The solubility in ethanol at 25° (about 45 mg./100 ml.) of the aldehyde derivative is about twice that of the ketone derivative, suggesting that the aldehyde may actually predominate in the original deamination product.

Isolation of 2-Keto-1,3-dibenzylidenecyclohexane from Deamination Mixtures.—(A) In a control experiment the preparation[10] of 2-keto-1,3-dibenzylidenecyclohexane was carried out in the presence of added sodium nitrite and acetic acid. A 55–70% yield of dibenzalketone of correct m.p. was obtained, indicating that the method should be capable of detecting cyclohexanone in aminocyclanol deamination mixtures, if present.

(B).—A 151-mg. (1 millimole) portion of D,L-*cis*-2-aminocyclohexanol hydrochloride[1b,1o] was treated in the cold with 2.0 millimoles of sodium nitrite, 1.0 millimole of sodium acetate and 9 millimoles of acetic acid, plus water. Sodium hydroxide (10 millimoles), benzaldehyde (2.4 millimoles) and 4 ml. of ethanol were added after 10 minutes. After long standing 37 mg. of yellow crystals, m.p. 116–118°, separated. A mixed m.p. with the dibenzalketone prepared above was not depressed.

Non-reaction of *d,l-cis*-2-Aminocyclohexanol with Nitrous Acid at Low *p*H.—(A) The aminocyclanol hydrochloride was boiled for 1 or 2 minutes with one equivalent of sodium nitrite in excess dilute aqueous hydrochloric acid. Although a peppermint odor indicated a trace of reaction, on benzoylation a high recovery of the starting material as its N-benzoyl derivative, m.p. 187–189°, was obtained.

(B).—The procedure in (A) was modified by using excess sulfuric acid for 0.5 hour at 0°, then boiling the mixture under reflux for 2 hours. Again a high recovery of starting material (N-benzoyl) was obtained.

(10) Vorländer and Kunze, *Ber.*, **59**, 2082 (1926).

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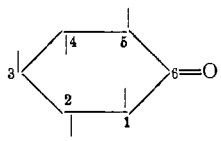
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

N → O Acyl Migration in Epimeric Acetyl Inosamines[1]

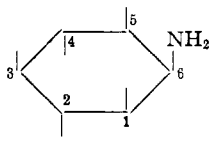
BY G. E. MCCASLAND

(1) The amino-group in *cis*-2-acetaminocyclohexanol is liberated by dilute hydrochloric acid faster than in *trans*. The result is attributed to faster N → O migration in the *cis* epimer. (2) The amino-group of N-acetylinosamine "SA" is liberated faster than that of its epimer "SB," indicating that the "SA" amino-group is *cis* to its two neighboring hydroxyls. (3) The hexacetyl derivative of "aminodesoxyinositol II" has been prepared and is not identical with the hexacetylinosamines "SA," "SB," or "EA." (4) The effect of configuration on the relative basicity of the epimeric 2-aminocyclohexanols is negligible. Each is a weaker base than cyclohexylamine.

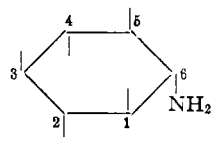
Anderson and Lardy[2] recently reported that the O → N migration is faster in O-acyl derivatives of inosamine-SA than in SB, and that SA is the almost exclusive product of platinum-catalyzed hydrogenation of the oxime of *cis*(1,3,5)-inosose (I). They concluded from these results that the epimer which had been temporarily designated[1d] "SA" has the *cis*(1,3,5,6) configuration (II-A), and that "SB" has the *cis*(1,3,5) configuration (II-B).



I
cis(1,3,5)



II-A
cis(1,3,5,6)
("SA")



II-B
cis(1,3,5)
("SB")

(Hydroxyls to be supplied)

Before learning of Anderson and Lardy's work we had started some experiments on the N → O acyl migration of N-acetylinosamines, and it now seemed desirable to complete these experiments as a check on their proof of configuration.

N → O Migration Mechanisms.—It is well known that the acid-catalyzed deacylation of a 2-acylaminoalkanol (III) in water or alcohol commonly proceeds *via* the 2-acyloxyalkylammonium salt, IV (N → O migration). Isolation of IV is possible when its hydrolysis to the 2-hydroxyalkylammonium salt (V) is slow.[3] Treatment of IV with base liberates the acyloxyalkylamine, which undergoes a rapid reverse migration (O → N) to III. So far as we know the O → N shift always occurs with retention of configuration.

