SEPARATION OF (±) NOR-EPHEDRINE FROM (±) NOR-ψ-EPHEDRINE

G. FODOR and J. KISS.

Institute of Organic Chemistry.

The stereospecifity[1, 2, 3, 4] of N → O acyl migrations in the realm of diastereomeric 2-amino alcohols[1–4] has been revealed during the last five years. *Cis* modifications appeared to undergo a faster shift (*e.g.* in compounds of acyclic and alicyclic types) than the corresponding *trans*-epimers. Furthermore the conversion of *cis* N-acylamino alcohols into the appropriate amino ester salts proved in every case to take place with retention of configuration, whereas *trans*-2-aroyl amino cyclopentanols[5] furnished on the action of hydrogen chloride the salts of *cis*-2-amino-cyclopentanol-O-esters obviously due to an inversion of configuration at the hydroxyl bearing carbon atom.

These observations could be evaluated in order to establish the configurations of a series of diastereomeric pairs (inosamines[6], amino-borneols[7], glucosamines[8], 2-amino-3-tetralinols[9]) first in the 2-amino-alcohol series but later also in the 3-amino alcohols: tropines[10], ecgonines[11], granatanols[12], and so on. Epimeric arylaliphatic 2-amino-1-aryl-1-propanols, *e.g.* N-acyl-*nor*-ephedrine as compared with N-acyl-*nor*-ψ-ephedrine behave in a similar stereospecific manner[15a], *i.e.* the latter underwent acyl migration at a higher rate and with retention, whereas the former showed a notably lower reaction rate involving inversion at C_1.

On this basis *cis*-conformation regarding OH and $NHCH_3$ groups has been ascribed to ψ-ephedrine the reverse, *trans* one being attributed to ephedrine[2].

Another, preparative aspect of the investigations mentioned above emerged at an early stage, *i. e.* the separation of epimeric N-acyl-amino alcohols[2], the *cis* form being converted by HCl in ethanol into the amino-ester *salt,* whilst the *amide* remains unchanged. Obviously an ammonium *salt* could, in turn, easily be separated by its greater solubility in water from the epimeric *amide.* First (±) N-benzoyl-*nor*-ephedrine and the ψ-epimer were submitted to this treatment, proving the correctness of our presumptions. We succeeded in separating ψ-ephedrine, *i.e.* (±) O-benzoyl-ψ-ephedrine hydrochloride by the same method as well. However, the generalization of these principles could not be realized since some free amino alcohol bases suffer presumably undesired changes during the last step, *i.e.* on both acid[13] and alkaline[14] deacylations.

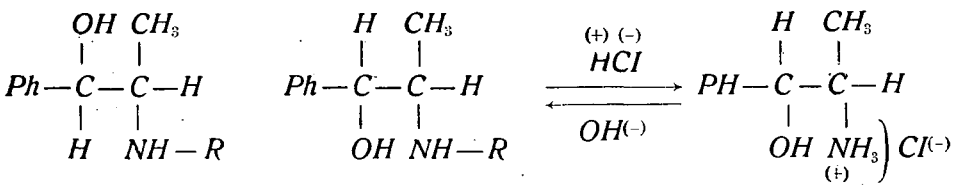
Consequently, the extension of the method to epimeric N-carbobenzoxy amino alcohols was propounded[15a] this acyl group rendering acyl migration

possible as the basis for separation and on the other hand the protecting group being able to be removed ultimately from the already separated epimers by hydrogenolysis under very mild conditions which are unable to violate any sensitive moiety of the molecule.

A preliminary paper[15b] recorded a few years ago the succesful adoption of this method in converting a mixture of the two racemates of N-benzyloxycarbonyl-2-amino-1-phenyl-1-propanols (Ib) and (IIb) on the action of HCl in dry ethanol into (±) O-benzyloxycarbonyl-*nor*-ψ-ephedrine hydrochloride (IIIb) beside unchanged (±) N-benzyloxycarbonyl-*nor*-ephedrine (Ib). The quite different solubility of the *salt* (IIIb) from that of the *amide* (IIb) in ethanol allowed separation easy. Both (IIb) and (IIIb) as well as (Ib) were, in turn, cleaved by hydrogenolysis over Pd-charcoal into pure (±) *nor*-ephedrine (Ia) and (±) *nor*-ψ-ephedrine (IIa) respectively.

