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Ring Cleavage Reactions of *trans*-2-Amino-3a,4,5,6,7,7a-hexahydrobenzoxazole

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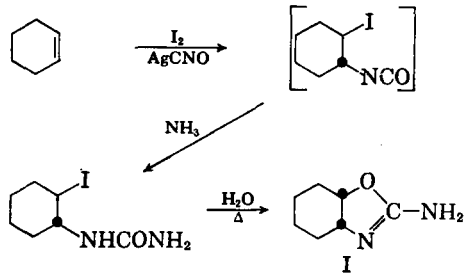
The facile cleavage of the heterocyclic ring of *trans*-2-amino-3a,4,5,6,7,7a-hexahydrobenzoxazole (III) is described. Hydrolysis of the aminooxazoline III gave *trans*-2-hydroxycyclohexylurea (V). Methanolysis of III afforded a mixture of pseudoureas, IVa and IVb, from which a pure tautomer was isolated. In boiling benzene containing a catalytic amount of *p*-toluenesulfonic acid, III was converted to the trimeric biguanide VI. The characterization and proof of the skeletal structure of VI is described. The corresponding *cis*-aminohexahydrobenzoxazole I was found to be stable under identical conditions.

Cis and *trans*-2-amino-3a,4,5,6,7,7a-hexahydrobenzoxazole (I and III) were prepared as part of a study directed toward the synthesis of cyclic carbamates and pseudoureas of potential pharmacological interest. The known *cis*–isomer I was prepared from cyclohexene by the method of Birckenbach and Linhard.[1]



Although the original investigators[1] did not assign the stereochemistry to I, the method of preparation assures a *cis*-fusion.[2] This conclusion was confirmed by the unambiguous synthesis of the corresponding *trans*-isomer III.

The *trans*-isomer III was prepared in good yield by the cyclization of *trans*-2-aminocyclohexanol (II)[3] with cyanogen bromide[4,5] under well defined conditions. From one experiment before these conditions were determined, a 15% yield of III was obtained in addition to an 8. 5% yield of a basic crystalline trimer of III, m.p. 176–176.5°. This substance (hereafter referred to as the trimer VI) exhibited an ultraviolet absorption maximum at 234 mμ (ε 17,500), infrared absorption bands at 3.00, 3.23, 5.97, 6.12, and 6.40 μ and was tentatively assigned the *s*-triazine structure VII on the basis of the spectral and analytical data. However, an authentic sample of VII, prepared by the reaction of the aminoalcohol II with cyanuric chloride in the presence of sodium hydroxide,[6] was found to be different from VI by melting point and infrared spectroscopy.

Several observations concerning the chemical behavior of III led to a rational hypothesis for the structure of the trimer VI. When an aqueous solution of III was heated under reflux for two hours, the known *trans*-2-hydroxycyclohexylurea (V)[7] was formed in 58% yield. Similarly, when a methanol solution of III was heated for an extended period of time, a 50% yield of a crystalline mixture of pseudoureas, IVa and IVb, was isolated.[8] The nitrogen and methoxyl analyses of this mixture tallied with the anticipated values for III plus a mole of methanol and the two C=N infrared absorption bands at 5.97 and 6.13 μ indicated the presence of both tautomers. Repeated recrystallization of this mixture from ethyl acetate–ether afforded a pure tautomer, m.p. 128–129.5°, which showed only the 6.13 μ absorption band and was converted to the original mixture when allowed to stand in methanol solution. The skeletal structure of this pure 128° melting tautomer[9] was established as that of a pseudourea (IVa or IVb) by analysis (C, H, N, OCH_3), infrared spectrum and its conversion to V.

These ring cleavage reactions of III suggested that the trimer VI is derived from III by the same type of ring-opening—that is, by attack of the primary amino group of one molecule of III on

(1) L. Birckenbach and M. Linhard, *Ber.*, **64**, 1081 (1931).

(2) *Cf.* the reaction of cyclohexene with iodine in the presence of silver *p*-toluenesulfonate to give *trans*-2-iodocyclohexyl *p*-toluenesulfonate, S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Am. Chem. Soc.*, **70**, 821 (1948) and the reaction of *trans*-2-benzamidocyclohexanol with thionyl chloride to give *cis*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzoxazole, W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, **72**, 2187 (1950).

