Reaction of *trans*-2-Acylaminocyclanols with Thionyl Chloride[1]

R. A. B. BANNARD, N. C. C. GIBSON, AND J. H. PARKKARI
Defence Research Establishment Ottawa, Ottawa, Canada

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trans-2-Acetamidocyclohexanol (**1**; $n = 2$, R = CH_3) on addition to thionyl chloride in chloroform at 0° was converted rapidly and quantitatively to D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride (**2**; $n = 2$, R = CH_3) judging from shifts in the methyl proton resonances of the n.m.r. spectra of the amide and the reaction solution. The intermediate chlorosulfinate was estimated to have a half-life of less than 2.25 min. The oxazoline salt was isolated in 98% yield by sublimation of the crude product *in vacuo* and was identified by its i.r. and n.m.r. spectra and by its facile and almost quantitative hydrolysis to *cis*-2-aminocyclohexanol hydrochloride. The oxazoline salts **2** ($n = 1$, R = CH_3, C_6H_4-*p*NO_2 and $n = 2$, R = C_6H_5, C_6H_4-*p*NO_2) were readily obtained in 95% yield or better by the same general method and it was shown that the *trans*-2-acetamidocyclanols are the preferred starting materials for conversion to *cis*-2-aminocyclanol derivatives by the thionyl chloride inversion reaction. The oxazoline bases **4** ($n = 1$, R = CH_3, C_6H_4-*p*NO_2 and $n = 2$, R = CH_3, C_6H_4-*p*NO_2) were readily obtained in high yield from the corresponding salts and differences in the i.r. and n.m.r. spectral characteristics of the salts and bases are reported.

La D,L-méthyl-2 cyclohexano-4,5-*cis* oxazoline (**2**; $n = 2$, R = CH_3) est rapidement et quantitativement produite en ajoutant le chlorure de thionyle à 0 °C à l'acétamido-2 cyclohexanol-*trans* (**1**; $n = 2$, R = CH_3) dans du chloroforme. On estime que le demi temps de vie du chlorosulfinate intermédiaire est moins que 2.25 min. Ce résultat est mis en évidence par un glissement dans le signal des protons du groupement méthyle dans les spectres r.m.n., de l'amide et de la solution réactionnelle. Le chlorhydrate de l'oxazoline est isolé avec un rendement de 98% par la sublimation sous vide du produit brut. On a établi la structure du composé en se servant de données obtenues par spectroscopie i.r. et r.m.n. et on l'a vérifiée par une méthode d'hydrolyse simple qui conduit avec un rendement pratiquement quantitatif au chlorhydrate de l'amino-2 cyclohexanol-*cis*. On obtient facilement les chlorohydrates des oxazolines **2** ($n = 1$, R = CH_3, C_6H_4-*p*NO_2 et $n = 2$, R = C_6H_5, C_6H_4-*p*NO_2) avec des rendements d'au moins 95% en utilisant la même méthode générale et on a démontré que les acétamido-2 cyclanols-*trans* sont les produits de départ les plus utiles pour obtenir les dérivés d'aminocyclanol-2-*cis* par la réaction d'inversion à l'aide du chlorure de thionyle. On obtient facilement les bases oxazolines **4** ($n = 1$, R = CH_3, C_6H_4-*p*NO_2 et $n = 2$, R = CH_3, C_6H_4-*p*NO_2) avec de bons rendements à partir des sels correspondants et on décrit des différences dans les spectres r.m.n. et i.r. des sels et des bases.

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In 1950, Johnson and Schubert (1) and McCasland and Smith (2) reported simultaneously and independently studies on the reaction between *trans*-2-benzamidocyclanols **1** ($n = 1, 2$, R = C_6H_5, C_6H_4-*p*NO_2) and thionyl chloride, which led by an inversion process to D,L-2-phenyl-4,5-*cis*-cycloalkanoöxazoline hydrochlorides **2** ($n = 1, 2$, R = C_6H_5, C_6H_4-*p*NO_2). Hydrolysis of the latter with aqueous hydrochloric acid proceeded with retention of configuration to provide low over-all yields (40–50%) of *cis*-2-aminocyclanol hydrochlorides **3** ($n = 1, 2$). These two groups of workers considered the oxazoline salts, which they found to be unstable and difficult to isolate in a pure condition, to arise by the internal S_N2 displacement of a hydroxyl or chlorosulfinate group by the oxygen atom of the amide carbonyl group. This viewpoint was strengthened by Winstein and Boschan's (3) classic study of the participation of the benzamido group in neighboring displacements in which they showed, among other things, that *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate was converted almost quantitatively to the corresponding oxazoline tosylate in refluxing glacial acetic acid in 6 min. They also examined the reaction between *trans*-2-benzamidocyclohexanol and thionyl chloride at 0°, ultimately isolating *cis*-2-benzamidocyclohexanol in high yield by hydrolysis of the intermediate oxazoline hydrochloride **2** ($n = 2$, R = C_6H_5), which they considered to result by internal displacement of a chlorosulfinate group which had been introduced into the molecule by a rapid initial reaction of the hydroxyl group with thionyl chloride. These workers also determined the rate of displacement

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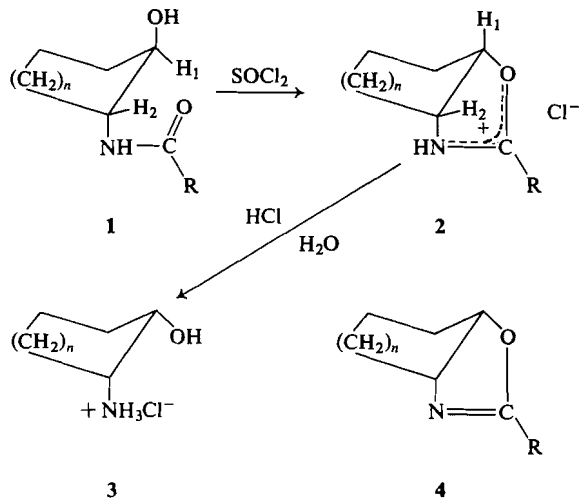
of the tosyl group from *trans*-2-benzamidocyclohexyl tosylate under solvolytic conditions in anhydrous ethanol at 74°, from which it was clear that the half-life of the substrate under these conditions is approximately 6.5 min at 74° or 1060 h at 0°. No effort was made, however, to study the rate of conversion of *trans*-2-acylaminocyclanols to the oxazoline salts by thionyl chloride.

