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Amino Acids and Peptides. XX.[1] Reduction of α-Substituted α-Diazo Esters. Convenient Synthesis of α-Hydrazinocarboxylic Acids and Their Derivatives from α-Amino Acids

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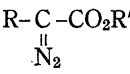
α-Substituted α-diazoesters (I), readily prepared from α-amino acid esters, were reduced with various reductants to give corresponding α-hydrazinocarboxylic acids (II) and their derivatives.

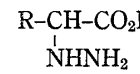
Several investigations were also undertaken in order to synthesize α,α-disubstituted α-hydrazinocarboxylic acid derivatives (VII) from I.

α-Hydrazinocarboxylic acids (II), structurally resemble to naturally occurring α-amino acids, have recently been noted as potent inhibitors of some enzymes in amino acid metabolism[3] and also of the cell growth of a certain bacteria.[4]

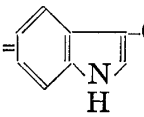
A variety of synthetic methods has been employed for biochemically and pharmacologically attractive II, such as reduction of a hydrazone of an α-keto acid,[3c,5] functionalization of a carbonyl compound in a Strecker-like synthesis,[6] reaction of hydrazine with an α-halo acid[5a,7] and reduction of N-nitroso derivative of an amino acid.[8] However, the reduction of α-substituted α-diazo esters (I),[9] readily available from α-amino acids, has scarcely been examined.[10] During the course of our study on reactivity of I toward various reductants we found a convenient synthesis of II and its derivatives as shown in Chart 1.



I



II

Sodium amalgam was effective for the direct synthesis of II from I. On stirring with 2% sodium amalgam in an aqueous ethanol solution for several hours, I was easily reduced and simultaneously hydrolyzed to give II in a moderate yield (IIa: R=$C_6H_5CH_2$, y. 56%. IIb: R=*p*-$HOC_6H_4CH_2$, y. 53%. IIc: R=  , y. 37%).

1) Part XIX: S. Yamada, N. Takamura, and T. Mizoguchi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2539 (1975).
2) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
3) *a*) C.C. Porter, L.S. Watson, D.C. Titus, J.A. Totaro, and S.S. Byer, *Biochem. Pharmacol.*, **11**, 1067 (1962); *b*) S. Shifrin, B.N. Ames, and G. Ferro Luzzi-Ames, *J. Biol. Chem.*, **241**, 3424 (1966); *c*) E.J. Glamkowski, G. Gal, M. Sletzinger, C.C. Porter, and L.S. Watson, *J. Med. Chem.*, **10**, 852 (1967); *d*) K. Kobashi, N. Harada, H. Sassa, and J. Hase, *Yakugaku Zasshi*, **91**, 1127 (1971) (in Japanese).
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9) N. Takamura, T. Mizoguchi, K. Koga, and S. Yamada, *Tetrahedron Letters*, **1971**, 4495; *idem*, *Tetrahedron*, **31**, 227 (1975).
10) B. Gisin and M. Brenner, *Helv. Chim. Acta*, **53**, 1030 (1970).

When I was treated with a large excess of $NaBH_4$ in an ethanol solution, II was not obtained and only the product isolated was α-hydrazonocarboxylic acid esters (III) (IIIa: R=$C_6H_5CH_2$, R'=C_2H_5, y. 56%. IIId: R=$(CH_3)_2CH$, R'=C_2H_5, y. 15%). IIIa was hydrolyzed with 1N HCl to corresponding ethyl 2-oxo-3-phenylpropionate (IVa) in a good yield (y. 94%), which was identified as its semicarbazone derivative (mp 166—167°, lit.,[11] mp 167°). III was also reduced with 2% sodium amalgam in an aqueous ethanol solution to afford II (IIa: R=$C_6H_5CH_2$, y. 39%. IId: R=$(CH_3)_2CH$, y. 63%). Attempts to prepare II from III by usual catalytic hydrogenation in acetic acid or ethanol led, in most cases, to practically complete cleavage of the N–N bond, consequently affording the corresponding α-amino acids. We found that use of Pt catalyst in ethyl acetate in the presence of acetic anhydride was effective for the reduction of IIIa to ethyl 2-(1,2-diacetylhydrazino)-3-phenylpropionate (Va, y. 45%) with slight cleavage of the N–N bond. Hydrolysis of Va thus obtained with 6N HCl gave IIa in a fairly good yield (y. 72%).

