aminocyclohexyl chloride (VIII), m. p. 159–161°. Recrystallization from benzene gave a colorless product, m. p. 163.5–164.5°.

Anal. Calcd. for $C_{13}H_{16}ONCl$: C, 65.68; H, 6.78; Cl, 14.92. Found: C, 66.03; H, 6.79; Cl, 14.78, 14.95.

Hydrolysis of *d,l-trans*-2-Benzoylaminocyclohexyl Chloride (VIII).—A mixture of 0.119 g. of the chloride VIII, 10 ml. of ordinary acetic acid (undried), and 0.105 g. of silver acetate was heated under reflux with stirring for five hours. The silver chloride was removed by filtration, and the light red filtrate was made basic with dilute (1:1) ammonium hydroxide solution. The cloudy mixture was then concentrated at 20 mm. until crystals began to form, then cooled, and the precipitate was separated by suction filtration and washed with cold water. The crude tan product amounted to 0.077 g. (70% yield), m. p. 170–175°. Recrystallization from benzene gave 0.034 g. of colorless crystals, m. p. 183–185°, undepressed on admixture with the sample of *d,l-cis*-2-benzoylaminocyclohexanol described above.

***d,l-trans*-2-Phenyl-4,5-cyclohexanoöxazoline (IV).**—*d,l-trans*-2-aminocyclohexanol hydrochloride (3.03 g.) was treated with ethyl iminobenzoate (3.73 g.) in ethylene dichloride (200 ml.) just as described above for the *cis* series. The insoluble salts amounted to 1.80 g., and the distillation gave 1.25 g., b. p. 103–104° (20 mm.) and 1.70 g., b. p. 170–175° (19 mm.). The latter fraction melted at 73–77° and represented crude *trans*-oxazoline. Further purification (see above) yielded after a final evaporative distillation at 70–80° (0.10 mm.), colorless material, m. p. 66.2–67.6°.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51. Found: C, 77.60; H, 7.48.

The above oxazoline was easily selectively hydrolyzed to what is undoubtedly *d,l-trans*-2-benzoyloxycyclohexylamine hydrochloride (VII), by allowing the hydrochloride (prepared in anhydrous ether) to stand overnight in air (see above). After sublimation at 135–140° (<0.015 mm.) the product melted at 261–263° (dec.) with darkening at 257° when introduced at 250°. This material showed no m. p. depression on admixture with the specimen of VII described below.

Exhaustive hydrolysis with dilute hydrochloric acid gave a crude hydrochloride, m. p. 163–166°, which after three recrystallizations from ethanol melted at 166.5–169°. On admixture with pure *d,l-trans*-2-aminocyclohexanol hydrochloride (m. p. 175.5–177°), the m. p. was 166–172°, while on admixture with the pure *cis*-isomer, the m. p. was depressed to 142–155°.

Isomerization of *d,l-trans*-2-Benzoylaminocyclohexanol to the O-Benzoyl Derivative.—A solution of 0.85 g. of the N-benzoyl compound in 80 ml. of dry dioxane was saturated with hydrogen chloride and then heated under reflux for three hours. Toward the end of the second hour crystals began to form. After cooling these amounted to 0.39 g. (39% yield), m. p. 246–248° (dec.). Sublimation at 135–140° (<0.015 mm.) gave colorless crystals, m. p. 264–265° (dec.) with darkening at 257° when introduced in bath at 250°. Recrystallization from ethanol–ether did not change the m. p. behavior. Fodor and Kiss[12] report the m. p. of 284° for this substance, but no procedures or analyses are given.

Anal. Calcd. for $C_{13}H_{18}O_2NCl$: C, 61.05; H, 7.09. Found: C, 60.99; H, 6.93.

Summary

An examination of the behavior of *cis*- and *trans*-2-benzoylaminocyclohexanol toward thionyl chloride has provided evidence supporting the inversion-cyclization mechanism of oxazoline formation. The *trans* compound cyclized readily giving the *cis*-oxazoline which on acid hydrolysis yielded *cis*-2-aminocyclohexanol. With the *cis*-N-benzoyl compound, in contrast, there was no evidence of oxazoline formation, but instead the hydroxyl group was replaced by chlorine with inversion to the *trans* series.

Both the *cis* and *trans*-2-phenyl-4,5-cyclohexanoöxazoline were prepared by the interaction of the salts of the corresponding 2-aminocyclohexanols with ethyl iminobenzoate.

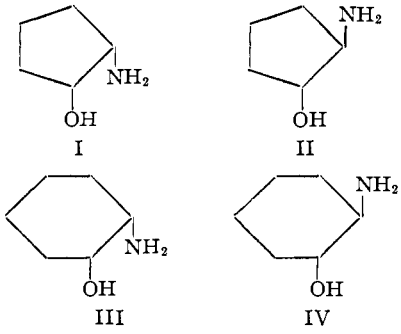
MADISON, WISCONSIN RECEIVED JANUARY 16, 1950

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

Stereochemistry of Aminocyclanols. Synthesis of *cis* Epimers *via* Oxazolines. The 2-Aminocyclopentanols*

BY G. E. McCASLAND AND DONALD ARTHUR SMITH[1]

In order to extend to the cyclopentane series our studies[2] of the effect of *cis-trans* configuration on stereochemical behavior we needed to prepare *d,l-cis*-2-aminocyclopentanol (I). The *trans* epimer (II) of this compound, or of 2-aminocyclohexanol, is readily obtained by amination of the corresponding epoxide. The *cis* epimer (III) of 2-aminocyclohexanol (N-acetyl) is obtained, in about 10% yield, by hydrogenation of the corresponding aromatic compound. This method is obviously not applicable to the cyclopentane derivative.