We first became interested in the acylaminocyclanol – thionyl chloride reaction several years ago when one of us (4) briefly examined the conversion of *trans*-2-acetamidocyclohexanol (**1**; $n = 2$, R = CH_3) to *cis*-2-aminocyclohexanol and its derivatives by this means. The yields obtained at that time were significantly better than those reported by Johnson and Schubert (1) starting from the benzamido analogue but not nearly as good as that reported by Winstein and Boschan (3). Because of our continuing interest in the conversion of *trans*-2-acylaminocyclanols to their *cis*-analogues we decided to reexamine the reaction from two standpoints, firstly to attempt to develop it into a useful synthetic method, and secondly to attempt to obtain an approximate measure of the rate of the reaction. It occurred to us in the latter connection that it should be possible, in principle at least, to follow the rate of the reaction by observing either the rate of appearance of D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride (**2**; $n = 2$, R = CH_3), or the rate of disappearance of *trans*-2-acetamidocyclohexanol or the intermediate chlorosulfinate by looking for shifts in the methyl resonances in the n.m.r. spectrum of the reaction mixture.

We first examined the addition of *trans*-2-acetamidocyclohexanol (1 mol) dissolved in anhydrous chloroform to thionyl chloride (3.85 mol) at 0°.[2] Because of the exothermicity of the reaction even when moderated by the presence of the solvent, addition of the amide required 20 min. A sample taken immediately thereafter for n.m.r. examination revealed no trace of the starting material, judging from the complete absence of an acetamido methyl proton resonance



at τ 8.01, (Fig. 1*a*) and the presence of a new methyl resonance equivalent to three protons at τ 7.41, together with broad methine resonances at τ 4.90 and 5.91 and methylene resonances from τ 7.8–8.6 in the reaction solution (Fig. 1*b*). The spectrum was measured at intervals for a period of 48 h and although the solution, which was originally pale pink, gradually became deep red in color, there was no change in the appearance of the spectrum. The oxazoline hydrochloride **2** ($n = 2$, R = CH_3) could be isolated in quantitative crude yield, m.p. 98.5–100.5°, as described in the Experimental, 2 h after the addition of the amide had been completed and it was therefore concluded that the n.m.r. spectrum obtained within 5 min of completion of the addition indicated that the reaction had proceeded to completion within 25 min.

Subsequent experiments conducted on a semimicro scale at 0° in which the addition of the amide was completed in 1.25 min established that the reaction had proceeded to completion in less than 9 min from the start of addition of the amide, judging from the fact that the n.m.r. spectrum of the reaction solution was identical with that of Fig. 1*b*. Assuming that the formation of chlorosulfinate is virtually instantaneous and that four half-lives of the chlorosulfinate would be required to produce a spectrum of oxazoline salt apparently free of contaminants, it is concluded that the half-life of the chlorosulfinate cannot exceed 2.25 min at 0°. Thus the rate of oxazoline salt formation from the chlorosulfinate of the hydroxyamide **1** ($n = 2$, R = CH_3)

[2]These conditions represented the best features of procedures due to Winstein and Boschan (3) (temperature and molar proportions) and Elliott (5) (addition of amide in solvent). Most other workers (1–3, 6–8) have used portionwise addition of the amide to neat thionyl chloride.

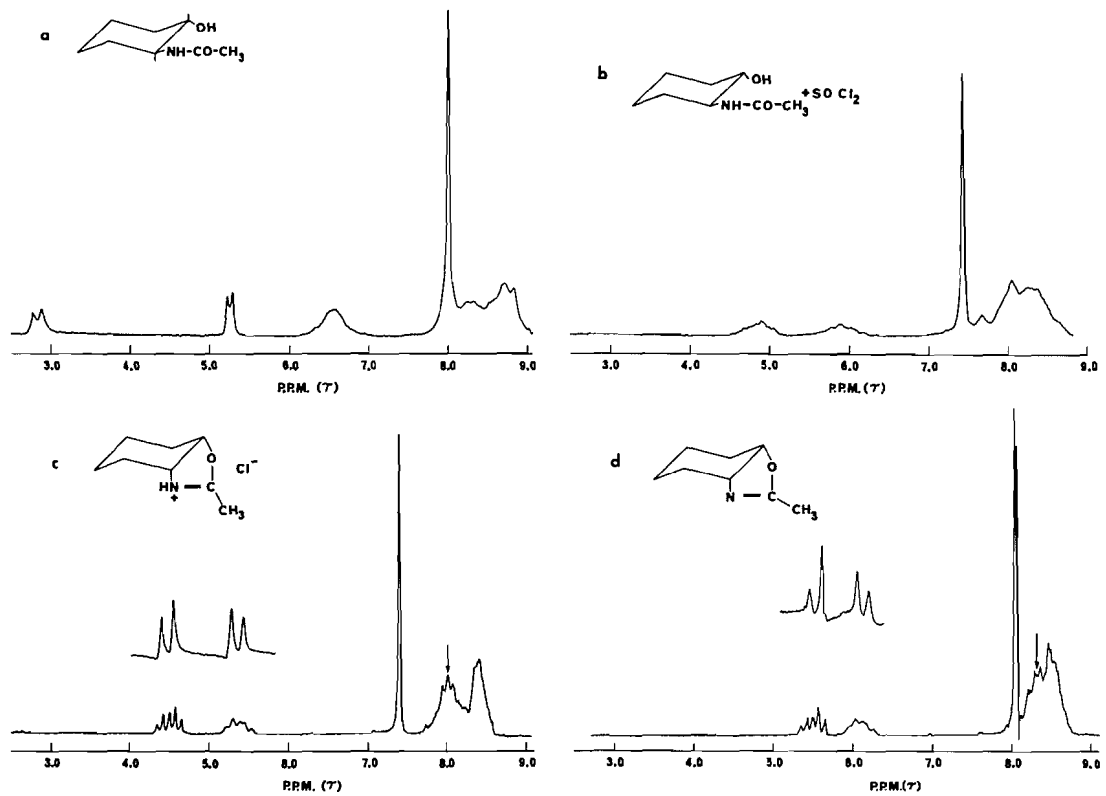
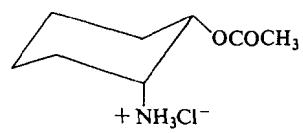


