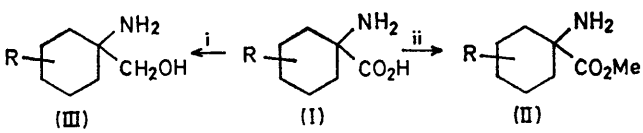
Deamination of Amino-substituted Cyclohexane-methanols and -carboxylic Esters

By **R. J. W. Cremlyn,* R. M. Ellam, and T. K. Mitra,** Department of Chemical Sciences, The Hatfield Polytechnic, Hatfield, Hertfordshire

Several 1-aminocyclohexane-methanols and -carboxylic acid methyl esters have been deaminated and the results are discussed in relation to the deamination of the corresponding amino-acids.

PREVIOUSLY we reported [1,2] the synthesis and deamination of a series of alicyclic α-amino-carboxylic acids. The results showed that deamination of highly substituted amino-acids gave considerable amounts of unsaturated products, although the unsubstituted amino-acids or those containing small substituents gave mainly substitution products.

Austin and Howard [3] have shown that in the deamination of open-chain α-amino-acids, the carboxy-group acts as a configuration-holding group, leading solely to substitution products with retention of configuration. In the deamination of alicyclic α-amino-carboxylic acids (I) the carboxy-group no longer plays such a role to any great extent, since we observed [2] elimination products with highly substituted acids and substitution products for unsubstituted or methyl- and dimethyl-acids with inversion as well as retention of configuration. The results were interpreted in terms of the size of the carboxy-group. The possibility of other electronic effects was not ruled out, and in order to investigate such effects further we have carried out the deamination of some related compounds in which the carboxy-group was modified, namely the amino-esters (II) and amino-methanols [4] (III). The esters were obtained by the Fischer–Speier method (see Scheme 1).



(III) (I) (II)

Reagents: i, $LiAlH_4$; ii, MeOH–HCl (g)

SCHEME 1

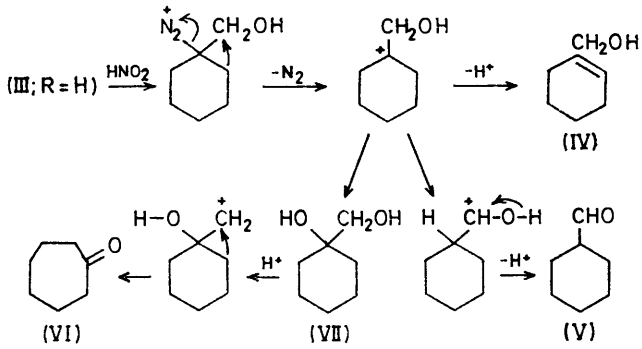
Deamination of 1-aminocyclohexanemethanol (III; R = H) gave a mixture of 1-hydroxycyclohexanemethanol (VII) (substitution) and cyclohex-1-enemethanol (IV) (elimination), accompanied by cyclohexanecarbaldehyde (V) and cycloheptanone (VI). The formation of a substantial amount of elimination product is in sharp contrast to the deamination of 1-aminocyclohexanecarboxylic acid which quantitatively afforded 1-hydroxycyclohexanecarboxylic acid,[2] suggesting that the latter reaction takes place *via* the conformer containing the less hindered equatorial amino-group. The products from 1-aminocyclohexanemethanol were analysed by comparison of their retention times with those of the authentic compounds. The formation of some of the unsaturated alcohol (24%) probably arises from reaction occurring *via* the conformer with the axial amino-group (possibly because NH_2 is not such a sterically demanding group as $^{+}NH_3$) leading to 1,2-*trans*-diaxial elimination, since in the amino-methanol the stable zwitterionic structure is no longer possible.

Likewise, deamination of methyl 1-aminocyclohexanecarboxylate (II; R = H) also gave some elimination product (methyl cyclohex-1-enecarboxylate; 16%) again suggesting that some reaction takes place *via* the conformer containing the axial amino-group. The deamination of the amino-methanol (III; R = H) afforded more elimination product (IV) than was obtained from the corresponding amino-ester (II; R = H), and an examinion of molecular models suggests that the axial hydroxymethyl group offers greater steric interaction with the 3,5-hydrogen atoms or substituents, than an axial carboxylic acid group.

