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Synthesis of Optically Active α-Aminomethylketones.[1] Amino Acids. XXIV.

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The preparation of an optically active α-aminomethylketone, an isostere of an α-amino acid, is described. L-2-Amino-1-(*p*-methoxyphenyl)butan-3-one ($[\alpha]_D$ +109°) was obtained from O-methyl-L-tyrosine through the reaction stages I–V.

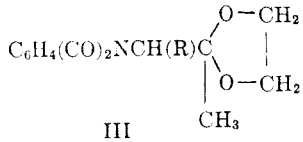
It is known that α-aminomethylketones of the formula $R{\cdot}CH(NH_2)COCH_3$, isosteres of α-amino acids,[2] show a certain biological activity.[2–4] The isostere of DL-tyrosine, 2-amino-1-(*p*-hydroxyphenyl)butan-3-one, exhibits antimitotic activity.[2]

The preparation of optically active α-aminomethylketones following previously described methods[5–10] has proved to be unsatisfactory.

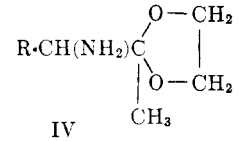
We have prepared L-2-amino-1-(*p*-methoxyphenyl)butan-3-one hydrochloride (V) derived from O-methyl-L-tyrosine through the reaction stages I–V: the diazoketone I[11] was converted to the methylketone (II) following the procedure of Wolfrom and Brown.[12] From II the cyclic ketal (III) was prepared, giving, after hydrazinolysis, the amino-ketal (IV), which in turn was converted, with ethanol-hydrochloric acid to the aminoketone hydrochloride (V), $[\alpha]_D^{20}$ +109°. Dissolution of the aminomethylketone hydrochloride (V) in diluted ammonia yielded 2,5-di-(*p*-methoxybenzyl)-3,6-dimethylpyrazine (VI).

$C_6H_4(CO)_2NCH(R)COCHN_2$ I

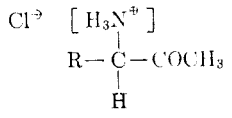
$C_6H_4(CO)_2NCH(R)COCH_3$ II



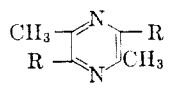
III



IV



V



VI

R = *p*-methoxybenzyl

Optical rotations of O-methyl-L-tyrosine and of its isostere are given in Table I.

TABLE I

OPTICAL ROTATIONS OF O-METHYL-L-TYROSINE AND ITS ISOSTERE

	$[\alpha]_D$ H_2O	$[\alpha]_D$ C_2H_5OH
O-Methyl-L-tyrosine hydrochloride[a]	−14.3° (*c*, 2.10)	+12.1° (*c*, 0.99)
L-2-Amino-1-(*p*-methoxyphenyl)butan-3-one hydrochloride (V)	+58° ± 2° (*c*, 1.18)	+109° ± 2° (*c*, 2.16)

[a] Behr and Clarke, *J. Am. Chem. Soc.*, **54**, 1630 (1932).

EXPERIMENTAL

All melting points are corrected; boiling points are uncorrected.

L-1-(p-Methoxyphenyl)-2-phthalimidobutan-3-one (II). A solution of L-1-diazo-4-(*p*-methoxyphenyl)-3-phthalimidobutan-2-one prepared according to Balenović, Thaller, and Filipović[11] (I, 2 g.) in chloroform (15 ml.) was treated with 47% hydriodic acid (4 ml.) at room temperature. After the vigorous reaction had subsided, the chloroform layer was washed with water, an aqueous sodium thiosulphate solution, again with water, dried (Na_2SO_4), and evaporated to dryness. The residue was treated with hot ethanol (charcoal) and, on cooling, colorless needles of L-1-(*p*-methoxyphenyl)-2-phthalimidobutan-3-one separated. Yield, 1.52 g. (82%), m.p. 89–90°. Repeated recrystallization from benzene-petroleum ether and acetone-water gave the analytical sample, m.p. 95–99°, $[\alpha]_D^{20}$ −266.3° ± 1° (*c*, 2.28 in benzene).

Anal. Calc'd for $C_{19}H_{17}NO_4$ (323.33): C, 70.57; H, 5.30. Found: C, 70.01; H, 5.47.

The *oxime* was prepared by the standard method. Repeated recrystallization from methanol-water gave the pure product with m.p. 156–157°.

Anal. Calc'd for $C_{19}H_{18}N_2O_4$ (338.35): C, 67.44; H, 5.36. Found: C, 67.54; H, 5.08.

L-1-(p-Methoxyphenyl)-2-phthalimidobutan-3-one ethylene ketal (III). A mixture of the methylketone (II) (8 g.), ethanediol (3 ml.), *p*-toluenesulphonic acid (0.3 g.), and benzene (60 ml.) was refluxed for 12 hours in a round-bottomed flask fitted with a total condensation take-off adapter. The reaction mixture was washed with an aqueous sodium bicarbonate solution, with water, and then was dried (Na_2SO_4). After the benzene was evaporated, dry ether (50 ml.) was added to the residue. Crystals of DL-1-(*p*-methoxyphenyl)-2-phthalimidobutan-3-one ethylene ketal separated and further crops were obtained by twice reducing the volume of the mother liquor. Total yield of the racemic ketal (III) was 1.3 g. (14%). The ethereal mother liquor was evaporated, and the residue was dissolved in benzene and filtered through a column of alumina (35 g.). The ben-

(1) A part of this paper was presented at the 3rd International Congress of Biochemistry, Brussels, August 1955.