FIG. 1. (*a*) The 60 MHz n.m.r. spectrum of *trans*-2-acetamidocyclohexanol in chloroform.
(*b*) The 60 MHz n.m.r. spectrum of *trans*-2-acetamidocyclohexanol + excess thionyl chloride in chloroform (recorded 25 min after initiation of the reaction).
(*c*) The 60 MHz Spectrum of D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride in chloroform (insert shows methine proton resonances resulting from irradiation of H-3 and -6 at τ 8.01).
(*d*) The 60 MHz n.m.r. spectrum of D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline in chloroform (insert shows methine proton resonances resulting from irradiation of H-3 and -6 at τ 8.30).

in chloroform – thionyl chloride is at least 2.8×10^4 times faster than by solvolysis of the hydroxyamide *p*-toluenesulfonate in ethanol at 0°.

The oxazoline salt **2** ($n = 2$, $R = CH_3$) is extremely hygroscopic and on attempted recrystallization from anhydrous chloroform – ether or absolute ethanol – ether decomposes with the formation of a difficultly separable mixture of D,L-*cis*-1-acetoxy-2-aminocyclohexane hydrochloride (**5**) and D,L-*trans*-1-chloro-2-acetamidocyclohexane (**6**). The *O*-acetylamine hydrochloride **5** probably results from a simple acidic partial hydrolysis of the oxazoline salt by traces of moisture in the solvents, with concomitant N → O acyl migration (9–12) and the chloroamide **6** is likely formed by opening of the ring by backside displacement of the oxazoline oxygen



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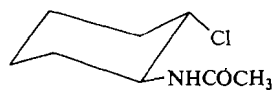

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by the chloride ion present in hot solutions of the salt (3, 5, 13). The crude oxazoline hydrochloride was readily purified by sublimation *in vacuo* and was obtained in 98% yield as a colorless crystalline solid, which was readily hydrolyzed quantitatively to *cis*-2-aminocyclo-

hexanol hydrochloride **3** ($n = 2$), by brief heating with 10% aqueous hydrochloric acid (*cf.* 1, 2, 4). This two-step reaction sequence thus provides an almost quantitative conversion of *trans*-2-acetamidocyclohexanol to *cis*-2-aminocyclohexanol hydrochloride.

The isolated oxazoline salt **2** ($n = 2$, R = CH_3) gave a much sharper spectrum (Fig. 1*c*) than that obtained directly from the reaction solution and some shifts in the positions of the resonances were noted presumably because of the removal of the thionyl chloride from the system.[3] For example, the methine resonances were now seen to be sharp (H-1) and broad (H-2) multiplets at τ 4.50 and 5.38 respectively. A sharp methylene triplet was now evident at τ 8.01, which decoupling experiments clearly indicated to be due to H-3*a*,*e* and -6*a*,*e* (see below).[4] The methyl resonance had shifted slightly to τ 7.40 and was now clearly seen to be a doublet ($J \approx 0.5$–0.8 Hz). Irradiation of H-2 caused this doublet to collapse to a singlet. Similarly, irradiation of the methyl doublet caused the broad multiplet at τ 5.38 to sharpen, confirming the long range coupling between H-2 and the methyl group. Irradiation of H-3*a*,*e* and -6*a*,*e* at τ 8.01 caused the methine multiplets at τ 4.50 and 5.38 to collapse to an AB quartet ($J_{1,2} = 8.5$–9.0 Hz).

The n.m.r. spectrum of the oxazoline free base **4** (R = CH_3, $n = 2$) (Fig. 1*d*) shows some significant differences (see Table 1) from that of the oxazoline hydrochloride **2** (R = CH_3, $n = 2$) from which it was readily prepared, *e.g.* the oxazoline methyl proton doublet is shifted upfield to τ 8.03 ($J \approx 1.5$ Hz). Irradiation of H-2, which is shifted upfield to τ 6.10, caused the methyl doublet to collapse to a sharp singlet, again indicating long range coupling between H-2 and the oxazoline methyl protons. The signal for H-1 is also shifted upfield to τ 5.50 and now appeared as a double triplet. Irradiation of the H-3*a*,*e* and -6*a*,*e* triplet at τ 8.30 caused the methine multiplets from H-1 and -2 to collapse to an AB quartet ($J_{1,2} \approx 8.5$ Hz).