(3) Prepared by the ammonolysis of cyclohexene oxide by the excellent method of L. R. Hawkins and R. A. B. Bannard, *Can. J. Chem.*, **36**, 220 (1958).

(4) *Cf.* the reaction of *o*-aminophenol with cyanogen bromide to give 2-aminobenzoxazole, M. P. Pierron, *Ann. chim. et. phys.*, [8] **15**, 191 (1908).

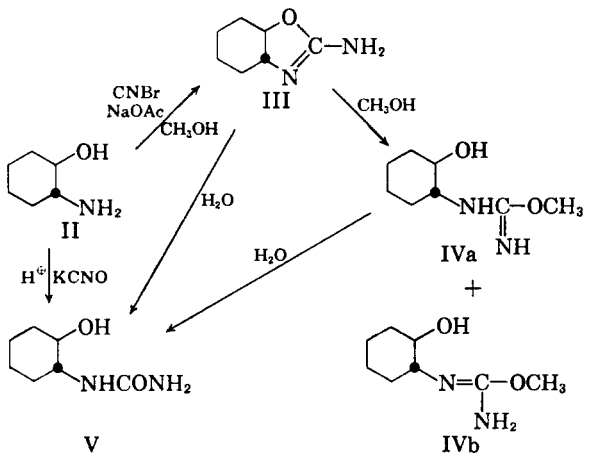
(5) It is interesting to note that a related reaction, cyclization of *trans*-2-aminocyclohexanol with phosgene is reported to give only low yields of the oxazolidinone, M. Mousseron, F. Winternitz, and M. Mousseron-Canet, *Bull. soc. chim. France*, 737 (1953).

(6) By the method of D. W. Kaiser, J. T. Thuston, J. R. Dudley, F. C. Schaefer, I. Heckenbleikner, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951).

(7) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2297 (1955).

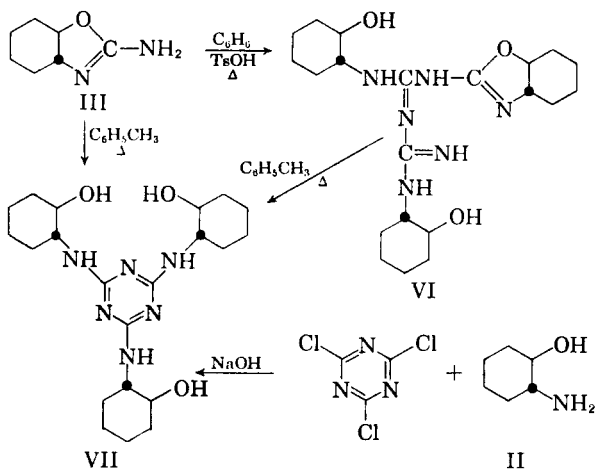
(8) Essentially the same results were obtained when a methanol solution of III was allowed to stand at room temperature overnight.

(9) Because of the insolubility of the 128° melting pseudourea in solvents suitable for spectral analysis and our failure to isolate the other tautomer in pure form, the position of the double bond could not be determined.



the heterocyclic ring of a second molecule followed by attack of this intermediate on a third molecule of III leading to VI (or a double bond tautomer). The spectral properties of VI are in agreement with this structure.[10] If this hypothesis is correct, one would expect the trimer VI to be formed in an inert solvent and to be transformed into its ring-chain tautomer VII. This indeed proved to be the case.

When a benzene solution of III containing a trace of *p*-toluenesulfonic acid was heated under reflux for two and one-half hours, an 86% yield of VI was formed, and when either III or VI was heated in boiling toluene, the *s*-triazine VII was formed in good yield. These results established the skeletal structure of VI, the position of the double bonds being in doubt.



