Tetrahedron Letters No. 31, pp 2701 - 2704, 1975. Pergamon Press. Printed in Great Britain.

# HYDRAZINO ACIDS AND PEPTIDES. A NEW GENERAL SYNTHESIS OF L-α-HYDRAZINO ACIDS FROM L-α-AMINO ACIDS

Kazuo Achiwa and Shun-ichi Yamada

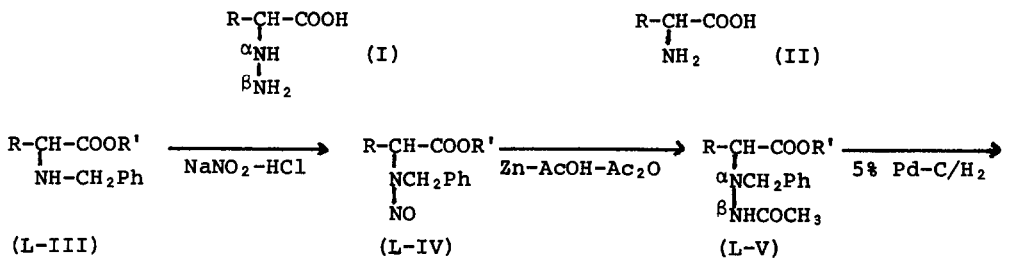
Faculty of Pharmaceutical Sciences, University of Tokyo,

Bunkyo-ku, Tokyo, Japan

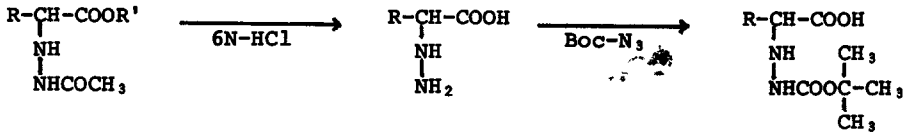
(Received in Japan 30 May 1975; received in UK for publication 16 June 1975)

α-Hydrazino acids (I) have aroused interest widly in recent years mainly because of their biological activity[1-3], their close structural relationship to the naturally occurring α-amino acids and also their isolation from nature[4]. In spite of a variety of their synthetic studies over the past several decades[5], surprisingly no method for the direct conversion of L-α-amino acids (L-II) to L-α-hydrazino acids (L-I) has been reported presumably due to the high chemical reactivity of their N-N bonding on hydrogenolysis.

We want to describe here a new general procedure for this direct conversion via the hydrogenolysis of the protecting $N^{\alpha}$-benzyl group of V whose N-N bonding, as expected, become stable enough for the fission by $N^{\beta}$-acylation as shown below.




(L-III) (L-IV) (L-V)

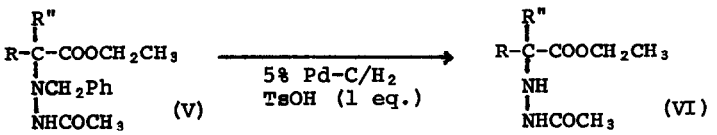


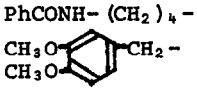

(L-VI) (L-I) (L-VII)

A synthesis of L-α-hydrazino-β-phenylpropionic acid (L-I: R=$PhCH_2$-) from L-phenylalanine (L-II: R=$PhCH_2$-) was shown as a typical example. The N-benzyl-L-phenylalanine ethyl ester [6] [L-III: R=$PhCH_2$-, R'=$CH_3CH_2$-, b.p. 172-175° (4 mmHg), $[\alpha]_D^{20}$ -7.0°(c=2.2, EtOH)] easily obtainable from L-phenylalanine was treated with 1.2 equivalent of $NaNO_2$ in 1N-HCl (2 eq.) at 80°c for 30 min. to give the N-nitroso derivative[6b] (L-IV: R=$PhCH_2$-, R'=$CH_3CH_2$-) in a quantitative yield. Successive reduction of IV with Zn-dust in AcOH-$Ac_2O$ (3:1) afforded the $N^{\beta}$-acetyl-L-α-hydrazino acid ester[6] [L-V; R=$PhCH_2$- , R'=$CH_3CH_2$-, oil; $[\alpha]_D^{20}$+21.3° (c=1.2, EtOH)] in 80% yield. Hydrogenation of V in the presence of p-toluenesulfonic acid (1 eq.) over 5% Pd-C catalyst in ethanol yielded the debenzylated compound[6] [L-VI: R=$PhCH_2$-, R'=$CH_3CH_2$-, oil; $[\alpha]_D^{20}$ -2.5° (c=1.2, EtOH)] in 85% yield. On the other hand, in the absence of the acid (hydrochloric acid or p-toluensulfonic acid), the debenzylation under the same conditions did not proceed. Subsequent hydrolysis of VI in 6N-HCl at 110° for 30 min. under a nitrogen atomosphere followed by isolation using Amberlite IR-120 gave the L-α-hydrazino acid[6] [L-I: R = $PhCH_2$-, m.p.; 193-196°, $[\alpha]_D^{20}$ -16.0°(c=0.7, 6N-HCl)] in 87% yield. Both specific rotations and melting points of L-I and the $N^{\beta}$-t-butoxycarbonyl derivative[6] [L-VII: R=$PhCH_2$-, m.p.; 188-189°, $[\alpha]_D^{20}$+26.0° (c=0.36, DMF)] are in good agreement with those of the reported[7,8]. This reaction sequence clearly represents a useful method to prepare optically active α-hydrazino acids without racemization.

