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A NEW AMINE RESOLUTION METHOD AND ITS APPLICATION TO 3-AMINOBENZODIAZEPINES

Kenneth E. Rittle*, Ben E. Evans,* Mark G. Bock, Robert M. DiPardo, Willie L. Whitter, Carl F. Homnick, Daniel F. Veber and Roger M. Freidinger

Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

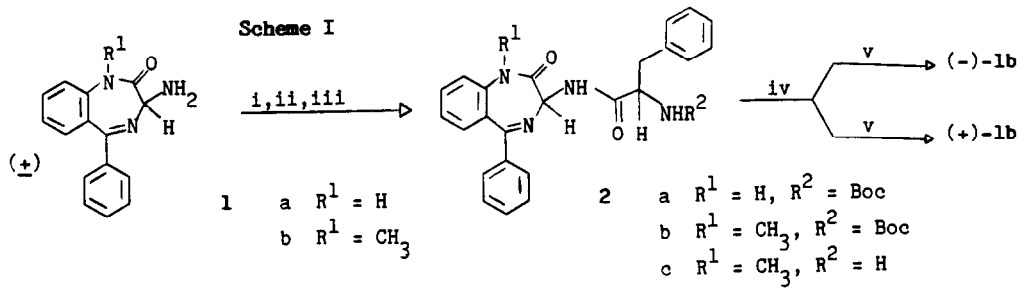
SUMMARY: A new method for the resolution of amines and its application to 3-aminobenzodiazepines **1** is described. The method involves the synthesis and separation of a pair of phenylalanyl amide diastereomers followed by removal of phenylalanine via the Edman degradation to give the individual enantiomers of **1** with high chiral purities.

Resolution of amines has traditionally been acomplished by crystallization of diastereomeric salts. Covalent derivatives, amides in particular, offer potential advantages such as high crystallinity and chromatographic separability, advantages widely exploited in the parallel resolution of alcohols via their esters. Use of such derivatives is precluded for all but the most stable amines, however, by the rigor of the conditions required for their cleavage. Resolution methods using readily cleaved acyl derivatives have not been forthcoming. We report here the development of such a method involving the preparation and separation of a pair of diastereomeric phenylalanyl amides followed by removal of phenylalanine via the Edman degradation.[1] The method is illustrated by the resolution of **1**, a vital intermediate in our recent synthesis of non-peptidal antagonists for the peptide hormone cholecystokinin.[2]

Compound **1a**[3] was coupled (Scheme I) with Boc-L-Phe[4] to give protected amine **2a**[5] as a 1:1 mixture of diastereomers. In an aside dictated by the final structures desired, methylation provided the amides **2b** (1:1, 87%). Removal of Boc and neutralization gave amides **2c** which were separated by chromatography on silica gel (CH_2Cl_2:MeOH:H_2O:HOAc, 90:10:1:1) into a high R_f (TLC: R_f = 0.36; HPLC: 100% diastereomeric purity) and a low R_f (R_f = 0.24; 99.2%) component.

Each diastereomer of **2c** was warmed with phenylisothiocyanate (1.1 eq.) followed by trifluoroacetic acid. Chromatographic purification (silica gel, 90:10:1:1) gave the resolved amines (white foams). The higher R_f amide diastereomer **2c** gave the 3S amine[6] (-)-**1b** (HPLC: >97.6%, $[\alpha]_D^{25}$ =

Scheme I



i) Boc-D- or-L-Phe, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride (EDC), 1-Hydroxybenzotriazole (HBT), DMF, 25°C, 30 min. ii) MeI, NaH, DMF, 0°C. iii) EtOAc, HCl(g), 0°C, 10 min. iv) separation by chromatography or fractional crystallization. v) C_6H_5NCS, CH_2Cl_2, Δ, 10 min. followed by TFA, 52°C, 18 min.

-236°) while the lower R_f diastereomer provided the 3R enantiomer (+)-**1b** (HPLC: >96.7%, $[\alpha]_D^{25}$ = +227°). The enantiomeric compositions of 3S- and 3R-**1b**, assigned by HPLC on a chiral support[7], were 99.1:0.9 and 3.0:97.0, respectively. Seed material from this work allowed separation of **2c** diastereomers by simple crystallization of the HCl salts in subsequent runs. With Boc-D-Phe as resolving agent, this technique provided 12.0gm of chirally pure 3S-**1b** from 40.3gm of the racemate.

The amine resolution described here uses all known reactions of proven generality. It employs reagents readily available in D- or L-form, easily applied and easily removed. It frees the resolution process from the vagaries of crystallization and should thus provide a generally useful alternative or adjunct to conventional salt crystallization techniques.

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References and Notes

1. P. Edman, Acta Chem. Scand. 4, 283 (1950); R.A. Laursen and W. Machleidt in "Methods of Biochemical Analysis"; D. Glick, Ed.; J. Wiley & Sons : New York, 1980; Vol. 26, p.201.
2. Evans, B.E.; Bock, M.G.; Rittle, K.E.; DiPardo, R.M.; Whitter, W.L.; Veber, D.F.; Anderson, P.S.; Freidinger, R.M. Proc. Natl. Acad. Sci. USA, 83, 4918 (1986).
3. Bell, S.C., U.S. Patent 3,198,789; Chem. Abstr., 63, 18129f (1965).
4. Derivatives of O-benzyl-Thr, Val, Leu, Trp and Pro were also investigated. Best separations were obtained with Phe.
5. All new compounds were fully characterized by ^{1}H NMR, MS, HPLC, and microanalysis.
6. Stereochemistry was assigned by X-ray crystallographic analysis of the o-iodobenzamide (J. Springer and J. Hirshfield, unpublished results).
7. Composition was determined, after reaction with phenylisothiocyanate, on a Pirkle covalent phenylglycine column using hexane/2-propanol.

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