In view of the ready ring-opening of the *trans*-aminooxazoline III, it was thought to be of interest to study the behavior of the corresponding *cis*-isomer I under the same conditions. The *cis*-aminooxazoline I was recovered unchanged after prolonged heating in water, methanol or benzene containing a trace of *p*-toluenesulfonic acid. These results clearly show that the *cis*-isomer, I, is more stable than the *trans*-isomer, III.[11]

The aminooxazolines (I and III) were found to be relatively weak, long acting sympathomimetic agents; the pharmacology of the latter has been reported.[12]

EXPERIMENTAL[13]

cis-2-Amino-3a,4,5,6,7,7a-hexahydrobenzoxazole (I). *trans*-2-Iodocyclohexylurea[1] was prepared in 52.5% yield from cyclohexene (38.3 g., 0.467 mole), iodine (125 g., 0.493 mole), freshly prepared silver cyanate (70.0 g., 0.467 mole), anhydrous ether (700 ml.), and excess anhydrous ammonia and had m.p. 146–148° dec. For analysis, a portion was recrystallized from ethanol (containing a trace of sodium sulphite): m.p. 151–152° dec. (lit.[1] m.p. 155° dec.); λ_{max} 2.93, 3.02, 3.14, 6.03, 6.25, 6.43 μ.

Anal. Calcd. for $C_7H_{13}IN_2O$: N, 10.45. Found: N, 10.09.

Cyclization of the above iodourea (48.0 g., 0.183 mole) in boiling water (675 ml.) gave the aminooxazoline I as a viscous oil, λ_{max}^{neat} 3.05, 3.17, 5.97, 6.23 (shoulder), 6.40 (shoulder), 6.89 μ.

The hydrogen fumarate of I, prepared in 73% yield, had m.p. 210.5–211.5° dec., after one recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{28}N_4O_6$: N, 14.13. Found: N, 14.13.

The picrate of I was prepared in 74% yield and had m.p. 199–201° (lit.[1] m.p. 200–201°) after one recrystallization from methanol.

trans-2-Amino-3a,4,5,6,7,7a-hexahydrobenzoxazole (III). To a well-stirred solution of cyanogen bromide, prepared from sodium cyanide (17.8 g., 0.363 mole), bromine (58.0 g., 0.363 mole), and 5% aqueous methanol (800 ml.), cooled in an ice bath, *trans*-2-aminocyclohexanol (II, 38.0 g., 0.330 mole) dissolved in anhydrous methanol (350 ml.) was added, dropwise, over a 10-min. period. After the addition was complete, the solution was stirred at 0° for 10 min. and at room temperature for 1.5 hr. Aqueous ammonia (28%, *ca.* 50 ml.) was added and the reaction mixture was concentrated under reduced pressure. Cold 40% aqueous sodium hydroxide was added to the residue and the resulting strongly basic solution was extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate and the solvent was evaporated. Crystallization of the residue with ether gave 29.3 g. (64%) of the free base III, m.p. 127–138.5°. For analysis, a portion of this material was recrystallized from ether; m.p. 136–138°; λ_{max} 2.93, 5.95, 6.16 μ.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.63; N, 19.99. Found: C, 60.12; H, 8.70; N, 20.28.

The fumarate of the *trans*-aminooxazoline III was prepared in 93% yield, m.p. 215.5–216° dec. after one recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{28}N_4O_6$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.20; H, 7.19; N, 14.38.

(10) For example, biguanide shows $\lambda_{max}^{H_2O}$ 231 mμ (ϵ 9,500), J. C. Gage, *J. Chem. Soc.*, 221 (1949).

(11) A comparison of the relative stability of these fused heterocyclic systems with that of the corresponding carbocyclic systems, *cis*- and *trans*-hydrindane is of interest. Thus, while *trans*-hydrindane is approximately 0.7 kcal./mole more stable than the *cis*-isomer, *cis*-2-hydrindinone is ten times more stable than the *trans*-compound: W. G. Dauben and K. S. Pitzer in M. S. Newman's *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 37.

(12) E. V. Dietrich, *The Pharmacologist*, 1, 70 (1959).

(13) All melting points were determined on a Kofler block. The infrared spectra were determined as Nujol mulls, unless otherwise stated, with a Model 21 Perkin-Elmer Infrared Spectrophotometer, and the ultraviolet spectra in methanol with a Model 11 Cary Spectrophotometer unless otherwise stated.