The long range coupling between H-2 and the oxazoline methyl protons agrees with the observations of Weinberger and Greenhalgh (14) on the occurrence of long range coupling between methyl protons and methylene or methine protons attached to the carbon atom which is also attached to nitrogen in monocyclic oxazolines and thiazolines. Also, the change in chemical shift in the oxazoline methyl proton resonance observed for **2** and **4** (R = CH_3, $n = 2$)[5] is characteristic for such compounds (14). The magnitude of $J_{1,2}$ observed in the salt and free base is not at variance with the assignment of a *cis*-fused oxazoline–cyclohexane structure to **2** ($n = 2$, R = CH_3) since several heterocyclic ring systems (15–19), including 2-oxazolidine–cyclohexane (18) have recently been reported in which $J_{cis} > J_{trans}$ due to a combination of substituent electronegativity effects and dihedral angular variation between the protons.

Assuming a flexible *cis* cyclohexane–oxazoline ring fusion and free inversion of the cyclohexane ring, average coupling constants were assigned to the interacting methine and adjacent methylene protons. The chemical shifts of the methine protons and $J_{1,2}$ (8.5 Hz) were obtained from the experimental spectrum. Substitution of these values in a modified LAOCOON-2 computer program (20) resulted in a spectrum drawn by a Calcomp plotter which showed good correspondence with the methine resonance pattern of the experimental spectrum, thus supporting the *cis*-fused ring structure. Assumption of a rigid *trans*-fused ring structure with appropriate values for the coupling constants and chemical shifts in a similar analysis gave poor correspondence with the methine resonances of the experimental spectrum.[6]

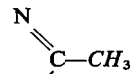
[3]Removal of the excess reagent and solvent *in vacuo* from the reaction mixture immediately after completion of the amide addition gave, on reconstitution in deuterochloroform, a spectrum identical with Fig. 1*c*.

[4]The approximate coincidence of the signals due to the methylene protons H-3 and -6 in 1,2-disubstituted cyclohexanes and cyclopentanes is not generally observed. However, this behavior was noted for such protons in all the cyclopentano- and cyclohexano-oxazolines examined herein.

[5]In structure **2** a proton is shown attached to the nitrogen atom, following the designation used for oxazolinium salts used in refs. 1–3. A referee has pointed out that the occurrence of long range coupling between methyl and H-2 in both the salt **2** and in the base **4**, the comparable sizes of the J values for these compounds and the circumstance that the signal for H-1 moves further upfield than does the signal for H-2 during the change from compound **2** to compound **4** may indicate that the proton is attached to oxygen rather than to nitrogen. Consequently, the location of the proton in the oxazoline ring is not certain, but in the absence of conclusive evidence to the contrary we prefer to use the protonated nitrogen structure.

[6]We are indebted to Prof. R. Y. Moir and Mr. R. S. Reeve, Department of Chemistry, Queen's University, Kingston, Ontario, for performing this analysis.

TABLE 1. Chemical shifts (τ) of acetamidocyclanols,* oxazoline salts, and bases†

Compound											
No.	*n*	R	Aromatic H	NH	OH	H-1	H-2	N*H*Ac		$(CH_2)_4$	$J_{1,2}$(Hz)‡
1	2	CH_3	—	2.87 d	5.34 d	6.55 m	6.55 m	8.01 s	—	7.8–9.0 m	—
1	1	CH_3	—	2.85 d	4.90 s	6.12 m	6.12 m	8.02 s	—	7.7–8.7 m	—
2	2	CH_3	—	—	—	4.50 m	5.38 m	—	7.40 d	7.8–8.6 m	8.5
2	2	C_6H_5	2.37, 3.20	—	—	5.20 m	6.03 m	—	—	8.5–9.4 m	8.5
2	2	C_6H_4-*p*NO_2	2.08, 2.54	—	—	5.29 m	6.05 m	—	—	8.5–9.4 m	8.5
2	1	CH_3	—	—	—	4.20 m	5.03 m	—	7.45 d	7.3–8.3 m	8.0
2	1	C_6H_4-*p*NO_2	1.37	—	—	4.00 m	4.75 m	—	—	7.3–8.2 m	7.5
4	2	CH_3	—	—	—	5.50 m	6.10 t	—	8.03 d	8.1–8.7 m	8.5
4	2	C_6H_4-*p*NO_2	2.67	—	—	6.11 m	6.67 m	—	—	8.8–9.5 m	8.5
4	1	CH_3	—	—	—	5.10 m	5.50 m	—	8.06 d	8.1–8.6 m	8.0
4	1	C_6H_4-*p*NO_2	1.78	—	—	4.78 m	5.17 m	—	—	7.7–8.4 m	7.5

*Only the acetamidocyclanols were sufficiently soluble in $CDCl_3$ to give good spectra (10–20% solutions).
†d, Doublet; m, multiplet; s, singlet; t, triplet.
‡By decoupling from methylene protons.

TABLE 2. Principal infrared absorption (cm^{-1}) of acetamidocyclanols,* oxazoline salts, and bases