I II III IV

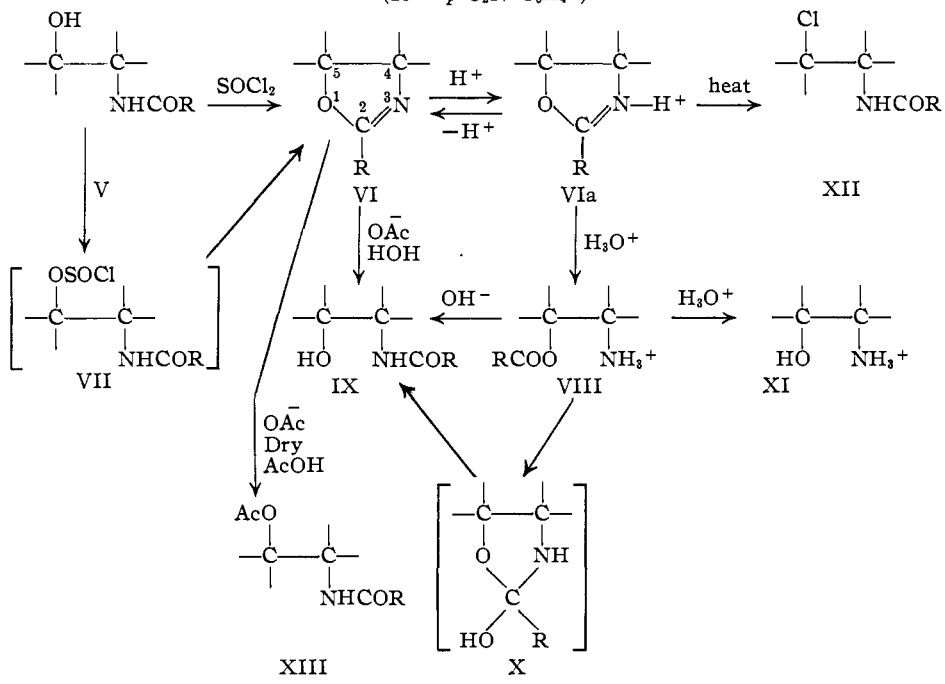
A previous publication[2a] described the preparation of *cis*-2-aminocyclohexanol by the detosylation of *trans*-2-benzoylaminocyclohexyl-*p*-toluenesulfonate in a wet acetic acid (or dry alcohol) solution of sodium acetate. For this and other

(*) Presented before the Organic Division at the Philadelphia meeting of the American Chemical Society, April 1950.

(1) Fellow of the Canadian Industries Limited, 1949–1950.

(2) For related publications see: (a) McCasland, Clark and Carter, THIS JOURNAL, **71**, 637 (1949); (b) Carter, Clark, Lytle and McCasland, *J. Biol. Chem.*, **175**, 683 (1948); also *J. Biol. Chem.*, **174**, 415 (1948).

CHART I
(R = *p*-O_2N-C_6H_4-)



detosylations a protonated oxazoline (*e. g.*, VIa) was postulated as the intermediate; however, in media of low proton-donating power the oxazoline itself may well be the intermediate. In the present work we have prepared and used the pure oxazolines,[3] thus avoiding difficulties often encountered in the preparation of *p*-toluenesulfonates.

We now wish to report the preparation of the required *cis*-2-aminocyclopentanol by this method. The method gives a 40–50% over-all yield of *cis* amino-alcohol from *trans* amino-alcohol. It also gives much better yields of *cis*-2-aminocyclohexanol than previous methods, and should be of general utility for such *trans* → *cis* conversions of 2-aminocyclanols (but not for *cis* → *trans*).[4] The results also help to confirm the proposed mechanism for detosylation, and help to elucidate the configurations[5] of the compounds described in this and in previous publications.

The *trans*-acylaminocyclopentanol (V) was converted to the oxazoline (VI) with thionyl chloride. (In this and in later reactions, *p*-nitrobenzoyl derivatives were more satisfactory than benzoyl because of their solubilities and melting points.) We believe that the displacement of –OH, or –OSOCl, occurs in this reaction with over-all inversion. It is also probable that the *trans* isomers of such cycloalkanoöxazolines, if capable of existence, are much less easily formed, and less stable, than the *cis* isomers.[6,4] Evidence, although of a negative character, for this viewpoint was provided by the failure of thionyl chloride to yield any isolable product with *cis*-2-acylaminocyclanols.

Geometry of Cyclohexane Ring

Geometric and trigonometric analyses of the oxazoline and cyclohexane rings are of interest in this connection. The molecular fragment $-C_4-NH-C_2-O-C_5-$ has a calculated minimum C_5-C_4 interatomic distance[7] of 1.53 Å., in substantial agreement with the normal C–C interatomic distance (1.54 Å.). Therefore the five-membered, saturated, oxazolidine ring should be strain-free. The molecular fragment

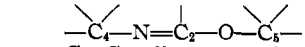
(3) For a general discussion of oxazolines, see (a) Wiley and Bennett, *Chem. Rev.*, **44**, 447 (1949); (b) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).