The detailed description of this method has been postponed as long as we should be able to extend our method precedingly to further models, *e.g.* to epimeric (±) 1.2-diphenyl-2-amino ethanols. Unfortunately, however, owing to solubility difficulties no acyl migration could be carried out in this case, at variance with the appropriate N-acetyl derivatives[2].

Nevertheless the short communication[15b] quoted above received recently notable attention being extensively treated in the monograph series[16] »*Organic Reactions*«. It deemed therefore timely to describe the experimental details of the present long-standing work.



a.) R=H

b.) R=*Ph.CH*$_2$*.O.CO-*

Experimental

(±) *N-Benzyloxycarbonyl-nor-ephedrine (Ib).*

(±) nor-Ephedrine (3 g, 0.02 mol) was dissolved in *N* HCl (20 ml) and to the ice-cold solution under vigorous mechanical stirring benzyl chloroformate (4 g, 0.025 mol) in benzene (4 ml) was added. After alkalinization of the reaction mixture with 2*N* NaOH added in several portions (total amount: 25 ml), the *amide* separated first as an oil but solidifying soon. After stirring for 1 hour it was filtered off to give a snow-white crystal powder (5.1 g). The product was washed with *N* HCl (50 ml) then with water (30 ml) finally dried in a desiccator over calcium chloride to give a substance (4.8. g, 90.2%) m. p. 98—101.5°. After recrystallisation from a mixture of ethanol (30 ml) and water (10 ml) hexagonal prisms (4.4 g) were obtained, m. p. 104—104.5°. (Found: C 71.45; H 6.95. $C_{17}H_{19}O_3N$ requires: C 71.56; H 6.67%.)

Mixture of (±) N-benzyloxycarbonyl derivatives of nor-ephedrine (Ib) and of (±) nor-ψ-ephedrine (IIb).

(±) *nor*-Ephedrine (10 g) in 14% aqueous hydrochloric acid (500 ml) was refluxed for 12 hrs. in order to afford epimerization. The solution was then treated with charcoal, after the removal of water ethanol (150 ml) was added and then repeatedly evaporated to dryness. The residue was dissolved in water (100 ml) decolorized with charcoal, cooled (ice) and acylated under Schotten-Baumann conditions with benzyl chloroformate (10 ml) in benzene (5 ml) with mechanical stirring. A mixture of both white crystalline *amides* (14.5 g) was obtained, m. p. 62—84°. (Found: C 71.18; H 6.38%.)

Separation of the mixture of the N-benzyloxycarbonyl derivative of (±)-nor-ephedrine (Ib) from that of (±) nor-ψ-ephedrine (IIb) by N→O acyl migration.

5.5 *N* HCl in anhydrous ethanol (10 ml) was added to the mixture obtained above (2.66 g) in dry ethanol (5 ml). After allowing to stand for 15 hrs. at room temperature colourless prisms separated (0.69 g), m. p. 98—100°. Mixed m. p. with N-benzyloxycarbonyl-(±) *nor*-ephedrine (Ib) was 99—102°. After setting aside the mother liquor for 36 hrs. white crystals in needles began to separate (0.28 g), m. p. 228° (decomp.). M. p. raised to 229° on recrystallisation from dry ethanol (15 ml). The substance was soluble in water. (Found: C 63.42; H 6.21. $C_{17}H_{20}O_3NCl$ requires: C 63.48; H 6.23%.) This crop consisted of (±) O-benzyloxycarbonyl-*nor*-ψ-ephedrine hydrochloride (IIIb).

O→N Acyl migration of (IIIb) into (±) N-benzyloxycarbonyl-nor-ψ-ephedrine (IIb). (±) O-benzyloxycarbonyl-*nor*-ψ-ephedrine hydrochloride (IIIb) (0.1 g) dissolved in hot water (10 ml) was made alkaline with 20% NaOH and cooled with ice. The separated *amide* became crystalline quickly. Recrystallization from a mixture of ethanol (5 ml) and water (15 ml) afforded colourless needles, m. p. 83°. (Found: C 71.59; H 7.02. $C_{17}H_{19}O_3N$ requires: C 71.45; H 6.67%.)