Compound														
No.	*n*	R	OH		NH	Imine salt	Oxazoline salt	C=O	N=C—O	Amide II	NO_2		C—O	
1	2	CH_3	3590 w	3438 s	3315 m	—	—	1660 s	—	1500 m	—		1260 m†	1066 m
1	1	CH_3	3590 w	3442 s	3310 sh	—	—	1655 s	—	1497 m	—		1258 m†	1060 m
2	2	CH_3	—	—	—	2100–2800 m	1810 w	—	1667 s	—	—		1270 m†	965 s
2	2	C_6H_5	—	—	—	2100–2888 m	1780 w	—	1640 s	—	—		1270 m†	980 w
2	2	C_6H_4-*p*NO_2	—	—	—	1940–2740 m	1790 w	—	1650 s	—	1525 s	1365 s	—	970 w
2	1	CH_3	—	—	—	2100–2800 m	1810 w	—	1670 s	—	—		1254 m†	970 w
2	1	C_6H_4-*p*NO_2	—	—	—	1940–2800 m	1790 w	—	1650 s	—	1535 s	1350 s	1255 m†	970 w
4	2	CH_3	—	—	—	—	—	—	1665 s	—	—		1220 s†	960 s
4	2	C_6H_4-*p*NO_2	—	—	—	—	—	—	1645 s	—	1525 s	1365 s	—	960 m
4	1	CH_3	—	—	—	—	—	—	1667 s	—	—	—	1237 m†	950 m
4	1	C_6H_4-*p*NO_2	—	—	—	—	—	—	1645 s	—	1525 s	1342 s	1258 m†	1010 m

*Only the acetamidocyclanols were sufficiently soluble in chloroform to provide good spectra (0.05 *M* solutions).
†A 0.05 *M* solution in $CDCl_3$.

The i.r. spectra of the oxazoline salt **2** and free base **4** ($n = 2$, R = CH_3) also showed some characteristic features (see Table 2). The salt has a very strong absorption at 1667 cm^{-1} and the base a strong band at 1665 cm^{-1} which are undoubtedly due to the 2-oxazoline N=C—O group (21, 22). The salt also has strong imine salt absorption at 2100–2800 cm^{-1} and a medium intensity salt band at 1810 cm^{-1}, both of which are, of course, absent from the base. The i.r. spectrum of the pure oxazoline salt **2** ($n = 2$, R = CH_3) could be readily observed on samples removed from the reaction solution 5 min after completion of the addition of the amide to the thionyl chloride when they were treated as described in the Experimental to eliminate the excess reagent. The i.r. spectrum of the oxazoline salt is markedly different from that of *trans*-2-acetamidocyclohexanol, the latter containing free and bonded hydroxyl absorptions at 3590 and 3438 cm^{-1}, NH absorption at 3315 cm^{-1}, and amide II absorption at 1500 cm^{-1}, all of which are absent from the spectrum of the oxazoline salt (see Table 2).

The influence of reaction conditions on the yield of oxazoline salt **2** ($n = 2$, R = CH_3) was examined. Control of the reaction temperature at 18–20° caused the yield to fall to 92%, whereas addition of thionyl chloride to a slurry of the amide in chloroform at 5–10° gave a 96% yield. Addition of the amide via a worm-feed addition-tube (23) to a solution of thionyl chloride in chloroform at 0° provided a 98% yield.

The behavior of *trans*-2-acetamidocyclopentanol **1** ($n = 1$, R = CH_3) in the reaction was completely analogous to that of the corresponding cyclohexyl derivative, furnishing D,L-2-methyl-4,5-*cis*-cyclopentanoöxazoline hydrochloride **2** ($n = 1$, R = CH_3) in 95% yield. The latter substance was also readily purified by sublimation *in vacuo* and was hydrolyzed quantitatively to *cis*-2-aminocyclopentanol hydrochloride **3** ($n = 1$) in the usual manner.

The aryloxazoline salts **2** ($n = 2$, R = C_6H_5, C_6H_4-*p*NO_2 and $n = 1$, R = C_6H_4-*p*NO_2) were prepared in yields of 95% or better by the same method.[7] These compounds were not amenable to purification by recrystallization or by sublimation *in vacuo*, but were obtained analytically pure directly from the reaction if proper precautions for the exclusion of moisture were observed. They were also readily convertible to the corresponding free bases **4** ($n = 2$, R = C_6H_5, C_6H_4-*p*NO_2 and $n = 1$, R = C_6H_4-*p*NO_2) in high yield but did not provide yields of *cis*-2-aminocycloalkanol hydrochlorides above 91% by acidic hydrolysis, presumably owing to complications introduced by the formation of the more difficultly separable benzoic and *p*-nitrobenzoic acids as by-products. Consequently, the *trans*-2-acetamidocyclanols are the preferred intermediates for the synthesis of *cis*-2-aminocyclanol derivatives and can provide the latter readily in almost quantitative yield. Nuclear magnetic resonance spectroscopy was not as useful a tool for following the formation of the 2-aryloxazoline salts as it was for the 2-methyloxazoline salts because of the absence of the 2-methyl group, the i.r. spectra of the aryl compounds being more useful in this connection. The chemical shifts of the protons in the 60 MHz n.m.r. spectra of the 2-substituted oxazoline salts and bases examined in this work are given in Table 1 together with those of the *trans*-2-acetamidocyclanols. The principal i.r. absorption frequencies of the *trans*-2-acetamidocyclanols, oxazoline salts, and bases are shown in Table 2.

Experimental[8, 9]

The i.r. spectra were measured as 0.05–0.10 *M* solutions in chloroform on a Perkin–Elmer Model 221 spectrophotometer. When spectra were required of oxazoline salts present in reaction mixtures containing excess thionyl chloride, a sample of the reaction solution (0.1 ml) was distilled to dryness three times at room temperature or below with 1 ml of chloroform or deuterochloroform at water pump pressure, taking precautions to prevent access of water vapor to the sample.

The n.m.r. spectra were measured on a Varian V-4300C spectrometer (60 MHz) using a Varian V-5321 integrator for base-line stabilization. Solutions were 10–20% in chloroform or deuterochloroform and were calibrated with reference to internal tetramethylsilane by the usual side-band technique.