(4) Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **70**, 2297(1949); **71**, 1101 (1949), reported the epimerization of threonine to *allo*-threonine, and *vice versa*, via the oxazoline. With such (open chain) compounds a 4,5-*trans*-oxazoline can also be formed, so that the reverse change was also effected.

(5) In most studies on oxazolines, configurations have not been considered. In the formation or reactions of racemic oxazolines not substituted at both the 4 and 5 positions (*i. e.*, with only one asymmetric center) stereochemical changes are obscured, because on inversion, each enantiomer assumes the configuration of the other.

(6) Attenburrow, Elliott and Penny (*J. Chem. Soc.*, 310 (1948)) have reported that *d,l*-N-benzoyl-O-tosyl-*allo*-threonine ethyl ester (*erythro*) reacts with potassium acetate-dry ethanol to give the 4,5-*trans*-oxazoline (*threo*). (This would be expected, since there is here no fused ring to hinder formation of the *trans* structure.) Ring cleavage with hydrobromic acid gives (*threo*) *d,l*-threonine, as would be expected. Treatment of N-benzoyl *allo*-threonine ester with thionyl chloride, however, gave both the *cis*- and *trans*-oxazolines. In this latter case partial inversion at C_4 may be due to enolization of the neighboring carbethoxy group; Elliott[32] has reported such an inversion under alkaline conditions.

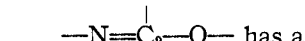
(7) Bond distances were taken from Pauling: C-C, 1.54 Å.; C-O, 1.43 Å.; C-N, 1.47 Å.; C=N, 1.32 Å. Bond angles were assumed to have the tetrahedral values of 109° for single bonds and 125° for double bonds.



however, has a minimum C_5–C_4 distance of 2.36 Å. Therefore, the unsaturated, oxazoline ring is a strained ring.

Fusion of the oxazoline ring at its 4,5 positions to a cyclopentane or cyclohexane ring may increase the oxazoline ring-strain, or create strain in the homocyclic ring. In predicting such effects it is necessary to take note of recent work[8a] which favors the "chair" form for cyclohexanes (at least for alkyl derivatives), and which emphasizes the importance of "equatorial" and "polar" tautomers. A calculation of the O–N interatomic distances in various forms of *cis*- and *trans*-2-aminocyclohexanol may provide a rough indication of the increases in strain to be expected in the corresponding cyclohexanoöxazolines.

According to our approximate calculations,[8] these distances are, for the *trans* epimer: chair (*p*,*p*), 3.7 Å.; boat (symmetrical[9]) 2.9–3.7 Å. For the *cis* epimer the values are: chair (*e*,*p*), 2.9 Å.; boat (symmetrical), 2.5–2.9 Å. Thus the range for *trans* is 2.9–3.7 Å.; and for *cis* 2.5–2.9 Å. Since the molecular fragment



has a calculated O–N interatomic distance of 2.42 Å., *trans*-2-aminocyclohexanol should less easily form an oxazoline than *cis*, except in the improbable circumstance that all the *cis*-2-aminocyclohexanol molecules have their maximum O–N distance, and all the *trans* molecules their minimum distance, respectively.

In the case of the more rigid, more coplanar, cyclopentane ring, *trans* oxazoline formation should be even less probable.

Ring Cleavage and Acyl Migrations

The opening of the oxazoline ring to give the acyloxyalkylammonium salt (VIII) takes place very rapidly in hot aqueous acid solution. We believe that the opening occurs at the C=N bond, with retention of configuration, so that VIII is the *cis* epimer.

When the free acyloxyalkylamine is liberated from VIII with aqueous sodium hydroxide, O → N migration occurs almost instantly, to give the *cis*-acylaminoalkanol (IX). Whether this occurs through the hydroxyoxazolidine (X) by a unimolecular mechanism[10,11] or by a dimolecular ester-amination, the expected result is retention of configuration. The oxazoline is not a probable intermediate here, because of its relative stability to base.

The acylamino compound IX is readily hydrolyzed to the desired *d*,*l*-*cis*-2-aminocyclopentanol, which was isolated as its hydrochloride (XI), m. p. 180–181° with decomposition, and characterized as its N-benzoyl derivative, m. p. 130–131°. In these reactions also, retention is the expected result.

A short-cut hydrolysis of the amino-ester hydrochloride VIII, or the oxazoline VI, likewise gives the desired product XI.

Cyclohexane Series

An exactly similar series of reactions was carried out with *trans*-2-*p*-nitrobenzoylaminocyclohexanol, giving the *cis* amino-alcohol hydrochloride in 40–50% over-all yield. A mixed melting point with the product[2a] obtained by catalytic hydrogenation of 2-acetaminophenol, and hydrolysis, was not depressed. Thus *cis*-2-aminocyclohexanol is now also readily accessible in good yield, from the *trans* compound.