The formation of the aldehyde (V) and the ketone (VI) may be formulated as indicated in Scheme 2. The aldehyde results from hydride ion shift and cycloheptanone (VI) by pinacol–pinacolone rearrangement [5,6] with nitrous acid of the initially formed diol (VII).

[1] R. J. W. Cremlyn, R. M. Ellam, and T. K. Mitra, *Indian J. Chem.*, 1970, **8** (3), 218.
[2] R. J. W. Cremlyn, R. M. Ellam, and T. K. Mitra, *J. Chem. Soc.* (*C*), 1971, 1647.
[3] A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3278.
[4] R. J. Cremlyn, *J. Chem. Soc.*, 1961, 4372.
[5] S. H. Tucker, 'An Electronic Outline of Organic Chemistry,' University of London Press, 1959, p. 315.
[6] P. A. S. Smith and D. R. Baer, *Org. Reactions*, 1960, **11**, 160.

G.l.c. analysis of the products of deamination of 1-amino-3,3,5-trimethylcyclohexanemethanol (VIII)



SCHEME 2

showed the isomeric aldehydes (IX), the cycloheptanone (X), the diol (XI) (two isomers: *cis,trans,trans* and *trans,cis,cis*), and two unsaturated alcohols [shown by n.m.r. as well to be a mixture of (XII) and (XIIa)]. Since authentic samples of the aldehyde (IX) and the cycloheptanone (X) were not available, these compounds were identified by comparison of the methyl values using the method for the prediction of retention data developed by Evans.[7] The differences in relative retentions of substituted and unsubstituted alcohols, unsaturated aldehydes, and ketones is due to the three methyl groups and so should be approximately constant (see Table 1).

TABLE 1

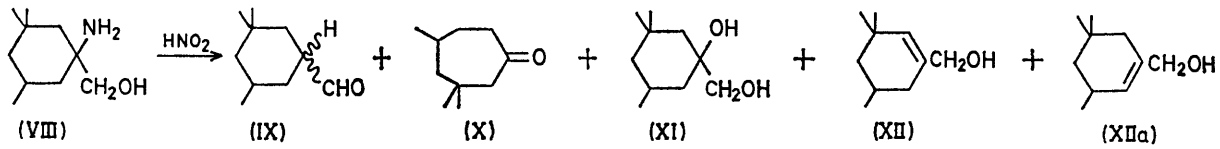
Relative retention data

Compound	Retention (cm)	log [R_s/$R_{m(or\ x)}$]	Increment due to 3 methyl groups
(VII) *	44·4	−0·3252	0·0752
(XI) *	52·8	−0·4004	
Methyl laurate *†	21·0	0	
(IV) *	13·5	+0·1919	0·0738
(XII) *	16·0	+0·1181	
(VI) *	8·0	+0·4191	0·0746
(X)	9·5	+0·3445	
(IX)	6·2	+0·5298	0·0681
(V) *	5·3	+0·5979	

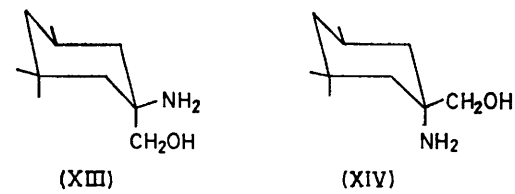
* Authentic compounds available. † Internal standard.

If R_s is the retention time of the internal standard (methyl laurate) and R_x and R_m the retention times of the unsubstituted and 3,3,5-trimethyl substituted compounds, respectively (see Table 1), then the relative retention increment due to the three methyl groups will be given by log (R_x/R_m). The results (Table 1) confirm the presence of the aldehyde (IX) and the trimethylcycloheptanones (X) in the deamination products.