D,L-*trans*-2-Aminocyclohexanol and Derivatives

trans-2-Aminocyclohexanol, m.p. 67.5–68.5°, *trans*-2-aminocyclohexanol hydrochloride, m.p. 180–181°, and *trans*-2-acetamidocyclohexanol, m.p. 126.5–127.5°, were prepared following methods described by Hawkins and Bannard (24), *cf.* McCasland *et al.* (26). *trans*-2-Benzamidocyclohexanol, m.p. 171–172°, was prepared by application of the acylation procedure of Leffler and Adams (25) as reported by Johnson and Schubert (1).

[7]Because of solubility restrictions, these acylaminocyclanols were added *via* a worm-feed addition-tube (23) to thionyl chloride – chloroform solutions at 0°.

[8]All melting points are uncorrected.

[9]Microanalyses by J. G. Helie of these laboratories.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.03; H, 7.76; N, 6.56.

trans-2-*p*-Nitrobenzamidocyclohexanol, m.p. 211–211.5°, was prepared similarly (*cf.* McCasland and Smith (2)).

Anal. Calcd. for $C_{13}H_{16}O_4N_2$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.08; H, 6.00; N, 10.70.

D,L-*2-Methyl-4,5-cis-cyclohexanoöxazoline Hydrochloride (2; n = 2, R = CH_3)*

A solution of *trans*-2-acetamidocyclohexanol (3.92 g, 0.025 mol) in anhydrous chloroform (12 ml, Fisher spectro grade dried over silica gel) was added dropwise with stirring at −5 to 0° over a period of 20 min to thionyl chloride (7.0 ml, *ca.* 0.095 mol) in an apparatus protected against the entry of moisture. The dropping funnel used for the addition was rinsed with an additional 2 ml of chloroform. The temperature of the resultant colorless opalescent solution was allowed to rise to 21° over a period of 30 min while stirring was continued, following which stirring was continued at the same temperature for a further 2 h. The excess thionyl chloride and chloroform were removed from the pale pink solution by distillation at a pressure of 50–60 mm, leaving a viscous pink oil. Chloroform (2 ml) was added and the solution was added dropwise to vigorously stirred anhydrous ether (450 ml) at room temperature. A colorless oil separated and the ether layer became yellow. The mixture was kept overnight at 0° during which the oil crystallized. The ether was decanted and retained and the pale yellow crystals were collected, washed with anhydrous ether (5 × 25 ml), taking care to keep them covered with ether until washing was complete, and then were dried *in vacuo*; wt. 4.17 g, m.p. 98.5–100.5°. A second small crop of crystals, 0.15 g, was recovered by extraction of the residual material in the flask and funnel with chloroform, followed by removal of the solvent *in vacuo*. Evaporation of the ether decanted from the crystals gave 0.289 g of dark evil-smelling oil, which on hydrolysis with 10% hydrochloric acid, furnished 70 mg of *cis*-2-aminocyclohexanol hydrochloride (equivalent to 81 mg of oxazoline salt). Total yield of crude oxazoline hydrochloride, 4.40 g (100%). Sublimation of 200 mg of the crude salt at 50° at 0.001 mm furnished 196 mg (98.0%) of colorless hygroscopic crystals of D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride, m.p. 104–106°.[10]

Anal. Calcd. for $C_8H_{14}ONCl$: C, 54.69; H, 8.03; N, 7.98; Cl, 20.18. Found: C, 54.70; H, 8.20; N, 8.04; Cl, 20.10.

D,L-*cis-1-Acetoxy-2-aminocyclohexane Hydrochloride (5) and* D,L-*trans-1-Chloro-2-acetamidocyclohexane (6)*

Attempted recrystallization of the oxazoline salt (500 mg) from ethanol–ether or chloroform–ether resulted in decomposition and furnished 314 mg (55%) of D,L-*cis*-1-acetoxy-2-aminocyclohexane hydrochloride, as colorless needles, m.p. 213–213.5° (dec.).

Anal. Calcd. for $C_8H_{16}O_2NCl$: C, 49.60; H, 8.33; N, 7.23; Cl, 18.30. Found: C, 49.51; H, 8.61; N, 7.13; Cl, 18.25.

This substance gave a positive ionic halogen test and its i.r. spectrum (0.1 *M* in chloroform) showed prominent bands at 3300–2400 (NH^+), 1728 (ester carbonyl), 1595 (N—H deformation), 1220, and 1013 cm^{-1} (C—O acetate). In addition, 64 mg (12.8%) of D,L-*trans*-1-chloro-2-acetamidocyclohexane[11] was recovered as fine colorless needles, m.p. 130–132°.

Anal. Calcd. for $C_8H_{14}ONCl$: C, 54.69; H, 8.03; N, 7.98; Cl, 20.18. Found: C, 54.55; H, 7.94; N, 7.77; Cl, 20.07.

This substance did not contain ionic halogen and its i.r. spectrum (0.1 *M* in chloroform) had prominent bands at 3445 (N—H, free), 3330 (N—H, bonded) 1665 (amide carbonyl), and 1503 cm^{-1} (amide II).

D,L-*2-Methyl-4,5-cis-cyclohexanoöxazoline (4, n = 2, R = CH_3)*

2-Methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride (2.69 g, 0.0153 mol) was shaken with 15 ml of 5% sodium hydroxide and 30 ml of ether. The ether layer was decanted and the aqueous phase was extracted with ether (4 × 30 ml). The ether solutions were combined, dried over anhydrous magnesium sulfate, decanted, and the ether was removed *in vacuo* The pale brown residue was fractionated in a micro-distillation apparatus at 13 mm pressure and furnished 1.90 g (89.3%) of colorless mobile liquid b.p. 75.5–76.5°, n_D^{25} 1.4698, with a very penetrating odor.

Anal. Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.01; H, 9.17; N, 10.02.