The N → O shift sometimes occurs with inversion, but more commonly with retention. Either VI or VII or their conjugate acids have been proposed[4] as intermediates in the reaction with retention. Welsh[5] has proposed a mechanism for the reaction with inversion.

While our experiments were in progress Fodor and Kiss[6] reported that *cis*-2-benzoylaminocyclohexanol in alcoholic hydrogen chloride gives a more rapid N → O migration than does the corresponding *trans* compound. By O → N migrations with excess base Fodor and Kiss then reconverted each of their amino-ester hydrochlorides back to its respective hydroxy-amide starting material, thus demonstrating retention of configuration for both N → O and O → N migrations under the conditions used (provided one rejects as improbable the occurrence of a single inversion in *both* the forward and reverse migrations.)

If it be assumed that N-acylinosamines in aqueous acid undergo N → O migration and not simple hydrolytic amide cleavage, and that the reaction involves one of the above mechanisms with retention, then an N-acylinosamine with a

(1) For related publications see (a) G. E. McCasland, THIS JOURNAL, **73**, 2293 (1951); (b) McCasland and Smith, *ibid.*, **72**, 2190 (1950); (c) McCasland, Clark and Carter, *ibid.*, **71**, 637 (1949); (d) Carter, Clark, Lytle and McCasland, *J. Biol. Chem.*, **175**, 683 (1948); (e) Carter, Belinskey, Clark, Flynn, Lytle, McCasland and Robbins, *ibid.*, **174**, 415 (1948).

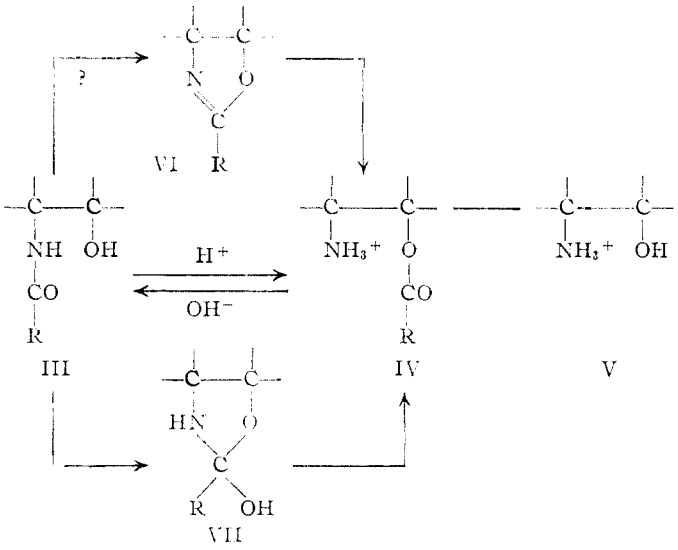
(2) (a) Laurens Anderson, personal communication; (b) L. Anderson and H. A. Lardy, *Abstracts*, Atlantic City Meeting, ACS. Sept., 1949; THIS JOURNAL, **72**, 3141 (1950).

(3) The considerable stability of some 2-acyloxyalkylammonium salts in aqueous acid may be attributed to proton repulsion by the ammonium ion group (away from the carbonyl group).

(4) See Bell, *J. Chem. Soc.*, 2966 (1931); A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).

(5) L. Welsh, THIS JOURNAL, **71**, 3500 (1949); **69**, 128 (1947).

(6) G. Fodor and J. Kiss, *Nature*, **164**, 917 (1949); THIS JOURNAL, **72**, 3495 (1950).



cis neighboring hydroxyl should react more rapidly than *trans*. (If the neighboring hydroxyl did not participate in the reaction, steric hindrance might cause the *cis* form to react more slowly.)

In order to test the validity of our method we first carried out N → O migration experiments with the epimeric 2-acetaminocyclohexanols in dilute aqueous hydrochloric acid. Total liberated amino-group (amino-alcohol and/or amino-ester) was determined at intervals by Van Slyke amino-nitrogen analyses on aliquot portions. With these compounds of known configuration the *cis* epimer liberated its amino-group five to six times faster than the *trans*.[7,8]

The reactions of the epimeric N-acetylinosamines were then studied under similar conditions. The SA epimer liberated its amino-group three to four times faster than the SB and therefore appears to have the *cis* configuration (II-A).