The cyclohexanoöxazoline hydrochloride (which reacts readily with aqueous silver nitrate) resolidifies after fusion at 142–144° to an isomeric compound of m. p. 180–181°, which is inert to hot silver nitrate solution, but gives a correct halogen analysis. We believe this compound to be 2-*p*-nitrobenzoylaminocyclohexyl chloride. The *cis* epimer of this compound was prepared from the *cis*-chloroalkylamine hydrochloride and found to melt at 160–161°; therefore the new compound has been assigned the *trans* configuration XII. It is, so far as we know, the first *trans*-chlorocyclanamine derivative. The surprisingly inert chlorine, which we expected only in the *cis* epimer, must be attributed to polar or steric effects operative in both epimers.[12]

In early experiments we also prepared *cis*-2-aminocyclopentanol (N-benzoyl) by reaction of the *trans*-*p*-toluenesulfonate with wet acetic acid–sodium acetate, but the yield was poor.

Oxazolines as Intermediates in Displacement Reactions.—In a previous publication[2a] we suggested that displacement of a group Y (*e. g.*, *p*-toluenesulfonoxy) from a compound of the type 2-Y-1-acylaminoalkane might proceed by way of a cyclic intermediate such as the oxazolinium ion (VIa). (The intermediate may also be the oxazoline itself.) This raised the ques-

(8) (a) Pitzer and Beckett, THIS JOURNAL, **69**, 977 (1947). (b) To estimate the O–N interatomic distance, the diagonal O–N of a polyhedron OC_1C_2N was calculated, where O is not in the plane C_1C_2N. The lengths of OC_1, C_1C_2, and C_2N (bond distances), and the angles OC_1C_2 and C_1C_2N (bond angles, assumed tetrahedral) are known. The only remaining datum needed is the angle between the planes C_1C_2N and OC_1C_2. From inspection of models it is apparent that this interplanar angle may have the following values: 180° for *trans* chair (*p*,*p*); 120° for *trans* boat ("amidships"); 60° for *trans* (*e*,*e*) or *cis* (*e*,*p*); and 0° for *cis* boat ("amidships"). It should be noted that the configurations of the atoms at the "bow" (or "stern") of the boat form are the same—*trans* (*e*,*e*) or *cis* (*e*,*p*)—as in the chair form; while the configurations on the two sides of the boat ("amidships") do not occur in the chair form.

(9) Only the symmetrical boat form was considered. The boat form can shift through a continuous series of non-symmetrical forms (in which each ring-carbon in turn becomes the "bow") while retaining nearly tetrahedral angles. But inspection of a model indicates that during such changes the *trans* O–N interatomic distance does not become less than 2.9 Å.

(10) Welsh, THIS JOURNAL, **69**, 131 (1947); **71**, 3500 (1949).

(11) Fodor *et al.*, *J. Org. Chem.*, **14**, 337 (1949).

(12) The isomerization of other oxazoline hydrochlorides to β-chloroalkylamides by heat alone, by hot thionyl chloride, or by hydrogen chloride in non-aqueous solvents, has been reported; *cf.* E. M. Fry,[8b] also Takeda, *Chem. Abs.*, **11**, 3241 (1917). In the case of 2-phenyloxazoline, even aqueous hydrochloric acid will effect this change (Gabriel and Heymann, *Ber.*, **23**, 2493 (1890)). Configuration of the products was in general not discussed.

tion: Will the oxazoline, or oxazolinium ion, itself yield the predicted products under each of the specified solvolysis conditions?

We have now some experimental evidence on this question. *d,l*-2-*p*-nitrophenyl-4,5-*cis*-cyclohexanoöxazoline reacted with a dry acetic acid solution of sodium acetate to give primarily the *trans*-acylaminoalkyl acetate (displacement at C_5 with inversion). When the same reaction was carried out with a small amount of added water, the product was primarily the *cis*-acylaminoalkanol (displacement at C_2— retention at C_5).

The results are in accord with prediction. Since the reaction of oxazoline with acetate in dry acetic acid is slow, it should be possible to isolate the oxazoline from a detosylation reaction mixture; however, we have not yet accomplished this.[6]

Experimental

All melting and boiling points are corrected. "Wet carbon" analyses[13] are starred (C*). Halogen analyses by Zacherl-Krainick method.[14] Remaining microanalyses are by R. Pyke.

Cyclopentane Series

Cyclopentanone.—The usual procedure[15a] with barium hydroxide and adipic acid gave a 75% yield of colorless liquid, b. p. 130–133°, $n^{20}D$ 1.4358.

Cyclopentanol.—The platinum-catalyzed hydrogenation[16] of cyclopentanone gave 75–80% yields, but required ten hours per run.

Raney nickel was more convenient for large scale preparation. At 100 atm. (130–140°) the hydrogenation showed an induction period of six to seven hours, followed by rapid completion in one hour. When a little cyclopentanol was added at the start, the induction period was eliminated[17] and the entire hydrogenation went to completion in one hour. A 90% yield of colorless product, b. p. 136–140°, $n^{20}D$ 1.4160, was obtained.

Cyclopentene.—For some experiments commercial cyclopentene (Brickman, Montreal) was used. For others, cyclopentene was prepared by a modified cyclohexene procedure.[15c] Dropwise addition of the sulfuric acid to stirred, cooled cyclopentanol, and avoidance of overheating were necessary for good yields. Phosphorus pentoxide did not improve the yields, 75% being the best obtained. The product was a colorless liquid, b. p. 43–46°, $n^{18}D$ 1.4218.