D,L-*cis-2-Aminocyclohexanol Hydrochloride (3, n = 2)*

Hydrolysis of the crude oxazoline hydrochloride (2.00 g) by heating it under reflux for 1 h with 10% hydrochloric acid (35 ml) gave, after evaporation to dryness and recrystallization from ethanol–ether, 1.69 g (97.7%) of D,L-*cis*-2-aminocyclohexanol hydrochloride as colorless platelets, m.p. 190–191.5°, alone, and in admixture with an authentic sample (4).

D,L-*2-Phenyl-4,5-cis-cyclohexanoöxazoline Hydrochloride (2, n = 2, R = C_6H_5)*

A stirred slurry of *trans*-2-benzamidocyclohexanol (2.74 g, 0.0125 mol) and anhydrous chloroform (100 ml) was kept at 0–8° in an apparatus protected against the entry of moisture while thionyl chloride (3.5 ml, 0.0483 mol) was added over a period of 21 min. The temperature of the resultant clear solution was allowed to rise to 21° over a period of 45 min and the solution was stirred at room temperature for an additional 2¾ h. The chloroform and excess thionyl chloride were removed by distillation at a pressure of 50–60 mm, leaving a very viscous pale yellow residue which was transferred quantitatively in 10 ml of chloroform to 250 ml of stirred anhydrous ether. The turbid mixture began to deposit colorless crystals almost immediately and was kept overnight at 0°. The crystals were collected, washed with anhydrous ether, and dried *in vacuo*; wt. 2.96 g (99.3%) m.p. 102–105°. Johnson and Schubert (1) report m.p 96.5–101° but no analytical data on the hydrochloride.

Anal. Calcd. for $C_{13}H_{17}ONCl$: C, 65.40; H, 7.18;

[10]If the crude oxazoline salt is allowed to stand for a prolonged period prior to further purification by sublimation, it slowly decomposes, *e.g.* after standing for 2 months 252 mg of crude oxazoline salt furnished only 222 mg (88.0%) of colorless sublimate.

[11]The structure of this compound was confirmed by measurement of the coupling constant (J = 10 Hz) between the methine protons in $CDCl_3$–C_6H_6 solution. We are indebted to Dr. R. R. Fraser for this measurement.

N, 5.87; Cl, 14.86. Found: C, 65.28; H, 6.99; N, 5.92; Cl, 14.87.

Hydrolysis of D,L-2-phenyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride with 10% aqueous hydrochloric acid as described for the methyl analogue furnished 91.0% of D,L-*cis*-2-aminocyclohexanol hydrochloride, m.p. 189–190° (4) and 96.5% of benzoic acid, m.p. 121.5–122°.

D,L-*2-p-Nitrophenyl-4,5-cis-cyclohexanoöxazoline Hydrochloride (2, n = 2, R = C_6H_4-pNO_2)*

The procedure was identical with that given above for D,L-2-phenyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride except that *trans*-2-*p*-nitrobenzamidocyclohexanol (3.30 g, 0.0125 mol) was used. The oxazoline salt separated as a solid during the removal of the excess chloroform and thionyl chloride *in vacuo* but was taken up in anhydrous chloroform (10 ml) and precipitated by addition to anhydrous ether as described for the methyl and phenyl analogues. The salt was collected, washed with ether, and dried *in vacuo*; wt. 3.34 g (94.4%), m.p. 144–145°[12] and again at 175–179°, *cf.* McCasland and Smith (2).

Anal. Calcd. for $C_{13}H_{15}O_3N_2Cl$: C, 55.24; H, 5.35; N, 9.91; Cl, 12.54. Found: C, 55.08; H, 5.28; N, 9.64; Cl, 12.50.

Hydrolysis of the oxazoline salt in the usual manner gave a 90% recovery of D,L-*cis*-2-aminocyclohexanol hydrochloride, m.p. 189–190°, and 91% of *p*-nitrobenzoic acid, m.p. 241–242.5°.

D,L-*2-p-Nitrophenyl-4,5-cis-cyclohexanoöxazoline (4, n = 2, R = C_6H_4-pNO_2)*

The oxazoline hydrochloride (731 mg) was shaken with a mixture of 18 ml of 5% sodium hydroxide and 25 ml of ether. The ether layer was decanted and the aqueous phase was extracted with ether (3 × 25 ml). The ether solutions were combined, dried over anhydrous magnesium sulfate, decanted, and taken to dryness *in vacuo* leaving a pale yellow solid, which was recrystallized from absolute ethanol and furnished 460 mg (72.5%) of pale yellow crystals. m.p. 120–121°. McCasland and Smith (2) report m.p. 120–121°.

D,L-*trans-2-Aminocyclopentanol*

D,L-*trans*-2-Aminocyclopentanol was prepared by the ammonolysis of 1,2-epoxycyclopentane (27) following the method used by Hawkins and Bannard (24) for preparation of the cyclohexane analogue, except that it was found necessary to extend the heating period to 4 h. The substance was obtained as a colorless oil, b.p. 65° at 1.5 mm, n_D^{25} 1.4920, in 81.5% yield.

Anal. Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.14; H, 11.21; N, 13.98.

The identity of the compound was confirmed by conversion to the hydrochloride, m.p. 193–194°, after recrystallization from ethanol–ether. McCasland and Smith (2) report m.p. 193–194°.

D,L-*trans-2-Acetamidocyclopentanol*

This substance was prepared according to the method described by Bannard and Hawkins (28) for the preparation of *N*-acetyl derivatives of the alkoxyaminocyclohexanols, and was obtained in 90% yield as a very viscous colorless oil, b.p. 118–120° at 0.02 mm, n_D^{25} 1.4995.

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.59; H, 9.27; N, 9.96.