Our results thus serve to confirm and strengthen the conclusions of Anderson and Lardy[2] regarding the configurations of these inosamines.[8a]

Such relative-rate measurements of N → O (or O → N) shifts (which need not involve precise measurements of absolute rates) should furnish a useful test for *cis–trans* configuration in other epimeric aminocyclanol pairs.[9]

(7) A *cis*-1,2-disubstituted cyclohexane such as *cis*-2-acetaminocyclohexanol presumably exists in an (*e*,*p*) "chair" conformation,[8] which is sterically favorable to migration (1–4 shift). The *trans*-epimer could exist in either (*p*,*p*) or (*e*,*e*) conformations. The (*p*,*p*) form would be very unfavorable to migration, while (*e*,*e*) would be about as favorable as the (*e*,*p*)-*cis* form. The behavior of the *trans* epimer will then presumably depend on the percentage of molecules possessing the sterically unfavorable (*p*,*p*) conformation under the conditions of the experiment.

(8) Pitzer and Beckett, THIS JOURNAL, **69**, 977 (1947).

(8a) FOOTNOTE ADDED IN PROOF.—"Aminodesoxyinositol III"[10] has not been available for examination in our laboratory. T. Posternak, *Helv. Chim. Acta*, **34**, 1600 (1951), has recently reported that "III" is identical with "inosamine-SB."[1d,2] By periodic acid and lead tetracetate rate studies Dr. Posternak independently arrived at the same *cis*-(1,3,5) configuration for "SB" indicated by the acyl migration studies.

(9) G. Fodor *et al.*, have recently reported (*J. Org. Chem.*, **14**, 337 (1949)) that certain epimeric N-acylephedrines also show pronounced differences in acyl-migration rates. With such open-chain compounds it is not necessarily true that the epimer which shows a faster migration has a *cis* configuration.

Comparison of Inosamines from Glucose and Inositol.—Inosamine (6-aminocyclohexanepentol) can theoretically exist in eight *meso* and 12 racemic forms. Recently Grosheintz and Fischer[10] synthesized several inosamines by cyclization of nitrodesoxyhexoses. A consideration of these authors' results suggests that their product "aminodesoxyinositol I" may contain four inosamines, of which two should be identical with isosamines "SA" and "SB" derived from *cis* (1,2,3,5)-inositol.[1d] The most probable configuration for their "aminodesoxyinositol II" would be *cis*(1,2,4,5)—not identical with any of the compounds derived from inositol.[8a]

To test this possibility the conversion of aminodesoxyinositol samples[11] to sharp-melting derivatives was undertaken. Aminodesoxyinositol I was (as predicted by the above authors) too inhomogeneous to permit the isolation of any pure derivative. However, aminodesoxyinositol II did give a pure hexaacetyl derivative, which was not identical with any hexaacetylinosamine previously reported.

Effect of Configuration on Basicity.—An electron-attracting, neighboring hydroxyl group should lower the basic strength of an amine regardless of configuration. In addition a secondary effect might conceivably result from greater proximity of the hydroxyl in the *cis* epimer (field effect or chelation).[12]

Potentiometric titrations of the 2-aminocyclohexanol hydrochlorides showed that the pK_a is 9.5 for *trans*, and 9.6 for *cis* (ionic strength 0.1). The effect of configuration is therefore negligible. As would be expected each aminocyclanol is less basic than cyclohexylamine itself (pK_a = 10.2).[13] Glasstone and Schramm recently reported that acyclic amino-alcohols are likewise less basic than the corresponding amines.[14]

Preparation of Ureas.—The urea and α-naphthylthiourea derivatives of *cis* and *trans* 2-aminocyclanols were prepared and characterized for conversion to heterocyclic derivatives but have not proved useful for this purpose.

Acknowledgments.—Early experiments in this investigation were carried out in the laboratory of Dr. H. E. Carter of the University of Illinois, whom the author wishes to thank for encouragement and advice. He is indebted to Dr. H. A. Lardy and Dr. Laurens Anderson for helpful discussions.

Experimental

Köfler micro-block melting points are designated "block"; other melting points are corrected capillary m.p.'s. Carbon–hydrogen microanalyses by Clark Microanalytical

(10) Grosheintz and Fischer, THIS JOURNAL, **70**, 1479 (1948).

