oxazoline, as reported recently by Johnson and Schubert.[13]

We have checked the identity of the Johnson–Schubert reaction product by more complete analysis, and by successive acid hydrolysis and basification which yielded the well-known and sharp-melting *trans*-2-benzoylaminocyclohexanol. This fully confirms formation of the *trans*-oxazoline.

Throughout the reaction between imino-ester hydrochloride and free aminocyclanol (or free imino-ester and aminocyclanol hydrochloride) with ethylene dichloride as solvent a large amount of insoluble solid phase is present. In order to obtain a homogeneous reaction we carried out experiments using the free bases of both reactants. The *cis*-epimer now gave a negligible amount of precipitate, and the oxazoline yield was increased to nearly 60%. Surprisingly enough, the *trans*-epimer still gave a substantial amount of precipitate. The precipitate was found to be the hydrochloride of N-(2-hydroxycyclohexyl)-benzamidine[12] (V). The isomeric imino-ester (VI) was also a possibility. In order to prove the structure a Van Slyke amino–nitrogen determination[14] was carried out, and it indicated the absence of a free primary amino group. Previously the infrared spectrum of the compound was determined, but apparently was insufficient for a certain choice between the two possibilities.



V VI

The above reaction also formed a substantial amount of the *trans*-oxazoline, which was isolated from the filtrate.

The hydrogen chloride needed for precipitation can have come only from a side-reaction with the solvent. Control experiments showed that long boiling of imino-ester with ethylene dichloride gave no precipitate; but boiling aminocyclanol and solvent gave a copious precipitate of aminocyclanol hydrochloride.

It was now of interest to try the same reaction on the epimeric aminocyclopentanols. Examination of models indicates that the more rigid, more coplanar cyclopentane ring should offer a great, if not a prohibitive, obstacle to *trans*-oxazoline formation. It was found that *cis*-aminocyclopentanol gives 34% or more oxazoline and a negligible hydrochloride precipitate. The same procedure applied to *trans* gave a substantial hydrochloride precipitate, and no oxazoline could be isolated. Although formation and isolation of *trans*-cyclopentanooxazoline may still be proved possible, the results indicate a marked difference in behavior between the epimeric cyclopentane derivatives.

Experimental

All melting and boiling points corrected; melting points determined on Kofler micro-block. Microanalyses for C and H and Dumas N by Mr. Robert S. Pyke.

Epimeric Racemic 2-Aminocyclohexanols and -pentanols.—These were prepared as previously described.[2c,2d]

Ethyl Iminobenzoate.—The hydrochloride was prepared from benzonitrile by the procedure of A. W. Dox[15] and the free base liberated with aqueous potassium carbonate and ether.

Reactions of Aminocyclanols with Ethyl Iminobenzoate

Reaction of *cis*-2-Aminocyclohexanol. (A) Free Base.—A solution of 2.30 g. of aminocyclanol and 3.73 g. of iminobenzoate in 200 g. of dried 1,2-dichloroethane was refluxed for 24 hours with exclusion of moisture. Only 0.02 g. of precipitate was formed. The filtrate was freed of solvent. The residue (4.47 g.) was vacuum-distilled, giving 0.58 g. of ethyl iminobenzoate and 2.64 g. of a colorless liquid, b.p. 157–158° (9 mm.). The latter was dissolved in cyclohexane. The solution was separated from an insoluble residue of benzamide (0.12 g.) and vacuum distilled, giving 2.40 g. of a colorless oil which rapidly crystallized. Short-path high-vacuum distillation at 0.04 mm. and 70° (bath) gave 2.36 g. (59%) of ***d,l-cis*-2-phenyl-4,5-cyclohexanoöxazoline-2** which froze to colorless crystals, m.p. 44–47°. A 0.5-g. portion when recrystallized from absolute ethanol gave 0.32 g. of crystals, m.p. 47–48° (reported[16] m.p. 46.0–46.6). Vacuum distillation for analysis caused no change in m.p.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.13; H, 7.75; N, 7.24.

(B) **Hydrochloride.**—When the procedure in (A) was changed by using the aminocyclanol hydrochloride in place of free base, 1.60 g. of ethyl iminobenzoate and 0.36 g. of the purified oxazoline, m.p. 47–48° were obtained. (The

(8) (a) L. Anderson and H. A. Lardy, THIS JOURNAL, **72**, 3141 (1950); (b) G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950).

(9) R. Criegee, L. Kraft and B. Rank, *Ann.*, **507**, 159 (1933).

(10) L. Pauling, "Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1942, pp. 316–334.

(11) Regarding the imino-ester reaction see: (a) D. F. Elliot, *J. Chem. Soc.*, 589 (1949); (b) R. M. Ross, Ph.D. Thesis, Wisconsin, 1948; (c) M. Bockmühl and R. Knoll, *C. A.*, **28**, 4539 (1934); (d) D. J. Loder, *ibid.*, **40**, 5457 (1946).