***d,l-trans*-2-Chlorocyclopentanol.**—Treatment of cyclopentene with excess hypochlorous acid[15b] gave a 43% yield of the colorless liquid after one distillation, b. p. 75–85° at 15 mm., $n^{23}D$ 1.4795.

1,2-Epoxycyclopentane.[18]—(a) The reaction of cyclopentene with perbenzoic acid was unsatisfactory. (b) Aqueous sodium hydroxide treatment[15d] of the chlorohydrin gave better results than treatment with fused potassium hydroxide in dry ether. A 40% yield of colorless liquid, b. p. 99–102°, $n^{23}D$ 1.4330, was obtained.

***d,l-trans*-2-Aminocyclopentanol Hydrochloride.**—(a) Direct aqueous amination of the chlorohydrin gave less than 10% yield. (b) The epoxide was heated with excess aqueous ammonia at 110° (sealed tube) for one hour. The free amino-alcohol was vacuum-distilled, dissolved in dilute hydrochloric acid, and the solution vacuum-distilled to dryness, giving a 40% yield of the hydrochloride,[16] colorless plates, m. p. 193–194°.

***d,l-trans*-2-*p*-Nitrobenzoylaminocyclopentanol.**—The general acylation procedure of Leffler and Adams[19] was used, giving an 86% yield of pale yellow prisms after one recrystallization from ethanol, m. p. 160–161°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.8; H, 5.61; N, 11.2.

***d,l*-2-*p*-Nitrophenyl-4,5-*cis*-cyclopentanoöxazoline-2.**—Two grams of *trans*-2-*p*-nitrobenzoylaminocyclopentanol was treated with 6.6 g. of purified thionyl chloride at room temperature. After three hours, the clear yellow solution was poured into 40 ml. of dry ether, and allowed to stand three hours more. The pale yellow precipitate was filtered (sintered glass), and washed successively with dry ether (10 ml.) and water (20 ml.). The residue was recrystallized from absolute ethanol, giving 0.35 g. of colorless needles, m. p. 138–140°. Neutralization of the aqueous filtrate with concentrated sodium hydroxide gave 0.85 g. more oxazoline, total yield 1.2 g. (65%). A sample purified for analysis melted at 139–140°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; N, 12.1. Found: C*, 61.9; N, 11.9.

The compound is readily soluble in dilute hydrochloric acid, and is precipitated unchanged on immediate addition of dilute alkali.

Treatment of the oxazoline with ethanolic picric acid yielded the picrate, yellow needles, m. p. 210°, with decomposition.

Anal. Calcd. for $C_{19}H_{17}N_5O_{10}$: N, 14.7. Found: N, 14.4.

***d,l*-2-*p*-Nitrophenyl-4,5-*cis*-cyclopentanoöxazoline-2 Hydrochloride.**—An absolute ethereal solution of the oxazoline was treated with dry hydrogen chloride, giving a gummy precipitate, which solidified to a white powder, yield 90%, m. p. 150–151°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3 \cdot HCl$: N, 10.45; Cl, 13.2. Found: N, 10.51; Cl, 13.6.

The compound tends to lose hydrogen chloride on standing.

***d,l-cis*-2-*p*-Nitrobenzoxycyclopentylamine Hydrochloride.**—Treatment of the oxazoline (0.5 g.) in the same manner as the cyclohexane derivative gave 0.6 g. of colorless needles, m. p. 178–179° after recrystallization from absolute ethanol–petroleum ether (1:4).

Anal. Calcd. for $C_{12}H_{15}N_2O_4Cl$: C, 50.27; H, 5.27; N, 9.77. Found: C, 49.9; H, 5.22; N, 9.84.

***d,l-cis*-2-*p*-Nitrobenzoylaminocyclopentanol.**—The procedure used for the cyclohexane derivative (see below) gave quantitative O → N migration. The acylaminocyclanol was obtained as colorless needles, m. p. 167–168°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.6; N, 11.2. Found: C*, 57.3; N, 11.5.

***d,l-cis*-2-Aminocyclopentanol Hydrochloride.**—Refluxing of either the oxazoline, or the amino-ester hydrochloride, or the *cis*-*p*-nitrobenzamide, with *N* hydrochloric acid for two to three hours gave the amino-alcohol hydrochloride, with yields of 72, 70 and 65%, respectively. The product was isolated as in the cyclohexane series, giving colorless leaflets, m. p. 179–180° with decomposition. Recrystallization from ethanol–benzene (1:4) failed to raise the m. p.

***d,l-trans*-2-Benzoylaminocyclopentanol.**—Acylation of *trans*-2-aminocyclopentanol with benzoyl chloride gave 86% of colorless leaflets, m. p. 120–121°.

(13) "Wet carbons" were determined by the method of Van Slyke and Folch, *J. Biol. Chem.*, **136**, 509 (1940).

(14) Zacherl and Krainick, *Microchemie*, **11**, 61 (1932); see also Stonestreet and Wright, *Can. J. Research*, **18B**, 246 (1940).

(15) (a) "Org. Syn.," Coll. Vol. I, second edition, p. 192; (b) *ibid.*, p. 158; (c) *ibid.*, p. 183; (d) *ibid.*, p. 185.

(16) Yohe and Adams, THIS JOURNAL, **50**, 1505 (1928).