(11) Dr. H. O. L. Fischer very kindly supplied samples of aminodesoxyinositols for these experiments.

(12) Such an effect is found in the first and second dissociation constants of maleic and fumaric acids, but the influence of a neighboring hydroxyl group would no doubt be very much weaker than that of a carboxylate ion group.

(13) Waksmundski, *Roczniki Chem.*, **18**, 865 (1938); *C. A.*, **33**, 6689 (1939).

(14) S. Glasstone and A. F. Schramm, THIS JOURNAL, **69**, 1213 (1947).

Laboratories, Urbana, Illinois. Nitrogen volumes are corrected to 0°/760 mm.

Relative Deacetylation Rates of *cis* and *trans* d,l-Acetaminocyclohexanols.—A 2.00 millimole sample of each N-acetyl compound[1b,1o] was dissolved in 1.00 *N* hydrochloric acid *q.s.* 25.0 ml.. in a glass-stoppered volumetric flask. The flasks were maintained in a thermostat at 25.0°. At intervals 5.00-ml. samples were removed for semi-micro Van Slyke amino nitrogen analyses.

Control samples were completely hydrolyzed by boiling under reflux for one hour. The nitrogen determination for *trans* agreed closely with theory, but the *cis* epimer gave an average result 11.5% high.[1a] The following table is corrected for the anomalous *cis* analyses, although the corrections are much too small to affect the qualitative rate results.

Time, hr.	0	23	47	96	216	∞
N Volume, ml. *cis*	0	1.2	2.2	3.7	7.3	9.0
trans	0	0.20	0.35	0.70	1.2	10.4
% Amine liberated						
cis	0	12	22	36	70	100
trans	0	2	4	8	13	100

The results show that during most of the reaction the liberation of *cis* amino-group proceeds 5–6 times faster than that of *trans*.

Relative Deacetylation Rates of N-Acetylinosamines "SA" and "SB."—The procedure was like that above, except as noted. A 40 millimolar solution of each N-acetylinosamine[1d,1e] in 1.00 *N* hydrochloric acid was used. The two flasks were kept in the same water-bath at 26 ± 2°. At intervals 2.00-ml. samples were removed for micro Van Slyke analyses.

Control analyses showed that "SA" gives normal nitrogen values, while "SB" gives anomalous results 9.5% high on the average.[1a] The corrected results are shown in the table:

Time, hr.	0	24	71	164	∞
N Volume, ml. SA	0	0.41	1.13	1.98	22.4
SB	0	0.15	0.30	0.64	24.5
% Amine liberated SA	0	1.8	5.0	8.8	100
SB	0	0.4	1.2	2.6	100

The results indicate that the SA amino-group is liberated 3–4 times faster than SB. The inosamine derivatives react several-fold less rapidly than the 2-aminocyclohexanol derivatives (despite higher concentration and temperature).

Hexacetyl Derivative of "Aminodesoxyinositol II" [*cis*-(1,2,4,5)-Inosamine ?].—A 500 mg. sample of "aminodesoxyinositol II" hydrochloride[10,11] was boiled with 20 ml. of acetic anhydride and 211 mg. of fused sodium acetate for one hour under reflux. The filtered solution was vacuum-distilled to dryness. The water-washed residue was dried *in vacuo*, giving 602 mg. of colorless needles, m.p. 233–235° (block) containing a few prisms of m.p. 210–220°.

Recrystallization from 9 ml. of ethanol gave 486 mg. of colorless needles, melting at 231–232° (block) after a polymorphic change at 215°. After freezing, the compound remelted at 229–231° (block).

A sample recrystallized for analysis melted sharply at 233–234° (block) after polymorphic change at 215°.

Anal. Calcd. for $C_{18}H_{25}O_{11}N$: C, 50.11; H, 5.84; N, 3.25. Found: C, 50.41; H, 6.06; N, 3.32.

The compound is not identical with any of the hexaacetylinosamines previously reported.[1o] On the basis of evidence reported by Grosheintz and Fischer[10] for the parent aminocyclitol, the most probable configuration appears to be *cis*(1,2,4,5).