(12) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1100 (1950), have recently reported that N-cyclohexyl-α-phenylacetamidine hydrochloride reacts with ethanolamine to give 2-benzyloxazoline. This suggests that an amidine may be a normal intermediate in the oxazoline formation from imino-ester and aminoalkanol. Perhaps the reaction stops at the amidine stage when conditions for cyclization to oxazoline are unfavorable. It is noteworthy that N-alkyl groups on the amidine do not interfere with oxazoline formation. (For our amidine (V) intramolecular cyclization is also possible.)

(13) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950).

(14) F. Pregl and H. Roth, "Quantitative Organic Microanalysis," 3rd English Ed., Blakiston, Phila., Pa., 1937, pp. 166–171.

(15) A. W. Dox, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, New York, N. Y., 1932, p. 6.

(16) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).

yield of purified product was not previously reported.[13]) The insoluble precipitate which separated during the reaction weighed 2.00 g.

Reaction of *trans*-2-Aminocyclohexanol. (A) Free Base.—The procedure was the same as for the *cis* free base (see above). The precipitate which separated during the reaction was collected and dried, weight 0.85 g., m.p. 227–230°.

The residue from the vacuum-distilled filtrate weighed 4.04 g., and on further distillation gave 0.68 g. of ethyl iminobenzoate, b.p. 93–94° (9 mm.), $n^{30}D$ 1.5190, and 1.50 g. of crude oxazoline, b.p. 158–160° (9 mm.) which soon solidified. The latter product was extracted with cyclohexane, leaving 0.13 g. of solid benzamide residue. A short-path high-vacuum distillation of the solute (after removal of cyclohexane) at 0.04 mm. and 80° (bath) gave 1.20 g. of solidified distillate, m.p. 60–66°. The material was recrystallized from absolute ethanol. The colorless crystals, collected at 0° in a Skau tube, weighed 0.83 g., m.p. 67.5–69.0°.

For analysis a sample was again distilled under high vacuum, m.p. 68.5–69.0° (reported[13] m.p. 66.2–67.6°).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.43; H, 6.92; N, 7.03.

The precipitate of m.p. 227–230° was recrystallized from methoxyethanol–ethylene dichloride (1:4). The ether-washed and vacuum-dried crystals weighed 0.64 g., m.p. 236–237°. The compound is believed to be ***d,l-trans*-N-(2-hydroxycyclohexyl)-benzamidine hydrochloride.** A sample crystallized twice more for analysis melted at 241–241.5°.

Anal. Calcd. for $C_{13}H_{19}N_2OCl$: C, 61.28; H, 7.52; N, 11.00. Found: C, 61.63; H, 7.47; N, 10.52.

A sample was analyzed with a micro Van Slyke nitrogen apparatus.[14] Only 0.19% N was found, indicating that the molecule contains no primary amino group. The compound is therefore the amidine hydrochloride (V), and not the isomeric imino-ester hydrochloride (VI) which would contain 5.50% amino-nitrogen.

To 0.10 g. of the hydrochloride in 2 ml. of water was added 2 ml. of 12% potassium hydroxide. The flocculent precipitate which separated was collected and vacuum-dried, m.p. 147–149°. It is believed to be ***d,l-trans*-N-(2-hydroxycyclohexyl)-benzamidine.** For analysis a sample was vacuum distilled at 0.004 mm., recrystallized from 1,2-dichloroethane and redistilled, raising the m.p. to 151–152°.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.84. Found: C, 72.04; H, 7.83; N, 12.28.

Treatment of the free base with dry ethereal hydrogen chloride regenerated the amidine hydrochloride of m.p. 242°. Electrometric titration of the free base in ethanol–water (1:2) with 9.88 millimolar hydrochloric acid gave an equivalent weight of 230 (calcd. 218).

(B) Hydrochloride.—When the aminocyclanol hydrochloride was used, 1.50 g. of precipitate separated during the reaction. From the filtrate 1.50 g. of oxazoline, m.p. 64–68°, was obtained. The extraction with cyclohexane left 0.32 g. of insoluble residue (benzamide), and gave 0.93 g. of oxazoline, m.p. 64–66.5°. The melting point was raised to 68.5–69° by ethanol recrystallization and final high-vacuum distillation.

(C) Two-phase Reaction.—No oxazoline could be isolated from a reaction[11a] of ethereal iminobenzoate with aqueous aminocyclanol hydrochloride.

(D).—The reaction when carried out as in (A) but using one-fourth the volume of solvent gave 2.37 g. of precipitate, and the yield of oxazoline was decreased.