1,5-Bis(trans-2-hydroxycyclohexyl)-2-trans-hexahydrobenzoxazolidene biguanide (VI). (*a*) *By isolation as a by-product from a trans-2-aminooxazoline* III *synthesis.* In one experiment run as described above but for a longer period of time (*ca.* 4 hr.), there was obtained a 14% yield of III (isolated as the fumarate) and an 8.5% yield of the biguanide VI, m.p. 176–176.5°; λ_{max} 3.00, 3.23, 5.97, 6.12, 6.40 μ; $\lambda_{max}^{H_2O}$ 234 mμ(ϵ 17,500); $\lambda_{max}^{CH_3OH}$234 mμ (ϵ 17,500); $\lambda_{max}^{0.1N\ HCl}$ 234 mμ (ϵ 18,000).

Anal. Calcd. for $C_{21}H_{36}N_6O_3$: C, 59.97; H, 8.63; N, 19.99; O, 11.41; mol. wt. 420; neut. eq. 210. Found: C, 59.81; H, 8.58; N, 19.85; O, 11.85; mol. wt. (Rast) 454; neut. eq. (potentiometric titration) 216.

(*b*) *By the acid catalyzed trimerization of the trans-2-aminooxazoline* III. A solution of the oxazoline III (2.00 g., 0.0143 mole), *p*-toluenesulfonic acid monohydrate (*ca.* 10 mg.), and dry benzene (40 ml.) was heated under reflux for 2.5 hr. and allowed to stand at room temperature overnight. The insoluble material was collected on a filter and was washed with benzene followed by acetone. The crystalline solid (1.73 g., 87%), so obtained, had m.p. 174–177°. Recrystallization from acetone gave 0.55 g. (28%) of the pure trimer IX, m.p. 173–174° [undepressed on admixture with a sample obtained by method (a)].

N^2,N^4,N^6-Tris(trans-2-hydroxycyclohexyl)melamine (VII). (*a*) *By treatment of cyanuric chloride with trans-2-aminocyclohexanol* (II). A mixture of the aminoalcohol (II, 10.0 g., 0.0870 mole), cyanuric chloride (5.32 g., 0.0289 mole), and water (50 ml.) was heated slowly to boiling with the simultaneous dropwise addition of 0.1*N* sodium hydroxide solution at a rate such that the reaction mixture was slightly alkaline during the heating period. The addition of 3 equivalents of base required 2 hr. After standing overnight, the *s*-triazine VII was collected on a filter and washed thoroughly with water; yield 12.0 g. (97%), m.p. 263–265°. A portion was recrystallized from dimethylformamide for analysis; m.p. 267–268°; λ_{max} 2.99, 6.00, 6.23, 6.55, 6.60, 6.85, 12.56 μ; λ_{max} 218 mμ (ϵ 57,000).

Anal. Calcd. for $C_{21}H_{36}N_6O_3$: C, 59.97; H, 8.63; N, 19.99. Found: C, 59.85; H, 8.61; N, 20.07.

(*b*) *By thermal isomerization of the biguanide* VI. A solution of the biguanide VI (0.300 g., 0.714 mmole) and toluene (5.0 ml.) was heated under reflux for 23 hr. and was then concentrated under reduced pressure. Trituration of the oily residue with warm acetone afforded 0.130 g. (43%) of the *s*-triazine VII, m.p. 264–266° undepressed on admixture with the sample obtained above in (*a*). The infrared spectra of the two products were identical.

(*c*) *By thermal isomerization of the trans-aminooxazoline* III. A solution of III (0.300 g., 0.00214 mole) and toluene (5.0 ml.) was heated under reflux for 6 hr. and evaporated *in vacuo* to dryness. Trituration of the residual oil with warm acetone gave 0.040 g. (31%) of the melamine VII, m.p. and mixed m.p. 266–267°.

3-(trans-2-Hydroxycyclohexyl)-2-methylpseudourea (IVa) *and 1-(trans-2-hydroxycyclohexyl)-2-methylpseudourea* (IVb). A solution of the aminooxazoline III (11.8 g., 0.0938 mole) and absolute methanol (30 ml.) was boiled for 48 hr. and evaporated to dryness *in vacuo*. The residual oil (12.1 g.) was dissolved in boiling benzene and allowed to stand at room temperature. The crystalline solid (6.81 g.), so obtained, had m.p. 120–130° (very small amount melting at 165°); λ_{max} 5.96, 6.13, 6.43 μ. Recrystallization of this product from ethyl acetate–ether gave 3.49 g. (22%) of the mixture of tautomeric pseudoureas, IVa and IVb, m.p. 122–127°; λ_{max} 2.99, 3.08, 5.98, 6.14, 6.43 μ.