(17) It is known that hydrogen donor solvents, *e. g.*, alcohols, will reduce ketones in the presence of Raney nickel even without hydrogen gas. (See D. P. Hallada, *University of Illinois Organic Chemistry Seminar Abstracts*, November 18, 1949). However, the autocatalytic effect observed by us requires some mechanism by which more than one molecule of ketone is reduced per molecule of alcohol oxidized.

(18) (a) Rothstein and Rothstein, *Compt. rend.*, **209**, 761 (1939); (b) Godchot and Mousseron, *ibid.*, **194**, 2061 (1932).

(19) Leffler and Adams, THIS JOURNAL, **59**, 2256 (1937).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.36. Found: C, 70.6; H, 6.99.

Tosylation of *d,l-trans*-2-Benzoylaminocyclopentanol.—Two grams of the *trans* benzamide in dry pyridine was treated with a slight excess of *p*-toluenesulfonyl chloride at 0°. After twenty-four hours at 20°, the clear red solution was cooled to 0° and treated with 3 ml. of 6 *N* hydrochloric acid and 3 ml. of water. The gummy precipitate was filtered off and recrystallized from ethanol, giving 0.16 g. of "A" (see below), colorless needles, m. p. 125–126°.

The above filtrate was neutralized with sodium carbonate, and the liquid organic phase was separated. Vacuum-distillation of this phase gave a dark solid residue. The residue was extracted with ethanol, and the evaporated extract was recrystallized from benzene–ligroin, giving 800 mg. of 2-benzoylaminocyclopentyl *p*-toluenesulfonate, colorless needles, m. p. 168–169°. A sodium fusion test for sulfur was positive.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: N, 3.89. Found: N, 3.59.

***d,l-trans*-2-Hydroxycyclopentyl-*p*-toluenesulfonamide.**—Alkaline hydrolysis at room temperature of 100 mg. of N-(*trans* - 2 - benzoyloxycyclohexyl) - *p* - toluenesulfonamide (Product "A" above) followed by neutralization, and recrystallization gave 50 mg. colorless needles, m. p. 95–96°.

Anal. Calcd. for $C_{12}H_{17}NO_3S$: N, 5.48. Found: N, 5.41.

The compound fell into the N-alkyl sulfonamide solubility class, and gave a positive sodium fusion test for sulfur. However it is different from "le *p*-toluène sulfo-2-aminocyclopentanol" reported by Mousseron.[18b]

***d,l-cis*-2-Benzoylaminocyclopentanol.**—(a) Leffler-Adams acylation[19] of *cis*-2-aminocyclopentanol from the oxazoline gave a 90% yield of colorless prisms, m. p. 130–131°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: N, 6.83. Found: N, 6.96.

(b) Treatment of 200 mg. of the *trans*-tosyl compound with wet acetic acid–sodium acetate gave only 15 mg. of product, identical with that in (a).

Cyclohexane Series

***d,l-trans*-2-Aminocyclohexanol Hydrochloride.**—The compound was prepared as previously described.[2a] After twenty-four hours' shaking some chlorohydrin remains unchanged; for maximum yield, this residue should be recycled.

***d,l-trans*-2-*p*-Nitrobenzoylaminocyclohexanol.**[19]—Leffler-Adams acylation gave a 90% yield of pale yellow needles, m. p. 210–211° after recrystallization from ethanol.

***d,l-trans*-2-*p*-Nitrobenzoylaminocyclohexyl Acetate.**—The procedure used by Raiford and Mortensen[20] for the benzoyl derivative gave a 50% yield of colorless prisms, m. p. 179–180°.

Anal. Calcd. for $C_{15}H_{18}N_2O_5$: N, 9.15. Found: N, 9.40.

Ethyl *p*-Nitrobenzimidate Hydrochloride.—Dry hydrogen chloride was bubbled through a suspension of 1.0 g. of *p*-nitrobenzonitrile in 20 ml. of absolute ethanol for three hours at 0.5°. The resultant clear solution was poured into 50 ml. of dry ether, and the white precipitate collected. Recrystallization from absolute ethanol–petroleum ether (5:1) gave 0.5 g. of colorless needles, m. p. 142–143° if placed in a hot-bath. The material resolidified after melting and gave a second m. p. of 199–200°. The higher melting compound was identified as *p*-nitrobenzamide by mixed m. p. with a known sample.

***d,l*-2-*p*-Nitrophenyl-4,5-*cis*-cyclohexanoöxazoline-2.**—(a) Treatment of the *trans*-*p*-nitrobenzamide with concentrated sulfuric acid gave a poor yield of the oxazoline,[21] m. p. 120–121°. (b) Three grams of the *trans*-*p*-nitrobenzamide was treated at 25° with a fourfold excess of thionyl chloride. After several hours at 25°, the yellow solution was poured into dry ether at 0°. The white precipitate was collected, and washed successively with dry ether and 30 ml. of water. The cold aqueous washings were neutralized with concentrated sodium hydroxide, giving a white precipitate. On recrystallization from absolute ethanol, this yielded 1.8 g. (64%) of pale yellow leaflets, m. p. 120–121°. Repeated recrystallization and vacuum sublimation failed to change the m. p.

In some runs the thionyl chloride reaction mixture was vacuum-distilled to dryness. The crude hydrochloride, after washing with ether, melted at 140–144°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.73; N, 11.4. Found: C, 63.5; H, 5.66; N, 11.5.