Reaction of *cis*-2-Aminocyclopentanol. (A) Free Base.—Treatment of the aminocyclopentanol free base as above, but using half-quantities, gave only 0.001 g. of precipitate. Vacuum-distillation of the filtrate left a pale yellow oil (1.91 g.) which on further distillation gave 0.26 g. of ethyl iminobenzoate and 1.08 g. of crude oxazoline (oil), b.p. 141–142° (7 mm.), $n^{27}D$ 1.5880. A cyclopentane extract of the latter was filtered from a precipitate of short needles (0.008 g.) and distilled. The residual oil solidified to oily prismatic plates. Sublimation at 0.03 mm. gave 0.87 g. of sublimate. Recrystallization from ethanol and resublimation gave 0.64 g. of crystals, m.p. 50–51°, of ***d,l-cis*-2-phenyl-4,5-cyclopentanoöxazoline-2.**

A sample for analysis was again crystallized and sublimed without improvement of m.p.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.96; H, 7.00; N, 7.48. Found: C, 77.32; H, 7.02; N, 7.25.

(B) Hydrochloride.—The reaction using 2.75 g. of hydrochloride gave 1.34 g. of precipitate, 0.88 g. of ethyl iminobenzoate and 1.85 g. of crude oxazoline.

Reaction of *trans*-2-Aminocyclopentanol. (A) Free Base.—The *trans*-aminocyclopentanol was treated in the same manner as its homolog above. The insoluble material which separated from the reaction was a viscous oil. The solution was decanted and vacuum distilled giving 2.71 g. of a viscous brown oil. Further distillation yielded 0.68 g. of ethyl iminobenzoate and 1.37 g. of a high-boiling residue. All attempts to isolate an oxazoline (or any other pure compound) from the latter fraction have been unsuccessful.

The insoluble viscous oil first obtained was dissolved in warm ethanol. Removal of solvent left 1.37 g. of gummy white solid, which was recrystallized from methoxyethanol–ethylene dichloride (1:4), giving sheaves of radiating needles with a few prisms. The crystals were ether-washed and dried, weight 1.20 g. Both crystal forms resolidified after melting at 120°, and melted again at 187.5–188.5°. A second crystallization from 1:1 solvent-mixture raised the m.p. to 190–191° (weight 0.97 g.).

Further recrystallization and sublimation[17] at 0.004 mm. left the melting point unchanged. By analogy with the C_6 reaction product the compound is believed to be ***d,l-trans*-N-(2-hydroxycyclopentyl)-benzamidine hydrochloride.**

Anal. Calcd. for $C_{12}H_{17}N_2OCl$: C, 59.86; H, 7.12; N, 11.64. Found: C, 59.30; H, 7.09; N, 11.43.

A solution of 0.40 g. of this hydrochloride in 1.0 ml. of water was neutralized with 1.0 ml. of 5% sodium hydroxide. An oil separated which crystallized on shaking. The filtered, vacuum-dried precipitate weighed 0.22 g., m.p. 128–130° (dec.). The material was successively sublimed at 0.001 mm., recrystallized from 1,2-dichloroethane and resublimed, giving 0.10 g. of tiny needles, m.p. 132–133°.

The melting point was unchanged by further crystallization. The product is presumed to be ***d,l-trans*-N-(2-hydroxycyclopentyl)-benzamidine.**

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72. Found: C, 70.81; H, 7.62; N, 13.52.

(B) Hydrochloride.—The reaction of 2.76 g. of the hydrochloride gave 2.02 g. of sticky white precipitate, 0.63 g. of ethyl iminobenzoate, and a high-boiling residue from which no oxazoline could be isolated.

Conversion of the *trans*-Oxazoline to *trans*-2-Benzoylaminocyclohexanol.—A solution of 0.12 g. of the oxazoline prepared from *trans*-2-aminocyclohexanol (see above) in 1.0 ml. of 5% hydrochloric acid was heated to the b.p. and cooled. A voluminous precipitate of colorless needles (amino-ester hydrochloride) appeared, and redissolved on adding 5 ml. of water. Addition of excess 25% sodium hydroxide gave a precipitate of short colorless needles. These were collected, washed and dried, giving 0.08 g. of ***d,l-trans*-2-benzoylaminocyclohexanol,** m.p. 172–173.5°. After crystallization from 95% ethanol the yield was 0.068 g. (52%) and the m.p. 173.5–174°. A mixed m.p. with an authentic sample[2d] was not depressed.

Infrared Spectrum.[18]—A Nujol mull of the amidine obtained from *trans*-2-aminocyclohexanol was examined with a Baird infrared recording spectrophotometer. The resulting spectrum showed strong absorption maxima at 780, 1090, 1560, 1620, 2650, 3000 and 3350 $cm.^{-1}$.

Toronto, Canada Received December 7, 1950

(17) It is noteworthy that this product collected on a cold condenser as a viscous oil which later froze to an impure solid, but when a warm condenser was used the product was deposited as a pure crystalline sublimate. Presumably orientation of the molecules into the crystal lattice is facilitated at the higher temperature.

(18) We wish to thank Samuel P. Sadtler & Sons, Inc., Philadelphia for infrared measurements.