291. *The Stereochemistry of the 2-Aminocyclopentanols.*

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The stereochemical course of the reactions of the diastereoisomeric (±)-2-acylamino*cyclo*pentanols with hydrogen chloride and with thionyl chloride was investigated.

The *cis*-isomers (II) participated reversibly, without change of configuration, in both N ⟶ O acyl migration (II ⇌ III) and oxazoline formation (II ⇌ IV) whereas the *trans*-compounds (I) gave (III) and (IV) by irreversible reactions involving inversion of configuration.

The behaviour of the *trans*-acylamino*cyclo*pentanols thus conforms to that of derivatives of ephedrine, whereas the *cis*-isomers behave in a similar manner to the acyl derivatives of ψ-ephedrine.

Our investigations of N ⟶ O acyl migrations in the isomeric 2-benzamido*cyclo*hexanols at 25° (Fodor and Kiss, *Nature*, 1949, **164**, 917) led to conclusions, as to the configuration of the diastereoisomers, similar to those reached by McCasland, Clark, and Carter (*J. Amer. Chem. Soc.*, 1949, **71**, 637) by other means. As, however, the stereospecific differences between the diasteroisomers disappear at 90°, because of the flexibility of the *cyclo*hexane ring, we then found it advisable to continue our investigations on more rigid ring systems.

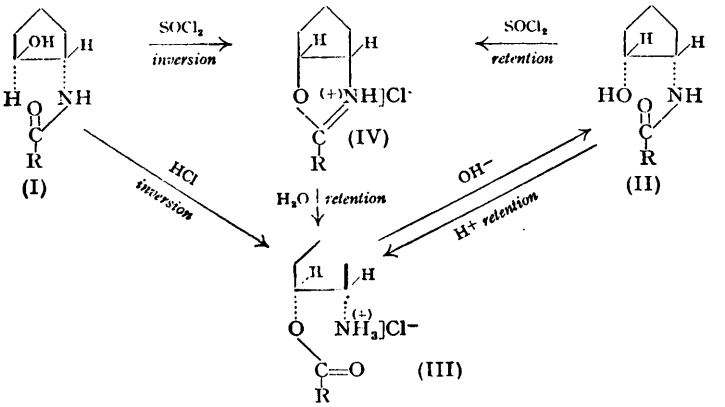
Meanwhile, McCasland and D. A. Smith (*ibid.*, 1950, **72**, 2190) have dealt with the geometry of the 2-amino*cyclo*pentonols in order to study the effect of configuration on the stereochemical behaviour. These workers prepared the *cis*-compound by tosylation and detosylation of the *trans*-isomer (Winstein *et al.*, *ibid.*, 1942, **64**, 2796; 1948, **70**, 812); although better results were achieved by application to the *cis*-oxazoline of the method described by Pfister, Robinson, Shabica, and Tischler (*ibid.*, 1949, **71**, 1101; cf. Fry, *J. Org. Chem.*, 1949, **14**, 887; Moersch and Moore, U.S.P. 2 513 346/1950).

They found that *cis*-2-amino*cyclo*pentyl *p*-nitrobenzoate, prepared from 2-*p*-nitrophenyl-*cis*-4 : 5-*cyclo*pentano-oxazoline, gave the 2-*p*-nitrobenzamido-alcohol by O ⟶ N acyl migration; they did not, however, examine the reverse, N ⟶ O acyl migration, or the action of thionyl chloride on the *cis*-2-acylamino*cyclo*pentanols.

We have obtained (±)-*trans*-2-benzamido- and -*p*-nitrobenzamido-*cyclo*pentanol (cf. I), and converted them, by the action of thionyl chloride, into the *cis*-isomers (cf. II). The *cis*- and *trans*-isomers were then treated under identical conditions with hydrogen chloride. The free and the bound hydrogen-ion concentrations, and therefore the conversion rate, could not be determined by acidimetric or potentiometric titration; the problem will be dealt with in detail later.