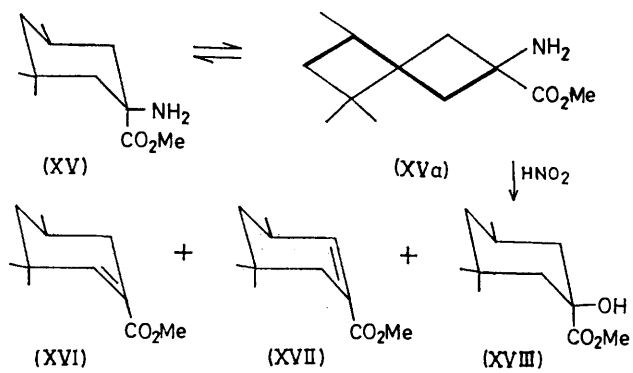
The equatorial amino-carbinol (XIII) (obtained by lithium aluminium hydride reduction of the Bucherer amino-acid [8]) gave more elimination products on deamination than did the axial amino-carbinol (XIV) (from reduction of the Strecker amino-acid [9]) (Table 2), analogously to the deamination of the corresponding amino-acids.[2] It is probable that a highly substituted amino-methanol exists substantially in a twist–boat conformation,[2,10,11] which in the Bucherer product (XIII) will tend to move the amino-group into an axial position and in the Strecker isomer (XIV) into an equatorial position. Deamination of the *cis,trans,trans*-ester (XV) with an equatorial amino-group gave the elimination products (XVI) and (XVII) (90%) together with the alcohol (XVIII) (*ca.* 10%) as compared with 44 and 45% of elimination products obtained



on deamination of the corresponding amino-acid [2] and methanol (XIII), respectively. The large proportion



of elimination obtained from the ester (XV) suggests that it exists substantially as the twist–boat conformation (XVa); probably because this would minimise

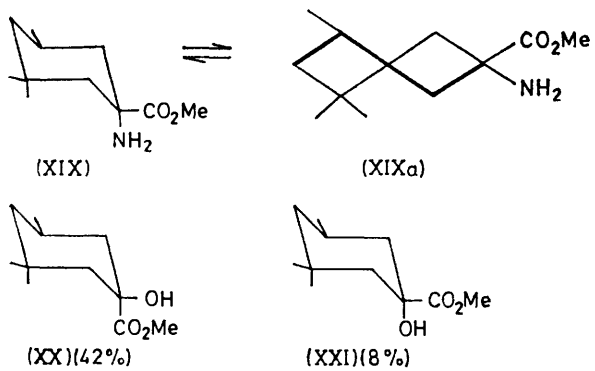


the severe steric 1,3-diaxial interaction between the ester and methyl groups. In (XVa) the ester group becomes pseudo-equatorial and the amino-group pseudo-axial, which would account for the high proportion of

[7] M. B. Evans, *Chromatographia*, 1969, **2**, 397.
[8] H. T. Bucherer and V. A. Liebe, *J. prakt. Chem.*, 1934, **141**, 5.
[9] A. Strecker, *Annalen*, 1870, **155**, 177.
[10] D. L. Robinson and D. W. Theobald, *Quart. Rev.*, 1967, **21**, 314.
[11] D. N. Kirk and P. M. Shaw, *J. Chem. Soc.* (*C*), 1970, 182.

elimination products isolated from the deamination. Deamination of the *cis,trans,cis*-ester (XIX), with an axial amino-group, and also gave a substantial amount of the elimination products (XVI) and (XVII) together with the alcohols (XX) and (XXI) (50%), compared with 25% elimination obtained on deamination of the corresponding Strecker amino-acid.[2]

A comparison of molecular models showed that the interaction between the ester group and the axial 3-methyl group would be minimised in the chair form (XIX) in comparison to the twist–boat conformation (XIXa), because in the chair form the ester group will be equatorial and amino-group axial. The observed



50% elimination possibly indicates an equilibrium of approximately equal amounts of the chair and twist–boat modifications. Finally, the models showed that the steric interaction between the axial 3-methyl group and the carboxy-, hydroxymethyl, and ester groups should increase in this order. This is in agreement with the increasing amounts of elimination observed (44, 45, and 90%) in the deamination of the corresponding 1-amino-3,3,5-trimethylcyclohexane-acid, -alcohol, and -ester, respectively. The results confirm our proposals that the course of deamination of alicyclic amino-acids is controlled by the size of the carboxy-group rather than any electronic effects of that group. Inductive effects play only a minor role in the deamination of alicyclic amino-acids.