The compound is soluble in dilute acid, and immediate addition of alkali precipitates it unchanged. (c) Repeated attempts to synthesize the oxazoline from ethyl *p*-nitrobenzimidate[22] and *cis*-2-aminocyclohexanol yielded only unchanged starting material.

***d,l*-2-*p*-Nitrophenyl-4,5-*cis*-cyclohexanoöxazoline-2 Hydrochloride.**—(a) This compound was present in the crude thionyl chloride product but could not be fully purified. Heating with a little water converted it to the amino-ester hydrochloride, but neutralization of a solution in cold water gave the oxazoline. (b) Dry hydrogen chloride was passed into a dry ethereal solution of the analytically pure oxazoline. The pale yellow powder obtained in 87% yield melted at 142–144°, and again at 170–175° after resolidification (see below). Attempted recrystallization caused partial decomposition.

Anal. Calcd. for $C_{13}H_{15}N_2O_3Cl$: C, 55.2; N, 9.91; Cl, 12.5; eq. wt., 282. Found: C*, 55.1; N, 9.71; Cl, 12.5; eq. wt., 265.

The compound is water-soluble, and reacts with aqueous silver nitrate. Immediate basification of an aqueous solution regenerates oxazoline along with some *cis*-*p*-nitrobenzamide.

***d,l-trans*-2-*p*-Nitrobenzoylaminocyclohexyl Chloride.**—Oxazoline hydrochloride (50 mg.) was fused, then cooled. The resultant solid, recrystallized from 80% ethanol, yielded 30 mg. of colorless needles, m. p. 180–181°; mixed m. ps. with the 2-chloro- and 2-hydroxy-, *cis*-*p*-nitrobenzamides were depressed.

The compound was insoluble in water and gave a positive Beilstein halogen test, but was totally inert to boiling alcoholic silver nitrate.

Anal. Calcd. for $C_{13}H_{15}N_2O_3Cl$: C, 55.2; N, 9.91; Cl, 12.5. Found: C*, 55.2; N, 10.0; Cl, 12.2.

***d,l-cis*-2-*p*-Nitrobenzoylaminocyclohexyl Chloride.**[19]—*cis*-2-Chlorocyclohexylamine hydrochloride was acylated by the method of Leffler and Adams, giving a purified yield of 60%, m. p. 160–161°.

Anal. Calcd. for $C_{13}H_{15}N_2O_3Cl$: C, 55.2; H, 5.35; N, 9.94. Found: C, 55.1; H, 5.22; N, 10.25.

***d,l-cis*-2-*p*-Nitrobenzoxycyclohexylamine Hydrochloride.**—A solution of 1.8 g. of the oxazoline in 20 ml. of 5% hydrochloric acid was heated just to boiling, and allowed to cool. The product crystallized in pale yellow needles, yield, 2.1 g., m. p. 230–232°, with decomposition. Several recrystallizations from absolute ethanol–petroleum ether (1:4) raised the m. p. to 235–236°.

Anal. Calcd. for $C_{13}H_{17}O_4N_2Cl$: C, 51.9; H, 5.70; N, 9.32. Found: C, 51.9; H, 5.59; N, 9.43.

This compound is slightly soluble in water, and reacted with aqueous silver nitrate.

***d,l-cis*-2-*p*-Nitrobenzoylaminocyclohexanol.**—(a) A suspension of 2.0 g. of the amino-ester hydrochloride in 20 ml. of water was basified with concentrated sodium hydroxide. The voluminous white precipitate was recrystallized from 95% ethanol, giving 1.6 g. of pale yellow needles, m. p. 173–175°. A sample recrystallized for analysis melted at 175–176°. (b) This compound can

(20) Raiford and Mortensen, THIS JOURNAL, **50**, 1201 (1928).

(21) Leffler and Adams[19] reported a m. p. of 129.5–130.5° for this oxazoline.

(22) *Cf.* Elliott, *Nature*, **162**, 657 (1948); *Chem. Abs.*, **43**, 3787 (1948); *J. Chem. Soc.*, 589 (1949).

also be prepared directly from the oxazoline, in 95% yield. A mixed m. p. with the product prepared by acylation of *cis*-2-aminocyclohexanol (from 2-acetaminophenol) was undepressed.

Anal. Calcd. for $C_{12}H_{16}O_4N_2$: C, 59.2; H, 6.12; N, 10.6. Found: C, 59.4; H, 6.03; N, 10.5.

d,l-cis-2-Aminocyclohexanol Hydrochloride.—(a) Two grams of the *cis*-*p*-nitrobenzamide was refluxed in 15 ml. of 4 *N* hydrochloric acid for three hours. After removal of *p*-nitrobenzoic acid, the solution was basified and extracted with chloroform–ether (1:1). The dried extract was saturated with dry hydrogen chloride, yielding the amino-alcohol salt, which was recrystallized from ethanol-benzene (1:5), giving 0.75 g. of colorless leaflets, m. p. 185–190°. A portion of the product was benzoylated and a mixed m. p. with the product (N-benzoyl) obtained from hydrogenation of 2-acetaminophenol was not depressed. (b) Hydrolysis of either the oxazoline or the amino-ester hydrochloride for five hours with 4 *N* hydrochloric acid gave 75 and 73% yields, respectively, of the same product.