In order to synthesize α-disubstituted α-hydrazinocarboxylic acid derivatives from I, several investigations were undertaken. On the basis of our previous study on the reaction of 2-diazo-3-phenylpropionic acid derivatives and some basic reagents,[12] *n*-butyl lithium was first employed as a reagent of choice, which may act as a nucleophile rather than a base (Chart 2).

When butyl 2-diazo-3-phenylpropionate (I, R=$C_6H_5CH_2$, R'=*n*-Bu) was treated with *n*-butyl lithium in tetrahydrofuran (THF) at −78°, followed by addition of methyl iodide, butyl 2-butylazo-2-methyl-3-phenylpropionate (VIa) was obtained in a moderate yield (y. 52%). VIa thus obtained was reduced with aluminum amalgam and subsequently hydrolyzed with 10% NaOH to give the desired product, 2-(2-butylhydrazino)-2-methyl-3-phenylpropionic acid (VIIa, y. 42%).

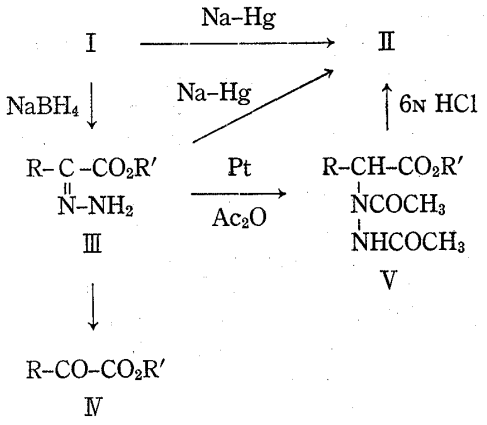


Chart 1

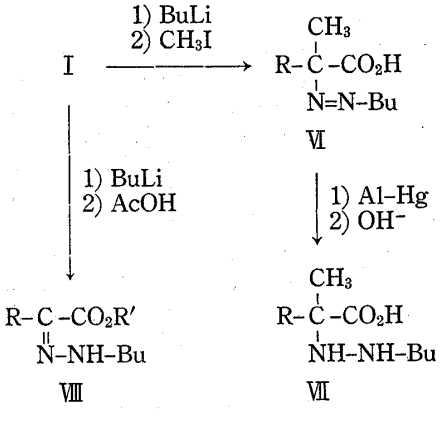
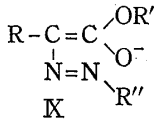


Chart 2

Methyl 2-butylhydrazono-3-phenylpropionate (VIIIa) was also prepared in a fair yield (y. 56%) from methyl 2-diazo-3-phenylpropionate (I, R=$C_6H_5CH_2$, R'=CH_3) when the diazo ester was treated with *n*-butyl lithium in THF at −78°, followed by addition of AcOH.

These results indicate that the intermediate of the reaction of I with the alkyl metal is probably IX. Further studies on reactivity and utilization of IX are now in progress.



11) J. Bougault, *Comptes rendus de l'Académie des Sciences*, **162**, 761 (1916).
12) N. Takamura, T. Mizoguchi, and S. Yamada, *Tetrahedron Letters*, **1973**, 4267; *idem*, *Chem. Pharm. Bull.* (Tokyo), **23**, 299 (1975).

Experimental[13]

2-Hydrazino-3-phenylpropionic Acid (IIa)——a) From Ethyl 2-Diazo-3-phenylpropionate: To a solution of ethyl 2-diazo-3-phenylpropionate[9] (1.02 g) in EtOH (30 ml) and H_2O (1 ml) was added 2% Na–Hg (50 g) under ice-cooling and the whole was stirred for 4 hr at room temperature. The colorless reaction mixture was filtered and the filtrate was adjusted to pH 5—6 with conc. HCl and cooled to give IIa as colorless crystals (0.50 g, 56%), mp 204—205° (decomp.). The IR spectrum of this compound was identical with that of IIa prepared by method b.

b) From Ethyl 2-Hydrazono-3-phenylpropionate (IIIa): To a solution of IIIa (1.03 g) in EtOH (30 ml) and H_2O (1 ml) was added 2% Na–Hg (50 g) under ice-cooling and the reaction mixture was stirred for 4.5 hr at room temperature and treated in a similar manner as above to afford IIa (0.35 g, 39%), mp 198—199° (decomp.). Recrystallization from H_2O gave colorless crystals, mp 205—206° (decomp.), lit.,[5a] mp 196—201°. *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.94; H, 6.40; N, 15.49. IR ν_{max}^{Nujol} cm^{-1}: 3240, 2700—2300, 2190, 1625, 1585, 1550, 1530, 1515, 1500. NMR (D_2O–NaOD) τ: 6.72 (2H, d, 7 Hz), 6.11 (1H, t, 7Hz), 2.23 (5H, s).