[12] W. E. Noland, J. F. Kneller, and D. E. Rice, *J. Org. Chem.*, 1957, **22**, 695.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (Nujol) were measured with a Perkin-Elmer 257 spectrometer. G.l.c. analyses were carried out with a Phillips PV 4000 instrument with a flame-ionisation detector. The column (3 m × 3 mm) was packed with 5% Carbowax 20M on 60—85 mesh Celite and nitrogen was the carrier gas at a flow rate of 60 ml min^{-1}. N.m.r. spectra were determined for $CDCl_3$ solutions with tetramethylsilane as internal standard on a Varian A60A spectrometer. The 1-aminocycloalkanecarboxylic acids were prepared as before.[1]

TABLE 2

The deamination of amino-alicyclic methanols (III)

Compound	Substitution products (%)			Elimination (%)	Aldehyde (%)
		Retention	Inversion		
(III; R = H) [a]	56			24 [c]	5
Methyl 1-aminocyclohexanecarboxylate	84			16	0
1-Aminocyclohexanecarboxylic acid	100			0	0
1-Amino-*cis,trans,cis*-3,3,5-trimethylcyclohexanemethanol (*ax*-NH_2) [a,b]	36	8	28	12 [c]	18
Methyl 1-amino-*cis,trans,cis*-3,3,5-trimethylcyclohexanecarboxylate (*ax*-NH_2)	50	10	40	50	0
1-Amino-*cis,trans,cis*-3,3,5-trimethylcyclohexanecarboxylic acid (*ax*-NH_2)	75	15	60	25	0
1-Amino-*cis,trans,trans*-3,3,5-trimethylcyclohexanemethanol (*eq*-NH_2) [a]	20	15	5	45 [c]	10
Methyl 1-amino-*cis,trans,trans*-3,3,5-trimethylcyclohexanecarboxylate (*eq*-NH_2)	10	(Single peak)		90	0
1-Amino-*cis,trans,trans*-3,3,5-trimethylcyclohexanecarboxylic acid (*eq*-NH_2)	56	51	5	44	0

[a] In the deamination of the amino-carbinol there was also unidentified material. [b] The terms *cis* and *trans* refer to the relation between the alkyl, and the alcohol, acid, and ester groups. [c] A small amount (*ca.* 5%) of the elimination product may arise from the competing pinacol-type rearrangement.

1-*Aminocycloalkanemethanols*.—Typically, 1-aminocyclohexanecarboxylic acid (14 g) was added gradually during 1 h to a stirred suspension of lithium aluminium hydride (10 g) in dry tetrahydrofuran (150 ml) at 0°. The mixture was boiled under reflux for 8 h and then stirred for 12 h at room temperature. The excess of reductant was destroyed with ethyl acetate (50 ml). 2N-Sodium hydroxide (250 ml) was added with cooling, and the mixture was extracted with ether (3 × 200 ml) to give an oil. Distillation under reduced pressure gave 1-aminocyclohexanemethanol (8 g, 60%), b.p. 120° at 0·5 mmHg (lit.,[12] 84° at 1 mmHg) (Found: C, 64·9; H, 11·4; N, 10·95. Calc. for $C_7H_{15}NO$: C, 65·0; H, 11·1; N, 11·0%), $\nu_{max.}$ 3500 (OH) cm^{-1}, τ 7·8 (NH_2 and OH) and 6·9 (CH_2OH).

The following amino-alcohols were prepared similarly: 1-*amino*-cis,trans,trans-3,3,5-*trimethylcyclohexanemethanol*, (50%), b.p. 150° at 0·5 mmHg (Found: C, 69·9; H, 12·2; N, 8·0. $C_{10}H_{21}NO$ requires C, 70·1; H, 12·3; N, 8·2%), $\nu_{max.}$ 3500 (OH) cm^{-1}, τ 7·75 (NH_2 and OH) and 6·8 (CH_2OH); 1-*amino*-cis,trans,cis-3,3,5-*trimethylcyclohexanemethanol* (40%), needles, m.p. 65—68° (from light petroleum–ether) (Found: C, 69·5; H, 12·1; N, 8·5%), $\nu_{max.}$ 3500 (OH) cm^{-1}, τ 7·55 (NH_2 and OH) and 6·5 (CH_2OH).