(2) Erlenmeyer and Kühne, *Helv. Chim. Acta*, **32**, 370 (1949).

(3) Lehmann, Bretscher, Kühne, Sorkin, Erne, and Erlenmeyer, *Helv. Chim. Acta*, **33**, 1217 (1950).

(4) Lehmann and Bretscher, *Helv. Physiol. et Pharmacol. Acta*, **10**, 20 (1952).

(5) Levene and Steiger, *J. Biol. Chem.*, **74**, 689 (1927).

(6) Dakin and West, *J. Biol. Chem.*, **78**, 91 (1928).

(7) Dakin and West, *J. Biol. Chem.*, **78**, 745 (1928).

(8) Levene and Steiger, *J. Biol. Chem.*, **79**, 95 (1928).

(9) Gabriel and Colman, *Ber.*, **35**, 3805 (1902).

(10) Sonn, *Ber.*, **40**, 4667 (1907).

(11) Balenović, Thaller, and Filipović, *Helv. Chim. Acta*, **32**, 745 (1949).

(12) Wolfrom and Brown, *J. Am. Chem. Soc.*, **65**, 1516 (1943).

zene was evaporated, and the residual yellow, viscous oil (7.06 g., 80%) was distilled at 155–165°/0.009 mm. L-1-(*p*-Methoxyphenyl)-2-phthalimidobutan-3-one ethylene ketal is a colorless, viscous oil, showing $[\alpha]_D^{23}$ −116° ± 1° (*c*, 1.00 in benzene).

Anal. Calc'd for $C_{28}H_{21}NO_5$ (367.39): C, 68.65; H, 5.76. Found: C, 68.58; H, 5.81.

L-2-Amino-1-(p-methoxyphenyl)-butan-3-one ethylene ketal (IV). A solution of compound III (11.76 g., 0.032 mole) and hydrazine hydrate (2 g.) in ethanol (72 ml.) was refluxed for three hours on a steam-bath. To the cooled reaction mixture chloroform was added (50 ml.), and the phthalyl hydrazide was filtered off (3.7 g., 72%). The chloroform solution was washed with water, treated with charcoal, and dried (K_2CO_3). After evaporation of the solvent a thick yellow oil remained. Yield of crude L-2-amino-1-(*p*-methoxyphenyl)butan-3-one ethylene ketal, 100%, $[\alpha]_D^{22}$ −53.5° (*c*, 1.96 in chloroform). The analytical sample was prepared as a partially racemized, colorless oil, by distillation at 120°/0.03 mm., $[\alpha]_D^{25}$ −19.7° ± 1.5° (*c*, 0.71 in chloroform).

Anal. Calc'd for $C_{13}H_{19}NO_3$ (237.29): C, 65.80; H, 8.07. Found: C, 66.07; H, 8.23.

L-2-Amino-1-(p-methoxyphenyl)butan-3-one hydrochloride (V). A solution of crude L-2-amino-1-(*p*-methoxyphenyl)-butan-3-one ethylene ketal (IV, 0.65 g.) in a mixture of concentrated hydrochloric acid (4 ml.) and ethanol (2 ml.) was left at room temperature for 24 hours. Then water (6 ml.) was added to the reaction mixture, and the aqueous layer repeatedly was extracted with chloroform, treated with charcoal, and evaporated *in vacuo* to dryness. Yield of crude L-2-amino-1-(*p*-methoxyphenyl)butan-3-one hydrochloride 0.46 g. (68%), $[\alpha]_D^{20}$ +61.5° ± 1° (*c*, 1.83 in ethanol). Recrystallization from absolute ethanol-ether (with addition of a drop of concentrated hydrochloric acid), or from concentrated hydrochloric acid, yielded colorless rods of the pure compound (0.08 g., 13%), m.p. 161° (decomp.). ($[\alpha]_D$ are given in Table I.)

Anal. Calc'd for $C_{11}H_{16}ClNO_2$ (229.70): C, 57.51; H, 7.02; N, 6.10. Found: C, 57.53; H, 7.06; N, 6.20.

2,5-Di-(p-methoxybenzyl)-3,6-dimethylpyrazine. The crude L-2-amino-1-(*p*-methoxyphenyl)butan-3-one hydrochloride (V, 0.26 g.) was dissolved in aqueous ethanol (1:4, 8 ml.), and 25% aqueous ammonia (0.5 ml.) was added. After standing for 24 hours at room temperature, the crystals of 2,5-di-(*p*-methoxybenzyl)-3,6-dimethylpyrazine were filtered off (0.06 g., 30%) and recrystallized from methanol-water, m.p. 122.5–123°.

Anal. Calc'd for $C_{22}H_{24}N_2O_2$ (348.43): C, 75.83; H, 6.94. Found: C, 76.10; H, 6.92.

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