c) From Ethyl 2-(1,2-Diacetylhydrazino)-3-phenylpropionate (Va): Va (0.56 g) and 6N HCl (5 ml) was heated at 110° for 35 min. After cooling the reaction mixture was adjusted to pH 5—6 with powdered $NaHCO_3$ and satd. $NaHCO_3$ to give colorless crystals (0.25 g, 72%), mp 205—206° (decomp.). The product was identified with authentic IIa prepared by method b.

2-Hydrazino-3-(4-hydroxyphenyl)propionic Acid (IIb)——To a solution of methyl 2-diazo-3-(4-hydroxyphenyl)propionate[9] (0.70 g) in EtOH (20 ml) and H_2O (0.7 ml) was added 2% Na–Hg (30 g) under ice-cooling and the mixture was stirred for 4 hr at room temperature and treated in the same manner as method a for IIa to give IIb (0.36 g, 53%), mp 250° (decomp.). Recrystallization from H_2O afforded colorless needles, mp 255—258° (decomp.) lit.,[5b] mp 280—282° (decomp.). *Anal.* Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.88; H, 6.11; N, 14.44. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3175, 2700—2000, 1640 (shoulder) 1590, 1535, 1515.

2-Hydrazino-3-(3-indolyl)propionic Acid (IIc)——To a solution of methyl 2-diazo-3-(3-indolyl)propionate[9] (1.03 g) in EtOH (30 ml) and H_2O (1 ml) was added 2% Na–Hg (40 g) under ice-cooling and the mixture was stirred for 4 hr at room temperature. Working-up of the pale brown reaction mixture in a similar manner to method a for IIa gave fine needles (0.36 g, 37%), mp 242—245° (decomp.), lit.,[3c] mp 260° (decomp.). *Anal.* Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.26; H, 5.98; N, 19.15. Found: C, 59.91; H, 5.96; N, 19.31. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3330, 3175, 2750—2300, 1635 (shoulder), 1615, 1580 (shoulder).

2-Hydrazino-3-methylbutyric Acid (IId)——To a solution of ethyl 2-hydrazono-3-methylbutyrate (IIId, 0.40 g) in EtOH (15 ml) and H_2O (0.5 ml) was added 2% Na–Hg (25 g) under ice-cooling and the mixture was stirred for 4 hr at room temperature and worked up in a manner similar to method a for IIa to give colorless prisms (0.08 g), mp 260° (decomp.). The mother liquor was concentrated *in vacuo* and put onto the column of Dowex 50W (30 ml (wet), H^+ type) which was washed with H_2O, followed by eluting with 5% NH_4OH. The fractions required were collected and the eluent was evaporated to dryness *in vacuo* to give colorless crystals (0.13 g), mp 245—250° (decomp.), (total yield 63%). Recrystallization from H_2O afforded an analytical sample, mp 263° (decomp.), lit.,[3d] mp 235°. *Anal.* Calcd. for $C_5H_{12}O_2N_2$: C, 45.44; H, 9.15; N, 21.20. Found: C, 45.51; H, 9.14; N, 20.81. IR ν_{max}^{Nujol} cm^{-1}: 3250, 2700—2300, 2195, 1620, 1580, 1545, 1530, 1500.

Ethyl 2-Hydrazono-3-phenylpropionate (IIIa)——To a solution of ethyl 2-diazo-3-phenylpropionate[9] (0.76 g, 3.72 mmol) in EtOH (50 ml) was added $NaBH_4$ (1.40 g, 37.2 mmol) at −30°. The mixture was stirred for 3.5 hr at room temperature and taken up in ether (100 ml), which was successively washed with H_2O, 5% AcOH, satd. NaCl, satd. $NaHCO_3$ and satd. NaCl and then dried over Na_2SO_4. Filtration and evaporation gave an oil, which was chromatographed on silica gel (30 g, eluent: C_6H_6 4–AcOEt 1) to give colorless crystals (0.43 g, 56%), mp 44—46°. *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.67; H, 6.95; N, 13.33. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3365, 3320, 3240, 3200, 3160, 1685, 1650, 1600, 1565. NMR ($CDCl_3$) τ: 8.66 (3H, t, 7 Hz), 6.12 (2H, s), 5.68 (2H, q, 7 Hz), 3.85 (2H, s), 2.70 (5H, s). Mass Spectrum *m/e*: 206 (M^+), 160, 133, 117 (base).