Treatment of (±)-*cis*-2-benzamido*cyclo*pentanol (II; R = Ph) in dioxan at 20° with 20 mols. of hydrogen chloride gave an 89% yield of (±)-*cis*-2-amino*cyclo*pentyl benzoate hydrochloride (III; R = Ph) besides 10% of an amorphous product. As expected (III; R = Ph) immediately reverted to (II; R = Ph) on treatment with alkali. Thus, in this series the N ⟶ O acyl migration was reversible as the configuration had been retained

(Welsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3500; Fodor and Kiss, *Acta Chim. Acad. Sci. Hungar.*, 1951, 130). Under identical conditions the *trans*-alcohol (I; R = Ph) was unreactive. At 100° in a sealed tube both the *cis*- and the *trans*-alcohol gave (III; R = Ph) in yields of 78% and 72%, respectively, and it was not possible to convert the latter



back into the *trans*-alcohol (I; R = Ph); presumably the N ⟶ O acyl migration was in this case accompanied by inversion of configuration. It can be assumed that the mechanism postulated by Welsh (*loc. cit.*) for 2-acylamino-alcohols, based on Winstein's general theory (*inter al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4669) is valid for this inversion. This observation led to a more practical preparation of *cis*-2-amino*cyclo*pentanol derivatives than the application of the thionyl chloride technique.

For solubility reasons further work was carried out on the *p*-nitrobenzamido-compounds; the extent and direction of the conversion at room temperature in this series resembled that of the benzamido-compounds. At higher temperatures the *cis*-alcohol (II; R = $C_6H_4{\cdot}NO_2$-*p*) underwent a 65% conversion into (III; R = $C_6H_4{\cdot}NO_2$-*p*) and gave also 10—18% of 2-chloro*cyclo*pentylamine of unknown configuration; the latter probably arose by a chlorination concomitant with the acyl migration, but a nucleophilic attack by chlorine ions on the 2-hydroxyoxazolidine intermediate cannot be excluded. The *trans*-amide (I; R = $C_6H_4{\cdot}NO_2$-*p*), on the other hand, gave about 87% of (III; R = $C_6H_4{\cdot}NO_2$-*p*) and approximately 12% of the *p*-nitrobenzoic acid salt.

The main product from the reaction of (II; R = $C_6H_4{\cdot}NO_2$-*p*) with thionyl chloride was the *cis*-oxazoline (IV; R = $C_6H_4{\cdot}NO_2$-*p*). That this reaction is accompanied by retention of configuration indicates that the oxazoline ring is formed from acylamino-alcohols containing a rigid ring, through a condensation of the diastereoisomer with spatially close functional groups, but by a nucleophilic attack in the isomer in which the groups are spacially opposed. The same is true for N ⟶ O acyl migration.

These findings are of interest; those for the *trans*-alcohols (I) are similar to our observations on ephedrine, norephedrine, and chloramphenicol, whereas the behaviour of the *cis*-compounds (II) agrees with that of the analogous derivatives of nor-ψ-ephedrine. With the results of other stereospecific reactions they support our concept of the *trans*-conformation of ephedrine and the *cis*-conformation of ψ-ephedrine (Fodor and Koczka, *J.*, 1952, 850; cf. Close, *J. Org. Chem.*, 1950, **15**, 1131).

The results also show that a *cis*-conformation of the hydroxy- and amino-groups can be inferred when the N ⟶ O acyl migration is reversible, whereas non-reversibility indicates a *trans*-conformation of the principal functions in these amino-alcohols. With alicyclic derivatives the configuration is similarly indicated.

Experimental

(±)-trans-2-*Amino*cyclo*pentanol*.—This was prepared by the method described by McCasland and Smith (*loc. cit.*), but without isolation of the epoxide, from 2-chloro*cyclo*pentanol (58 g.) and aqueous ammonia (1000 ml.; *d* 0·88); the amine hydrochloride (38 g., 48%) and unchanged chloro-compound (12 g.) were obtained.

Acyl Derivatives.—These were prepared as described by Leffler and Adams (*J. Amer. Chem. Soc.*, 1937, **59**, 2256) with benzoyl chloride and *p*-nitrobenzoyl chloride; the latter reagent, however, at 50° gave 2-p-*nitrobenzamido*cyclo*pentyl* p-*nitrobenzoate*, m. p. 170—172° (Found: N, 10·6. $C_{19}H_{17}O_7N_3$ requires N, 10·55%). Hydrolysis of this ester (3·1 g.) with N-sodium hydroxide (10 ml.) and ethanol (20 ml.) by Kunz's method gave the *p*-nitrobenzamido-alcohol.

