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

By G. Fodor and J. Kiss.

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.

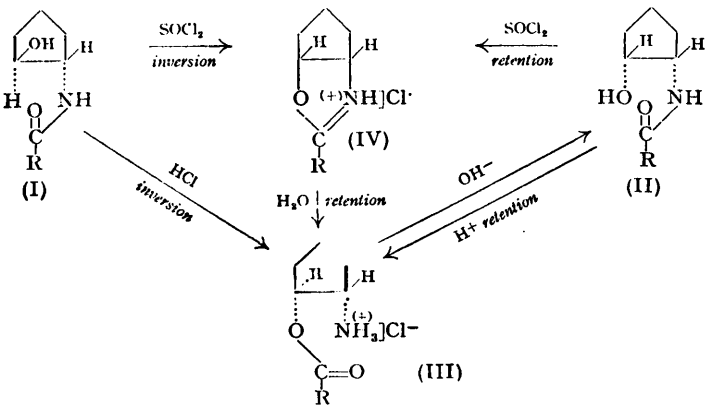
Meanwhile, McCasland and D. A. Smith (*ibid.*, 1950, **72**, 2190) have dealt with the geometry of the 2-amino*cyclo*pentonols in order to study the effect of configuration on the stereochemical behaviour. These workers prepared the *cis*-compound by tosylation and detosylation of the *trans*-isomer (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 = $C_6H_4{\cdot}NO_2$-*p*).—(*a*) This salt, m. p. 159—161° (decomp.), was obtained by treatment of the *trans*-amido-alcohol (I; R = $C_6H_4{\cdot}NO_2$-*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 = $C_6H_4{\cdot}NO_2$-*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 = $C_6H_4{\cdot}NO_2$-*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; $C_6H_4{\cdot}NO_2$-*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 = $C_6H_4{\cdot}NO_2$-*p*).—(a) When the *cis*-oxazolinium chloride (IV; R = $C_6H_4{\cdot}NO_2$-*p*) (0·5 g.) was heated with wet dioxan (16 ml.), and light petroleum (10 ml.) then added, (III; R = $C_6H_4{\cdot}NO_2$-*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 = $C_6H_4{\cdot}NO_2$-p) *and* trans-2-p-*nitrobenzamido*cyclo*pentanol* (I; R = $C_6H_4{\cdot}NO_2$-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.

This work was supported by the Hungarian Academy of Science. The authors express their thanks to Drs. Margaret Kovács Oskolás and Eva Fodor Varga for the microanalyses and to Miss A. Borbás and Mr. István György for technical assistance.

INSTITUTE OF ORGANIC CHEMISTRY,
THE UNIVERSITY, SZEGED, HUNGARY.

[*Received, June 11th,* 1951.]