Anal. Calcd. for $C_8H_{16}N_2O_2$: N, 16.27; OCH_3, 18.02. Found: N, 16.47; OCH_3, 18.48.

Repeated recrystallization of the above mixture from ethyl acetate–ether furnished a single pseudourea (0.65 g., 10%), m.p. 128.5–129.5°; λ_{max} 2.99, 3.07, 6.13, 6.43 μ.

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27; OCH_3, 18.02. Found: C, 55.79; H, 9.12; N, 16.10; OCH_3, 18.30.

A 0.38-g. (0.0022 mole) sample of the pure pseudourea, m.p. 128–129°, dissolved in absolute methanol (15 ml.) was allowed to stand at room temperature for 60 hr. Evaporation of the solvent under reduced pressure gave 0.38 g. of a crystalline solid, m.p. 117–122°, the infrared spectrum of which was essentially the same as the 122–127° melting product obtained from III.

trans-2-Hydroxycyclohexylurea (V) (*a*) *from trans-2-aminocyclohexanol* (II). *trans*-2-Hydroxycyclohexylurea (V) was prepared by the method of McCasland,[7] m.p. 168.5–170° (lit.[7] m.p. 168–169°); λ_{max} 2.89, 3.03, 6.03, 6.35 μ.

(*b*) *From the pseudourea, m.p. 128–129°.* A solution of the pseudourea (m.p. 128–129°, 0.30 g., 0.017 mole) and water (30 ml.) was heated under reflux for 1 hr. The reaction mixture was concentrated *in vacuo* to one-half its original volume and extracted with methylene chloride. Distillation of the solvent gave 0.05 g. (16%) of unchanged pseudourea, m.p. and mixed m.p. 127–129°. Evaporation of the aqueous phase to dryness gave 0.24 g. of a crystalline solid, m.p. 164–168°. Recrystallization from 95% ethanol afforded 0.063 g. (21%) of the hydroxyurea V, m.p. 167–170°, alone or admixed with the authentic sample.

(*c*) *From the trans-aminooxazoline III.* A solution of III (0.50 g., 0.0036 mole) and water (10 ml.) was boiled for 2 hr. and evaporated under reduced pressure. Trituration of the residue with benzene-ethanol gave 0.33 g. (58%) of the hydroxyurea V, m.p. 168.5–170.5°, alone or admixture with a sample prepared as in (*a*).

Treatment of cis-2-amino-3a,4,5,6,7,7a-hexahydrobenzoxazole (I) *with methanol.* A solution of 0.10 g. (0.71 mmole) of I and absolute methanol (5 ml.) was boiled for 52 hr. Evaporation of the solvent under reduced pressure gave 0.10 g. of a colorless oil which had an infrared spectrum identical with that of I and formed a picrate, m.p. 201–202°, alone or admixed with an authentic sample, in 70% yield.

Treatment of I with benzene in the presence of p-toluenesulfonic acid. A solution of the *cis*-oxazoline (I, 0.087 g., 0.62 mmole), *p*-toluenesulfonic acid (*ca.* 50 mg.) and dry benzene (10 ml.) was boiled for 25 hr. and allowed to stand at room temperature overnight. The solvent was evaporated under reduced pressure. The residual oil was dissolved in methanol (5 ml.) and was added to a methanol solution of picric acid to give the picrate (0.097 g., 69%) of I, m.p. 201–203°, alone or admixed with the authentic sample.

Treatment of I with boiling water. A solution of I (0.071 g., 0.5 mmole) and water (5 ml.) was heated under reflux for 24 hr. The cooled solution was extracted with methylene chloride; the organic extract was dried over magnesium sulfate and evaporated. Treatment of the residue with a methanol solution of picric acid gave 0.087 g. (69%) of the picrate of I, m.p. 200–203°, alone or admixed with the authentic sample.

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