(±)-cis- *and* -trans-2-*Benzamido*cyclo*pentanol.*—(*a*) These were obtained as described by McCasland and Smith (*loc. cit.*).

(*b*) Heating a dioxan (5 ml.) solution of the (±)-*trans*-benzamido-alcohol (I; R = Ph) (1 g.) with a 5N-solution (5 ml.) of hydrogen chloride in dioxan in a sealed tube for 2 hours at 100° gave the amino-benzoate hydrochloride (III; R = Ph), which was converted by O ⟶ N acyl migration into the *cis*-amide (II; R = Ph) (0·72 g., 72%).

(±)-2-p-*Nitrophenyl*-cis-4 : 5-cyclo*pentano-oxazolinium Chloride* (IV; R = C_6H_4·NO_2-*p*).—(*a*) This salt, m. p. 159—161° (decomp.), was obtained by treatment of the *trans*-amido-alcohol (I; R = C_6H_4·NO_2-*p*) with thionyl chloride in ethyl acetate (cf. McCasland and Smith, *loc. cit.*, who record m. p. 150—151°) (Found: N, 10·2; Cl^-, 12·8. Calc. for $C_{12}H_{12}O_3N_2$,HCl: N, 10·45; Cl^-, 13·2%).

(*b*) The (±)-*cis*-*p*-nitrobenzamido-alcohol (II; R = C_6H_4·NO_2-*p*) (2 g.) in anhydrous dioxan (30 ml.) was treated with thionyl chloride (2 ml.) for 3 hours at 25°; light petroleum was then added. After 2 days the mixture was heated on the steam-bath for a few minutes, and the solution decanted from the oil and allowed to cool. The separated crystals had m. p. 116—120°, raised on crystallisation to 123—124°. Analysis suggested that these were 2-*chloro*-1-p-*nitrobenzamido*cyclo*pentane* (Found: C, 52·8; H, 5·3; N, 10·3; Cl, 12·0. $C_{12}H_{13}O_3N_2Cl$ requires C, 53·7; H, 4·85; N, 10·4; Cl, 13·2%). The oily residue was triturated with water (15 ml.); after removal of the deep-coloured crystals (1·03 g.; m. p. 128°) the aqueous solution was made alkaline and a second crop of crystals (0·52 g.; m. p. 133—135°) obtained. These were identified by mixed melting-point determination as (±)-2-*p*-nitrophenyl-*cis*-4 : 5-*cyclo*pentano-oxazoline (cf. IV; R = C_6H_4·NO_2-*p*) (McCasland and Smith, *loc. cit.*). The picrate had m. p. 193—195° after recrystallisation from dry dioxan–light petroleum (Found: C, 46·4; H, 3·6; N, 15·3. Calc. for $C_{12}H_{12}O_3N_2,C_6H_3O_7N_3$: C, 46·8; H, 3·3; N, 15·2%) (McCasland and Smith, *loc. cit.*, record m. p. 210°). When the picrate was recrystallised from 96% alcohol the *picrate monohydrate* of 2-amino*cyclo*pentyl *p*-nitrobenzoate (III; C_6H_4·NO_2-*p*) was obtained; this had m. p. 166—168° (decomp.) (Found: C, 43·3; H, 3·95. $C_{12}H_{14}O_4N_2,C_6H_3O_7N_3,H_2O$ requires C, 43·4; H, 3·8%). This picrate monohydrate was also obtained by treatment of the amino-ester hydrochloride with sodium picrate.