Potentiometric Titrations of *cis* and *trans* 2-Aminocyclohexanols.—*d,l-cis* and *d,l-trans*-2-aminocyclohexanol hydrochlorides[1b,1o] were each titrated under identical conditions. A 758 mg. (5.00 millimole) sample of recrystallized vacuum-dried hydrochloride was dissolved in freshly-boiled distilled water *q.s.* 50.0 ml. at 25.0°, and immediately titrated at 25.0° with 0.9655 *N* sodium hydroxide. The *p*H of the well-stirred titration solution was determined after each addition of sodium hydroxide with a Macbeth *p*H meter, model A. The following results were obtained:

Ml. NaOH	0.00	0.50	1.50	2.00	2.50
*p*H (*trans*)	6.42	8.58	9.14	9.32	9.48
*p*H (*cis*)	6.38	8.63	9.23	9.40	9.58
Ml. NaOH	3.00	3.50	4.50	5.50	
*p*H (*trans*)	9.60	9.75	10.13	10.98	
*p*H (*cis*)	9.68	9.83	10.21	10.98	

The *p*H at the half-equivalence points was 9.50 for *trans* and 9.60 for *cis*. The pK_a values, at ionic strength 0.1, are therefore 9.5 for *trans* and 9.6 for *cis*.

***d,l-trans*-N-(2-Hydroxycyclohexyl)-urea.**—A 0.5-g. portion of *d,l-trans*-2-aminocyclohexanol[1b,1o] and 0.27 g. of potassium cyanate was dissolved in 3 ml. of water. The clear solution was concentrated in a vacuum desiccator to half-volume. The crystals which had separated were collected and dried. The product was recrystallized from alcohol–benzene, giving 0.2 g. of colorless needles, m.p. 163–165°. A portion recrystallized again for analysis melted at 168–169°.

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.34; H, 8.44; N, 17.59.

Attempted preparation of the *cis* urea in the same manner gave an unpurifiable product of wide melting range, perhaps due to cyclization.

***d,l-trans*-N-(2-Hydroxycyclohexyl)-N′-α-naphthylthiourea.**[15]—The free *trans* aminocyclanol[1b,1o] freshly prepared from 1.51 g. of hydrochloride was dissolved in 45 ml. of pyridine, and 1.93 g. of α-naphthyl isothiocyanate was added. The deep green mixture was refluxed five minutes at atmospheric pressure (mixture turned light orange), and the solvent then was distilled off *in vacuo*. The residual oil was extracted with two 20-ml. portions of boiling water. The hot aqueous extracts were decanted from the residual viscous brown oil and filtered hot.

The viscous oil was then extracted with 30 ml. of boiling ethanol. The residue was a crystalline powder, 0.2–0.3 g., m.p. 183–189° (probably N,N′-di-α-naphthylthiourea).

The ethanolic filtrate after standing one or two hours deposited colorless needles, weight 1.2 g., m.p. 167–169°. A second crop of 0.3 g. was obtained. The product was recrystallized from ethanol, yielding 0.9 g., m.p. 170–172°.

A sample recrystallized again for analysis showed no change in m.p. The compound was practically insoluble in acid or alkali, and it reduced alcoholic silver nitrate.

Anal. Calcd. for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.33; S, 10.67. Found: C, 68.40; H, 6.35; N, 9.21; S, 10.87.

***d,l-cis*-N-(2-Hydroxycyclohexyl)-N′-α-naphthylthiourea.**—The free *cis*-aminocyclanol[1b,1o] from 1.51 g. of its hydrochloride was treated as above up to the extraction with boiling ethanol. In this case the thiourea was mostly in the residual oil. The oil gradually turned crystalline, giving 1.1 g. of a discolored powder, m.p. about 130°: The powder was recrystallized from benzene, giving 0.7 g. of colorless needle clusters, m.p. 146–148°.

Dilution of the original ethanolic extract with water gave an oil. This oil partially dissolved in aqueous alkali. Neutralization of the filtered alkaline solution gave a precipitate which when dried and recrystallized from benzene yielded 0.19 g. of colorless needle clusters identical with those above. A sample recrystallized again from benzene, for analysis, melted at 149–150°.

Anal. Calcd. for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.33. Found: C, 68.15; H, 6.62; N, 9.34.

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(15) Maquenne and Roux (*Ann. chim.*, [8] 1, 112 (1904)) reported that a number of aminopolyols were converted to mercaptoöxazolines when treated by this same procedure using phenyl isothiocyanate.