D,L-*trans-2-Benzamidocyclopentanol*

This compound was prepared in 77.5% yield in the same manner as its cyclohexyl analogue, and had m.p. 120–121°. McCasland and Smith (2) report m.p. 120–121°.

Anal. Calcd. for $C_{12}H_{15}ON_2$: C. 70.21; H, 7.38; N, 6.83. Found: C, 70.03; H, 7.29; N, 6.82.

D,L-*trans-2-p-Nitrobenzamidocyclopentanol*

This substance was prepared in 75% yield in the same manner as its cyclohexyl analogue as reported by McCasland and Smith (2), m.p. 158–159°.

Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.58; H, 5.65; N, 11.19. Found: C, 57.50; H, 5.64; N, 11.27.

D,L-*2-Methyl-4,5-cis-cyclopentanoöxazoline Hydrochloride (2, n = 1, R = CH_3)*

The procedure was identical with that given in detail for the preparation of D,L-2-methyl-4,5-*cis*-cyclohexanoöxazoline hydrochloride except that *trans*-2-acetamidocyclopentanol (3.58 g, 0.0250 mol) was used. The crude oxazoline salt (red oil) failed to crystallize on standing in anhydrous ether. The ether was decanted, the oil was taken up in anhydrous chloroform (10 ml), treated with decolorizing charcoal at room temperature, filtered through celite, and the solvent was removed *in vacuo* yielding 4.09 g of brown solid. The latter material was sublimed at 50° at 0.001 mm pressure and furnished 3.87 g (94.7%) of colorless crystals, m.p. 94.5–96.5°.

Anal. Calcd. for $C_7H_{12}ONCl$: C, 52.02; H, 7.49; N, 8.67; Cl, 21.95. Found: C, 51.98; H, 7.26; N, 8.78; Cl, 22.11.

D,L-*2-Methyl-cis-4,5-cyclopentanoöxazoline (4, n = 1, R = CH_3)*

The procedure was identical with that described for the preparation of the cyclohexyl homologue except that D,L-2-methyl-*cis*-4,5-cyclopentanoöxazoline hydrochloride (2.59 g, 0.016 mol) was used. The oxazoline base was obtained as a colorless mobile oil with a very penetrating odor. Yield. 1.75 g (87.7%), b.p. 57.0–57.5° at 13 mm, n_D^{25} 1.4619.

Anal. Calcd. for $C_7H_{11}ON$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.96; H, 9.06; N, 11.27.

D,L-*cis-2-Aminocyclopentanol Hydrochloride*

2-Methyl-4,5-*cis*-cyclopentanoöxazoline hydrochloride (1.19 g, 0.00617 mol) was hydrolyzed in the usual manner and furnished 1.01 g (100%) of colorless platelets, m.p. 181–183°, after recrystallization from absolute ethanol and ethanol–ether. McCasland and Smith (2) report m.p. 179–180°.

Anal. Calcd. for $C_5H_{12}ONCl$: C, 43.64; H, 8.79; N, 10.18; Cl, 25.77. Found: C, 43.60; H, 8.75; N, 9.92; Cl, 25.56.

D,L-*cis-2-Aminocyclopentanol*

A solution of *cis*-2-aminocyclopentanol hydrochloride (6.88 g, 0.05 mol) and sodium hydroxide (4.0 g, 0.10 mol) in water (90 ml) was continuously extracted with ether for 3 days. The ether was removed *in vacuo* and the colorless residue was recrystallized from ether yielding 4.66 g (92.4%) of colorless needles, m.p. 71.0–73.0°.

[12]If the sample was placed in the capillary m.p. apparatus at a temperature below 135°, only the higher m.p. was observed, *cf.* Fry (13).

Anal. Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.09; H, 10.78; N, 13.64.

D,L-*2-p-Nitrophenyl-4,5-cis-cyclopentanoöxazoline Hydrochloride (2, n = 1, R = C_6H_4-pNO_2)*

trans-2-*p*-Nitrobenzamidocyclopentanol (3.07 g, 0.0123 mol) was added portionwise at −5 to 0° over a period of 8 min via a worm-feed addition tube to a magnetically-stirred solution of thionyl chloride (3.5 ml, 0.0483 mol) in deuterochloroform (9.0 ml) in an apparatus protected against the entry of moisture. The temperature of the clear yellow solution was allowed to rise to 29° over a period of 45 min and two 0.1 ml aliquots were removed for i.r. examination. The solution was stirred at room temperature for a further 2.5 h, following which the solution was transferred quantitatively with deuterochloroform (5 ml) to a round-bottom flask and the excess reagent and solvent were removed at 13 mm pressure, taking precautions to prevent the access of moisture. The crystalline residue 3.04 g (99.1%), had m.p. 153.5–155°. McCasland and Smith (2) report m.p. 150–151°, and Fodor and Kiss (29) report m.p. 159–161° for this compound.

Anal. Calcd. for $C_{12}H_{13}O_3N_2Cl$: C, 53.64; H, 4.88; N, 10.43; Cl, 13.20. Found: C, 53.55; H, 5.11; N, 10.40; Cl, 13.02.

This compound decomposes on attempted recrystallization from ethanol.

D,L-*2-p-Nitrophenyl-4,5-cis-cyclopentanoöxazoline (4, n = 1, R = C_6H_4-pNO_2)*

D,L-2-*p*-Nitrophenyl-4,5-*cis*-cyclopentanoöxazoline hydrochloride (1.05 g, 0.00391 mol) was converted to the free base in the usual manner, and, after removal of the ether *in vacuo*, was obtained as a pale yellow crystalline solid, 882 mg (96.9%), m.p. 138.5–140°. McCasland and Smith (2) report m.p. 139–140° for this compound.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.03; H, 4.88; N, 12.16.

This compound is best purified by recrystallization from ethanol.

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