(±)-cis-2-*Amino*cyclo*pentyl* p-*Nitrobenzoate Hydrochloride* (III; R = C_6H_4·NO_2-*p*).—(a) When the *cis*-oxazolinium chloride (IV; R = C_6H_4·NO_2-*p*) (0·5 g.) was heated with wet dioxan (16 ml.), and light petroleum (10 ml.) then added, (III; R = C_6H_4·NO_2-*p*) was obtained as needles (0·485 g.), m. p. 185—187° raised to 191—192° (decomp.) on recrystallisation from

Amide, 10^{-3} mole	Dioxan, c.c.	Mole HCl/mole amide	Conditions	Products from *cis*-isomer: unchanged alcohol, %	Products from *cis*-isomer: amino-ester salt, %	Products from *trans*-isomer: unchanged alcohol, %	Products from *trans*-isomer: amino-ester salt, %	Other products, %
cis- (II; R = C_6H_4·NO_2-p) *and* trans-2-p-*nitrobenzamido*cyclo*pentanol* (I; R = C_6H_4·NO_2-p)								
0·88	5	1·25	A	36·4	42·2	100	—	—
0·88	5	6·25	A	—	48·2	99·4	—	12·7 *
0·88	5	31·25	A	—	82·5	97·6	—	10·4 *
4	20	5·0	B	—	79·3	84·0	10·6	17·8 *
4	10	5·0	C	—	—	—	84·0	12·0 †
5	22	4·4	C	—	81·5	—	—	18·2 *
cis- (II; R = Ph) *and* trans-2-*benzamido*cyclo*pentanol* (I; R = Ph)								
1	—§	10	A	—	62·7	93·0	—	34·5 ‡
4·9	5	5	C	—	—	—	72·0	26·0 ‡
1	3	3·1	C	—	78·0	—	—	15·0 ‡
1	3	20·0	A	—	89·0	—	—	10·0 ‡
2·15	6	1·15	A	—	—	82·0	—	16·0 ‡
2·15	6	19·0	A	—	—	75·0	—	23·0 ‡

Conditions: A, 15 hours at 20°; B, 2 hours at 100°; C, 2 hours at 100° in a sealed tube.

* Chloro-compound from the *cis*-isomer.
† *p*-Nitrobenzoic acid salt.
‡ Amorphous product.
§ In ethanol (5 c.c.).

dioxan (40 ml.)–light petroleum (16 ml.). McCasland and Smith (*loc. cit.*) record m. p. 168° for their sample of this compound, prepared by the action of dilute hydrochloric acid on (IV; R = $C_6H_4 \cdot NO_2$-*p*).

(b) *From* trans-2-p-*nitrobenzamido*cyclo*pentanol* (I; R = $C_6H_4 \cdot NO_2$-*p*). The nitrobenzamido-alcohol (12 g.) was dissolved in dry dioxan (20 ml.), 7N-solution (30 ml.) of hydrogen chloride in dioxan was added, and the mixture was heated in a sealed tube for 2 hours at 100°. The product (III; R = $C_6H_4 \cdot NO_2$-*p*) (8·4 g.) had m. p. 189—191°. The mother-liquor was evaporated to dryness, and the residue treated with warm water (30 ml.). The insoluble portion (1·52 g.; m. p. 206—210°) appeared to consist mainly of 2-*hydroxy*cyclo*pentylammonium* p-*nitrobenzoate* (Found: N, 9·2. $C_{12}H_{16}O_5N_2,H_2O$ requires N, 9·7%) as, when its alkaline solution was acidified, *p*-nitrobenzoic acid was produced. The aqueous extract gave *cis*-2-*p*-nitrobenzamido*cyclo*pentanol (II; R = $C_6H_4 \cdot NO_2$-*p*) (1·7 g.), m. p. 164—166° when it was made alkaline.

Acyl-migration Experiments with the Diastereoisomers (I) *and* (II); *General Procedure.*—Each diastereoisomer was dissolved in dry dioxan containing a known quantity of hydrogen chloride, and experiments then carried out at 25°, and in sealed tubes immersed in a steam-bath. In the *p*-nitrobenzamido-series, when the reaction had ended the precipitate (III; R = $C_6H_4 \cdot NO_2$-*p*) was filtered off, the mother-liquor evaporated to dryness, and the residue extracted with water. A further crop of the amino-ester hydrochloride was obtained by evaporation, in a vacuum, of this extract.

With the benzamido-compounds this method of isolation proved unsatisfactory owing to similarities of solubility; therefore, separation was effected by fractional crystallisation from benzene–light petroleum. The experimental details are recorded in the table. Details of acyl migrations involving change of configuration have been described above.

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