N→O acyl migration of a mixture of adjusted samples of (±) N-benzyloxycarbonyl-nor-ephedrine (Ib) and of (±) N-benzyloxycarbonyl-nor-ψ-ephedrine (IIb).

(±) N-benzyloxycarbonyl-*nor*-ephedrine (Ib). (15.2 mg) and (±) N-benzyloxycarbonyl-*nor*-ψ-ephedrine (IIb) (152 mg) were dissolved in dry ethanol (0.75 ml) and *N* HCl in dry ethanol (2.5 ml) was added at room temperature. After 15 hrs. needles separated. After setting aside for 36 hrs. the reaction mixture was evaporated to dryness, the residual crystalline substance was extracted with hot water, leaving a product (149 mg) insoluble in water, m. p. 99—101°. Mixed with (±) N-benzyloxycarbonyl-*nor*-ephedrine (Ib) m. p. 100—102°.

Alkalinization of the aqueous solution with 17% ammonium hydroxide, filtration of the separated crystals and its subsequent recrystallization gave a substance (106 mg), m. p. 81—82° undepressed by (±) N-benzyloxycarbonyl-*nor*-ψ-ephedrine (IIb).

Hydrogenolysis of the benzyloxycarbonyl derivatives.

(1) (±) **N-Benzyloxycarbonyl-nor-ephedrine (Ib).** 10 *N* HCl (0.35 ml) was added to (±) N-benzyloxycarbonyl-*nor*-ephedrine (Ib) (0.53 g) dissolved in a

mixture of ethanol (15 ml) and water (10 ml). This solution was treated with palladised charcoal (0.3 g, 7% Pd 0) in ethanol (5 ml) and hydrogenated under shaking. The reaction was completed as CO_2 evolution ceased (checked by barium hydroxide). Complete hydrogenolysis lasted 3 hrs. The filtrate of the catalyst was evaporated to give a white crystalline product (0.38 g). After recrystallisation from dry ethanol (2.5 ml) it showed m. p. 193.5—195° undepressed by (±) *nor*-ephedrine (Ia) hydrochloride. It is to be noticed hydrogenolysis having not occured in neutral medium.

(2) (±) **N-Benzyloxycarbonyl-nor-ψ-ephedrine (IIb).**

(±) N-Benzyloxycarbonyl-*nor*-ψ-ephedrine (IIb) (265 mg) was dissolved in the mixture of methanol (10 ml) and water (8 ml) and hydrogenated over palladised charcoal (0.15 g) in the presence of 10 *N* hydrochloric acid (0.18 ml). The reaction lasted 10 minutes. After evaporating *in vacuo* white crystals were obtained, which on recrystallisation from dry ethanol showed m. p. 164—166°. On admixture with an authentic specimen of (±) *nor*-ψ-ephedrine hydrochloride (IIa) it melted at 165—166°.

(3) (±) **O-Benzyloxycarbonyl-nor-ψ-ephedrine hydrochloride (IIIb).** The *hydrochloride* (0.28 g) (IIIb) was dissolved in the mixture of methanol (6 ml) and water (6 ml) and hydrogenated over palladised charcoal (0.15 g) under shaking. The reaction was completed after 30 minutes. The filtrate of the catalyst was evaporated *in vacuo* affording a crystalline product (148.2 mg) m. p. 152—155°. After recrystallisation from alcohol m. p. raised to 156—157°, undepressed by an authentic specimen of (±) *nor*-ψ-ephedrine hydrochloride (IIa).

Summary

The mixture of (±) *nor*-ephedrine and (±) ψ-*nor*-ephedrine was converted into the benzyloxycarbonyl (*i. e.* carbobenzoxy) derivatives (Ib) and (IIb) and these, in turn, submitted to the action of HCl in dry ethanol. (IIb) furnished by acyl migration the O-acyl amine *salt* (IIIb), which could easily be separated by extracting from the water-insoluble *amide* (Ib). Hydrogenolysis of one epimeric form gave rise to pure *nor*-ephedrine (Ia), of the other to ψ-ephedrine (IIa).