Methyl 1-*Aminocycloalkanecarboxylate Hydrochlorides*.—In a typical run, a solution of 1-aminocyclohexanecarboxylic acid (5·0 g, 0·03 mol) in dry methanol (150 ml) was saturated with hydrogen chloride at 0°, and left at room temperature for 12 h. The solution was boiled under reflux for 1 h,

the excess of solvent was removed, and the crude product was recrystallised from acetonitrile–chloroform (1 : 1) to give *methyl* 1-*aminocyclohexanecarboxylate hydrochloride* (3·5 g, 60%), m.p. 200—203° (Found: C, 48·9; H, 8·1. $C_8H_{16}ClNO_2$ requires C, 49·5; H, 8·3%), $\nu_{max.}$ 3400 (NH) and 1720 cm^{-1} (CO). The following compounds were similarly prepared: *methyl* 1-*amino*-cis,trans,trans-3,3,5-*trimethylcyclohexanecarboxylate hydrochloride* (35%), m.p. 235—238° (decomp.) (Found: C, 55·7; H, 8·7. $C_{11}H_{21}ClNO_2$ requires C, 56·2; H, 8·95%), $\nu_{max.}$ 3350 (NH) and 1720 cm^{-1} (CO), *methyl* 1-*amino*-trans,cis,cis-3,3,5-*trimethylcyclohexanecarboxylate hydrochloride* (30%), m.p. 245—248° (decomp.) (Found: C, 57·0; H, 8·8%).

1-*Hydroxycyclohexanemethanol*.—1-Hydroxycyclohexanecarboxylic acid [12] was esterified with boron trifluoride–methanol [13] and the methyl ester was subsequently reduced by lithium aluminium hydride to give the alcohol (40%), b.p. 120° at 0·5 mmHg, m.p. 68—70° (lit.,[14] m.p. 73°) (Found: C, 65·2; H, 10·6. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%), $\nu_{max.}$ 3500 (OH) cm^{-1}.

1-*Hydroxy*-3,3,5-*trimethylcyclohexanemethanol*.—This was similarly obtained in 35% yield from the carboxylic acid, b.p. 190° at 0·5 mmHg (Found: C, 69·6; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·9; H, 11·6%), $\nu_{max.}$ 3500 (OH) cm^{-1}.

Cyclohex-1-*enemethanol*.—Cyclohex-1-enecarboxylic acid was converted into the methyl ester (methanol–sulphuric acid) and reduced with lithium aluminium hydride to give the alcohol (45%), b.p. 85° at 0·5 mmHg (lit.,[15] b.p. 96° at 18 mmHg) (Found: C, 74·8; H, 10·6. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·7), $\nu_{max.}$ 3500 (OH) cm^{-1}, τ 7·0 (OH), 6·15 (CH_2OH), and 5·5 (vinyl H).

3,3,5- *and* 3,5,5-*Trimethylcyclohex*-1-*enemethanol* (XII).—These were prepared by reduction of the corresponding methyl esters in 52% yield, b.p. 95° at 0·5 mmHg (Found: C, 77·8; H, 11·3. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%), $\nu_{max.}$ 3500 cm^{-1} (OH), τ 7·2 (OH), 6·0 (CH_2OH), 5·6 (vinyl H), and 5·4 (vinyl H of other isomer). G.l.c. showed a 1 : 1 ratio of the two isomers.

Deamination of the Amino-alcohols and -esters.—A solution of the amino-alcohol (0·5 g) in 2N-acetic acid (50 ml) and dioxan (5 ml) was cooled in an ice-bath. Sodium nitrite (2 g) in water (5 ml) was gradually added to the solution, which was then set aside for 48 h. The mixture was extracted with ether (3 × 20 ml): the extracts were well washed with sodium hydrogen carbonate solution (3 × 20 ml) and water, dried ($MgSO_4$), and evaporated. The residue was analysed by observing the i.r. absorption at 1700 cm^{-1} (C=O), and by g.l.c. (see Table 2). The deamination of the amino-ester hydrochlorides was carried out as previously described.[2]

The authors thank the Hertfordshire County Council for a Research Assistantship (to T. K. M.) and I.C.I. Ltd. (Pharmaceuticals Division) for some of the microanalyses.

[2/074 *Received*, 13*th January*, 1972]

[13] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 73.

[14] H. E. Baumgarten, F. A. Bower, and T. T. Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 3145.

[15] G. S. K. Rao and Sukh-Dev, *J. Indian Chem. Soc.*, 1956, **33**, 539.