Ethyl 2-Hydrazono-3-methylbutyrate (IIId)——To a solution of ethyl 2-diazo-3-methylbutyrate[9] (1.87 g, 12 mmol) in EtOH (50 ml) was added $NaBH_4$ (2.28 g, 60 mmol) at −20° and the mixture was stirred for 5 hr at room temperature. Working-up of the reaction mixture in a similar manner described above for IIIa gave a residue which was purified on column chromatography (silica gel, 100 g, eluent: C_6H_6 2–AcOEt 1) to give IIId as colorless crystals (0.28 g, 15%), mp 89—91°. *Anal.* Calcd. for $C_7H_{14}O_2N_2$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.10; H, 8.74; N, 17.46. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3285, 3200, 1690, 1620, 1580. NMR ($CDCl_3$) τ: 8.75 (6H, d, 7 Hz), 8.69 (3H, t, 7 Hz), 6.98 (1H, m), 5.70 (2H, q, 7 Hz) 3.75 (2H, s).

13) All the melting points were uncorrected. Infrared (IR) spectra were taken with Hitachi 215 spectrophotometer, Nuclear magnetic resonance (NMR) spectra were recorded at 60 Mc on JEOL-NMR spectrometer, Model JNM-MH-60II (Abbreviation; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). Mass spectra were taken with Hitachi Mass spectrometer, Model RMS-4. Molecular weight measurement was carried out with Hitachi-Perkin Elmer 115.

Ethyl 2-Oxo-3-phenylpropionate (IVa)——A solution of ethyl 2-hydrazono-3-phenylpropionate (IIIa, 0.80 g) in EtOH (15 ml) and 1N HCl (10 ml) was kept standing for 1.5 hr at room temperature. The reaction mixture was taken up in AcOEt and washed with H_2O, satd. $NaHCO_3$ and H_2O, and then dried over Na_2SO_4. After filtration the filtrate was evaporated to dryness *in vacuo* to leave an oil (0.70 g, 94%). IR $\nu_{max}^{liq.}$ cm^{-1}: 1725, 1620, 1600, 1585, 1500. NMR ($CDCl_3$) τ: 8.70 (3H, t, 7 Hz), 6.38 (2H, s), 5.69 (2H, q, 7 Hz), 2.81 (5H, s). Semicarbazone; colorless prisms, mp 166—167°, lit.,[11] mp 167°. *Anal.* Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.58; H, 6.05; N, 16.57. IR ν_{max}^{Nujol} cm^{-1}: 3470, 3350, 3190, 3140, 3040, 1705, 1690, 1605, 1590, 1575. NMR (d_6-DMSO) τ: 8.75 (3H, t, 7 Hz), 5.76 (2H, s), 5.57 (2H, q, 7 Hz), 3.15 (2H, s), 2.50 (5H, s), −0.59 (1H, s).

Ethyl 2-(1,2-Diacetylhydrazino)-3-phenylpropionate (Va)——Ethyl 2-hydrazono-3-phenylpropionate (IIIa, 2.06 g) and PtO_2 (200 mg) in AcOEt (30 ml) and Ac_2O (3 ml) was hydrogenated at atmospheric pressure of hydrogen. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give a colorless oil, which was dissolved in ether (50 ml), seeded and stored in a refrigerator to give colorless pillars (1.20 g), mp 95—97°. Concentration and cooling of the mother liquor yielded an additional 0.28 g of the product, mp 95—97° (total yield 45%). Recrystallization from EtOH–isopropyl ether–ether afforded colorless pillars, mp 96—97°. *Anal.* Calcd. for $C_{15}H_{20}O_4N_2$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.25; H, 6.80; N, 9.38. IR ν_{max}^{Nujol} cm^{-1}: 3250, 3220, 1725, 1708, 1640, 1600, 1528, 1500. NMR ($CDCl_3$) τ: 8.94 (3H, t, 7 Hz), 7.97 (3H, s), 7.95(3H, s) 6.92 (2H, d, 7 Hz), 5.96 (2H, q, 7 Hz), 4.55 (1H, t, 7 Hz), 2.72 (5H, s), 1.45 (1H, s).