This method may be preferred to the more cumbersome fractional crystallisation method of *Hoover* and *Hass*[17].

Acknowledgement. The authors wish to express their gratitude to *Miss M. Kovács-Oskolás* and *Dr. J. Kovács* for the microanalyses.

References

1. *Welsh, L. H.:* Mechanism and stereochemical course of acyl migrations in derivatives of ephedrine and ψ-ephedrine. J. Amer. Chem. Soc. **71**, 3500 (1949).

2. *Fodor, Gábor, Bruckner, Victor, Kiss, József* and *Öhegyi, Géza:* Use of acyl migration in separating diastereoisomeric amino alcohols. J. Org. Chem. **14**, 337 (1949).

3. *Fodor, G. and Koczka, K.:* The stereochemical course of the conversion of 2-ureido alcohols into oxazolidones. J. Chem. Soc. (London) 850, (1952).

4. *Fodor, G. and Kiss, J.:* Configuration of alicyclic amino-alcohols. Nature **164**, 917 (1949); Configuration of diastereoisomeric 2-amino-cyclohexanols and a suggested mechanism for acyl migration N→O. Acta Chim. Acad. Sci. Hung. **1**, 130 (1951); Acyl migration O→N in the diastereomeric 2-amino-cyclohexyl benzoates. J. Amer. Chem. Soc. **72**, 3495 (1950).

5. *Fodor, G. and Kiss, J.:* Stereospecific behaviour of the diastereomeric 2-acyl-amido-cyclo-pentanols in acyl migration N→O. Research **4**, 339 (1951); The stereochemistry of 2-amino-cyclo-pentanols. J. Chem. Soc. (London) 1589 (1952).

6. *McCasland, G. E.:* N→O Acyl migration in epimeric acetyl-inosamines. J. Amer. Chem. Soc. **73**, 2295 (1951).

7. *Van Tamelen, E. E., Tousignant, W. F. and Peckham, P. E.:* The structure of camphenamine. ibid. **75**, 1297 (1953).

8. *Fodor, G. and Ötvös, L.:* The conformation of D-glucosamine. Acta Chim. Acad. Sci. Hung. **5**, 205 (1954).

9. *Kiss, J.* and *Kóbor, J.:* Zur Kenntnis der Stereochemie des Tetralinringes. Acta Chim. Acad. Sci. Hung. **5**, 365 (1955).

10. *Fodor, G. and Nádor, K.:* Stereochemistry of tropine and pseudotropine. Nature **169**, 462 (1952).

11. *Fodor, G.:* Stereochemistry of the tropane alkaloids. Nature **170**, 278 (1952); *Fodor G., Kovács Ö.* and *Weisz I.:* The stereochemistry of cocaine. Nature **174**, 131 (1954).

12. *Alder, K.* and *Dortmann, H. A.:* Über den sterischen Verlauf der Reduktion von Pseudo-pelletierin. Die Konfiguration der N-Methyl-granatoline und ihren Nor-Verbindungen. Chem. Ber. **86**, 1548 (1953).

13. *Fodor, G.:* Synthetische Norephedrin und Isochinolin-abkömmlinge. Ber. dtsch. Chem. Ges. **76**, 1216 (1943).

14. *Bruckner, V.:* Über die Alkaliempfindlichkeit von α-(Alkoxyphenyl)-β-amino- und hydroxylamino-propanolen. J. prakt. Chem. (2), **142**, 301 (1935).

15. (a) *Fodor, G.:* Use of acyl migration in separating diastereoisomeric 2-amino-alcohols. Presented at the Meeting of the Chemical Department of the Trade Union of Hungarian Engineers and Technicians, Budapest, June 17, 1948.

(b) *Fodor, G., Kiss, J.:* Separation of Diastereoisomeric Amino Alcohols. Nature **163**, 287 (1949).

16. *Hartung, W. H.* in »Organic Reactions«, Vol. VII., p. 274. J. Wiley and Sons Ed., New-York, 1954.

17. *Hoover, F. W.* and *Hass, H. B.:* Synthesis of 2-amino-1-phenyl-1-propanol and its methylated derivatives. J. Org. Chem. **12**, 506 (1947).