Our method was therefor applied to various types of α-amino acids including α-alkyl-α-amino acid and the resulted data are listed in Table I and II.

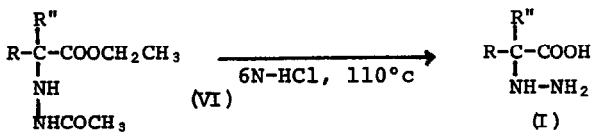
Table I

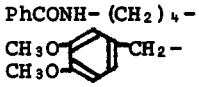


| | R | R" | V mp (°c) | V $[\alpha]_D$ (EtOH) | VI yield (%) | VI $[\alpha]_D$ (EtOH) |
|---|---|---|---|---|---|---|
| (L) |  | H | oil | +21° | 85 | -2.5° |
| (L) |  | H | 75-76 | -2.1° | 65 | -5.1° |
| (L) | $CH_3$- | H | oil | +34° | 50 | -28° |
| (L) | PhCONH-$(CH_2)_4$- | H | oil | +4.5° | 61 | -3.9° |
| (D) a) |  | $CH_3$- | 100-101 | -42° | 71 | -21° |

a) R-configuration.

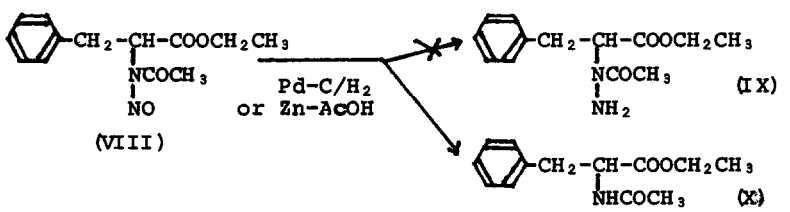
Table II



| | R | R" | I yield (%) | I mp (decomp) (°c) | I $[\alpha]_D$ |
|---|---|---|---|---|---|
| (L) |  | H | 87 | 193-196 | -16° (6N-HCl) |
| (L) |  | H | 83 | 223-225 | -11° (6N-HCl) |
| (L) | $CH_3$- | H | 80 | 198-203 | -40° (6N-HCl) |
| (L) | PhCONH-$(CH_2)_4$- | H | 90 | 186-188 | -5° (6N-HCl) |
| (D) a) |  | $CH_3$- | 80 | 185-187 b) | +10° ($H_2O$) |

a) R-configuration. b) monohydrate.

We have also examined the reduction of the $N^{\beta}$-nitroso derivative (VIII) with Zn-dust in AcOH or over Pd-C/$H_2$ and found the N-acetyl derivative (X) as a sole product, probably due to the high stability of the N-anion in X.



L-α-Hydrazino acids (I) thus obtained seem to be useful for the asymmetric synthesis of peptides[9] and also for the synthesis of modified peptides[10].

Further works on this line are active investigation.

## REFERENCES


1) As potential antimetablites.
a) A. Carmi, G. Pollak and H. Yellin; J. Org. Chem., 25, 44 (1960); b) G. Pollak, H. Yellin and A. Carmi; J. Med. Chem., 7, 220 (1964).

2) As inhibitors of amino acid decarboxylase.
a) S. Udenfriend, R. Connamacher and S. M. Hess; Biochem. Pharmacol., -, 419 (1961); b) S. Udenfriend and P. Zaltzman-Nirenberg; J. Pharmacol. Exptl. Therap., 138, 194 (1962); c) E. Hansson and W. G. Clark; Proc. Soc. Exptl. Biol. Med., 111, 793 (1962); d) C. C. Porter, L. S. Watson, D. C. Titus, J. A. Tataro and S. S. Byer; Biochem. Pharmacol., 11, 1067 (1962). e) C. R. Creveling, J. W. Daly and B. Witkop; J. Med. Chem., 9, 284 (1966); f) E. J. Glamkowski, G. Gal, M. Sletzinger, C. C. Porter and L. S. Watson; J. Med. Chem., 10, 852 (1967);g) M. Sletzinger, R. A. Fireston, D. F. Reinhold, C. S. Rooney and W. H. Nicholson; J. Med. Chem., 11, 261 (1968); h) K. Kobashi, N. Harada, H. Sassa and J. Hase; Yakugaku Zasshi, 91, 1127 (1971).

3) As inhibitors of the growth of cell and the transport activity.
Y. Anraku, T. Naraki and S. Kanzaki; J. Biochem., 73, 1149(1973).

4) H.J. Klosterman, G.L. Lamoureux and J.L. Parson; Biochemistry, 6, 170(1967).

5) S. Karady, M.G. Ly, S.H. Pines and M. Sletzinger; J. Org. Chem., 36, 1946, 1949 (1971) and references cited therein.

6) Satisfactory a) analytical and b) spectroscopic data were obtained for this substance.

7) H. Niedrich and R. Grupe; J. Prakt. Chem., [4], 27, 108 (1965).

8) R. Grupe and H. Niedrich; Chem. Ber., 100, 3283 (1967).

9) K. Achiwa and S. Yamada; Tetrahedron Letters, 1974, 1799.

10) R. Grupe, B. Baeck and H. Niedrich; J. Prakt. Chem., 314, 751 (1972) and references cited therein.