Butyl 2-Butylazo-2-methyl-3-phenylpropionate (VIa)——To a solution of butyl 2-diazo-3-phenylpropionate[9] (1.16 g, 5 mmol) in THF (20 ml) was added at −78°, a solution of 10% (w/v) C_4H_9Li in hexane (6.4 ml, 10 mmol) during a period of 10 minutes. After stirring for 10 min at −78° CH_3I (1.42 g, 10 mmol) in THF (10 ml) was added to the mixture and the whole was stirred for 3 hr at −78° and for additional 18 hr at room temperature. The reddish yellow reaction mixture was concentrated *in vacuo* and taken up in AcOEt, which was washed with H_2O, dried and evaporated to dryness to give a pale brown oil. The oil was purified on preparative thin-layer chromatography (TLC) (silica gel, eluent: C_6H_6) to afford VIa as a slightly yellow oil (0.79 g, 52%). *Anal.* Calcd. for $C_{18}H_{28}O_2N_2$: C, 71.01; H, 9.27; N, 9.20. Found: C, 70.96; H, 9.39; N, 9.02. IR $\nu_{max}^{liq.}$ cm^{-1}: 1738. NMR ($CDCl_3$) τ: 9.30—7.90 (14H, m), 8.73 (3H, s), 6.71 (2H, s), 6.16 (2H, t, 7 Hz), 5.93 (2H, t, 7 Hz), 2.84 (5H, s). Molecular weight measurement: Calcd., 304. Found, 306. Mass Spectrum *m/e*: 304 (M^+, not observed), 220, 192, 164, 146, 91 (base).

2-(2-Butylhydrazino)-2-methyl-3-phenylpropionic Acid (VIIa)——A mixture of butyl 2-butylazo-2-methyl-3-phenylpropionate (VIa, 0.40 g) and Al–Hg (5 g) in EtOH (20 ml) and H_2O (2 drops) was stirred for 3 hr at room temperature and then filtered. The filtrate and washings were concentrated *in vacuo* and diluted with ether, washed with 1% NaOH and H_2O, dried and evaporated to dryness to give an oil.

An ethanol solution (10 ml) of the oil and 10% NaOH (3 ml) was kept standing for 18 hr, concentrated *in vacuo* and taken up in H_2O (10 ml). The aqueous solution was washed with ether and then poured onto the column of Amberlite IR-120 (15 ml (wet), H^+ form), which was thoroughly washed with H_2O and eluted with 5% NH_4OH. The ninhydrin positive eluent was evaporated to dryness *in vacuo* to give VIIa (0.14 g, 42%). Recrystallization from 50% aqueous EtOH afforded colorless prisms, mp 157—161°. *Anal.* Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.21; H, 8.47; N, 11.15. IR ν_{max}^{Nujol} cm^{-1}: 3260, 3060, 2800—2200, 1610 (shoulder), 1588, 1530, 1510.

Methyl 2-Butylhydrazono-3-phenylpropionate (VIIIa)——To a solution of methyl 2-diazo-3-phenylpropionate[9] (0.95 g, 5 mmol) in THF (20 ml) was added dropwise at −78° a solution of 10% (w/v) C_4H_9Li in hexane (6.4 ml, 10 mmol) and the whole was stirred for 20 min at −78°. After an addition of AcOH (0.60 g, 10 mmol), the reaction mixture was stirred for additional 1 hr at the same temperature and concentrated *in vacuo* to remove THF. The residue was taken up in AcOEt, which was washed with H_2O, dried and evaporated to dryness to give an oil. The oil thus obtained was purified on preparative TLC (silica gel, eluent: C_6H_6 20–AcOEt 1) to afford a slightly yellow oil (0.69 g, 56%). IR $\nu_{max}^{liq.}$ cm^{-1}: 3310, 1700, 1600, 1560, 1495. NMR ($CDCl_3$) τ: 9.40—8.20 (7H, m), 6.90—6.30 (2H, m), 6.19 (3H, s), 6.15 (2H, s), 3.93 (1H, broad s), 2.76 (5H, s). Molecular weight measurement: Calcd., 248. Found, 249. Mass Spectrum *m/e*: 248 (M^+), 189, 188, 178, 177, 145, 131, 117, 116, 103, 91 (base).

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