Reaction of *cis*-2-*p*-Nitrobenzoylaminocyclohexanol with Thionyl Chloride.—The procedure used for the *trans* isomer gave only starting material at room temperature, and at higher temperatures extensive decomposition resulted.

Reactions of Oxazolines in Acetic Acid Solutions

Retention of Configuration with Wet Acetic Acid–Sodium Acetate: Formation of *d,l,cis*-2-*p*-Nitrobenzoylaminocyclohexanol.—A solution of 0.95 g. of acetic acid, 0.05 g. of water, 0.1 g. of fused sodium acetate, and 0.2 g. of the oxazoline was refluxed for three hours. The solution was cooled, and made alkaline with sodium carbonate. The white precipitate was recrystallized from dilute ethanol, giving 0.13 g. of colorless needles, m. p. 174–176°. A mixed m. p. with an authentic sample of *cis*-2-*p*-nitrobenzoylaminocyclohexanol was not depressed.

Inversion of Configuration with Dry Acetic Acid–Sodium Acetate: Formation of *d,l-trans*-2-*p*-Nitrobenzoylaminocyclohexyl Acetate.—An anhydrous solution was prepared by refluxing for two hours a mixture of 9.5 ml. of glacial acetic acid, 0.5 ml. of acetic anhydride and 1.0 g. of fused sodium acetate. A 1-ml. aliquot of this solution was added to 0.40 g. of the oxazoline, and the mixture refluxed four hours with exclusion of moisture. The resultant solution was cooled, and diluted with 4.0 ml. of water, giving a colorless oil, which solidified within half an hour. The solid was collected, and washed with 5 ml. of 5% hydrochloric acid. Recrystallization from absolute ethanol gave 0.20 g. of colorless prisms, m. p. 173–178°. A further recrystallization gave 0.12 g., m. p. 178–180°. A mixed m. p. with *trans*-2-*p*-nitrobenzoylaminocyclohexyl acetate was not depressed. (Basification of the above acid washings gave 30 mg. of unchanged starting material.)

The identity of the product was confirmed by hydrolysis of a portion with dilute alcoholic sodium hydroxide at 25° to *trans*-2-*p*-nitrobenzoylaminocyclohexanol. A mixed m. p. with an authentic sample was not depressed.

Summary

1. *trans*-2-Acylaminocyclanols react with thionyl chloride to give 4,5-*cis*-cycloalkanoöxazolines, which are easily hydrolyzed to *cis*-2-aminocyclanols. Configurations are discussed in relation to probable mechanisms.[23]

2. 2-*p*-Nitrophenyl-4,5-*cis*-cyclohexanoöxazoline reacts with dry sodium acetate–acetic acid with inversion to give primarily *trans*-2-acylaminocyclohexyl acetate. The presence of a small amount of added water changes the product to *cis*-2-acylaminocyclohexanol.

3. The O–N interatomic distance has been calculated for equatorial-polar and chair-boat tautomers of *cis* and *trans* 2-aminocyclohexanol. The results may aid in predicting the ease of formation of heterocyclic rings fused to cycloalkane rings.

(23) McCasland, Clark and Carter[28]; *cf.* Winstein, *et al.*, THIS JOURNAL, **64**, 2796 (1942).

TORONTO, CANADA RECEIVED JANUARY 19, 1950

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Reactions in the β-Furan Series—Synthesis and Reactions of 3-Chloromethylfuran and Some Related Compounds

BY EDWARD SHERMAN[1] AND E. D. AMSTUTZ

α-Furfuryl chloride is an interesting substance because of the various factors which contribute to its unique chemical characteristics. Thus it possesses the simple allylic structure, an extended allylic system and the β-halogen ether grouping. In order better to understand the contributions of these various systems toward the chemical behavior of the molecule in reaction we undertook the study of the isomeric halide, β-furfuryl chloride. Since the latter substance, which possesses only an allylic system, now proves to have a close relationship not only to α-furfuryl chloride but also to β-thenyl chloride, benzyl chloride and cinnamyl chloride the pertinent chemistry of these materials is briefly reviewed.

When α-furfuryl chloride was treated with strong aqueous potassium cyanide,[2] there was obtained a mixture of nitriles[3] reported[4] to consist of approximately 85% of 5-methyl-2-furonitrile and 15% of 2-furylacetonitrile. Under comparable conditions, 3-thenyl bromide has been reported[5] to yield, on subsequent hydrolysis, only 3-thienylacetic acid. Scott[6] was unable to detect the presence of "abnormal" products (*i. e.*, products of allylic reaction) in the reaction of benzyl chloride

(1) (a) Taken in part from a dissertation presented by Edward Sherman to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1949. (b) Present address: Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois.

(2) Kirner and Richter, THIS JOURNAL, **51**, 3131 (1929).

(3) (a) Reichstein, *Ber.*, **63B**, 749 (1930); (b) Runde, Scott and Johnson, THIS JOURNAL, **52**, 1284 (1930).

(4) Scott and Johnson, *ibid.*, **54**, 2549 (1932).

(5) Campaigne and LeSuer, *ibid.*, **70**, 155 (1948).

(6) Ref. 9, p. 651, footnote 12; ref. 4, p. 2551, footnote 7.