Some Derivatives of Tyrosine. Amino Acids. XXX*

V. Thaller

Chemical Institute, Faculty of Science, University of Zagreb, Strossmayerov trg 14, Zagreb

and

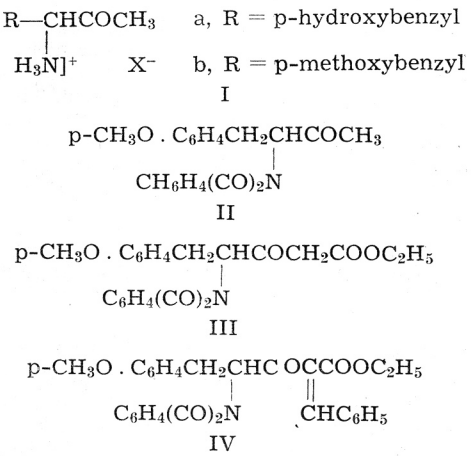
Department of Biochemistry, Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

Received November 25, 1955

A new synthesis of DL-1-(p-hydroxyphenyl)-2-aminobutan-3-one (Ia) is given. The optically active β-keto acid ester III and its racemic benzylidene derivative IV were prepared from L-tyrosine.

It has been shown that replacement of -COOH by $-COCH_3$ in α-amino acids gives compounds showing interesting biological activities[1-3]. The methyl-α-amino ketones thus obtained can be regarded as isosters of α-amino acids[1].

The preparation of the optically active methylaminoketone Ib starting from L-tyrosine was recently described by Balenović and Thaller[4]. One of the key intermediates in this synthesis, L-1-(p-methoxyphenyl)-2-phthalimidobutan-3-one (II), was hydrolyzed with hydriodic acid in glacial acetic acid with simultaneous racemisation to DL-1-(p-hydroxyphenyl)-2-aminobutan-3-one (Ia). Thus a new path for the synthesis of methyl-α-aminoketones, proceeding from N-phthaloyl-α-amino acids *via* their acid chlorides[5], diazoketones[5], and methyl ketones[4] has been found. The compound Ia was first prepared by Levene and Steiger[6] from tyrosine, using the Dakin-West reaction[7].



* Contribution No. 46 from the Chemical Institute; paper XXIX, K. Balenović, N. Bregant, T. Galijan, Z. Štefanac and V. Škarić, *J. Org. Chem.*, in press; XXVIII, K. Balenović and D. Cerar, *J. Chem. Soc.* **1955**, 1631.

The preparation of compound II by partial hydrolysis of the condensation product obtained from O-methyl-N-phthaloyl-L-tyrosinyl chloride[5] and sodium diethylmalonate according to Gabriel[8] was also attempted. As condensation product, L-1-(p-methoxyphenyl)-2-phthalimido-4-carboethoxybutan-3-one (III) was obtained. This compound was treated with hydrobromic acid in glacial acetic acid at 70°. Evolution of carbon dioxide was observed. As the reaction mixture showed no optical activity, the isolation of compound II was not attempted.

The condensation of compound III with benzaldehyde and traces of piperidine as catalyst proceeded also with racemisation. The resulting benzyldene derivative IV could not be hydrolysed and decarboxylated by heating with propionic and sulphuric acids according to Bowman's procedure[9].

EXPERIMENTAL

All melting points are corrected.

DL-1-(p-Hydroxyphenyl)-2-aminobutan-3-one hydriodide (Ia, X = I)

A solution of L-1-(p-methoxyphenyl)-2-phthalimidobutan-3-one[4] (2 g.) in glacial acetic acid (6 ml.) and hydriodic acid (sp. g. 1.7; 12 ml.) was refluxed for three hours. The phthalic acid was then filtered off (0.7 g., 67%) and the brown mother liquor evaporated under reduced pressure. The dark syrupy residue was dissolved in water, treated with charcoal and shaken several times with ether. The nearly colourless aqueous layer was then evaporated *in vacuo* under an atmosphere of nitrogen. The residue was dissolved at room temperature in ethanol (8 ml.) and absolute ether (120 ml.) added. DL-*1-(p-Hydroxyphenyl)-2-aminobutan-3-one hydriodide* separated in long colourless needles, yield 0.5 g. (26%), m. p. 197—199° (decomp.). From the mother liquor an additional crop of crystals was obtained; total yield 0.95 g. (50%).

Anal. 10.86 mg. subst.: 15.49 mg. CO_2, 4.69 mg. H_2O
$C_{10}H_{14}INO_2$ (307.14) calc'd.: C 39.12; H 4.59%
found: C 38.94; H 4.84%

DL-1-(p-Hydroxyphenyl)-2-aminobutan-3-one hydrochloride (Ia, X = Cl)

The hydriodide Ia (0.25 g.) was shaken for ten hours with a freshly prepared silver chloride suspension (obtained from 0.8 g. of silver nitrate) in 0.3% hydrochloric acid (90 ml.). After standing for 12 hours the supernatant liquid was poured off, and the precipitate washed with dilute hydrochloric acid. The combined supernatant and washings were evaporated under reduced pressure, and DL-*1-(p-hydrophenyl)-2-aminobutan-3-one hydrochloride* was obtained from the residue by recrystallization from ethanolic hydrochloric acid (5% gaseous hydrochloric acid in ethanol), as colourless needles, yield 0.11 g. (63%), m. p. 160—163° (decomp.) (Levene and Steiger[5] reported m. p. 165—166°.)

Anal. 11.63 mg. subst.: 23.49 mg. CO_2, 6.85 mg. H_2O
$C_{10}H_{14}ClNO_2$ (215.68) calc'd.: C 55.68; H 6.54%
found: C 55,12; H 6.59%

L-*1-(p-Methoxyphenyl)-2-phthalimido-4-carboethoxy-butan-3-one* (III)

A suspension of sodium diethylmalonate in benzene (80 ml.) was prepared from metallic sodium (1.38 g., 0.06 mole) and diethylmalonate (12.6 g., 0.08 mole), and a solution of O-methyl-N-phthaloyl-L-tyrosinyl chloride[7] (10 g., 0.03 mole) in benzene (50 ml.) added, with cooling and stirring. The clear reaction mixture was left at room temperature for five days, and then refluxed for one hour on a steam bath. After cooling, it was poured into a mixture of ice and 25% sulphuric acid (100 ml.). The benzene layer was washed with water, the solvent removed by evaporation, and steam distillation. The residue was extracted with benzene, the extract dried

($CaCl_2$) and the benzene evaporated. A yellow viscous oil remained (10.44 g.) which crystallized on addition of ethanol (20 ml.) into colourless needles of L-*1-(p-methoxyphenyl)-2-phthalimido-4-carboethoxybutan-3-one*, yield 7.07 g. (61.4%), m. p. 87—91°. Repeated recrystallization from ethanol yielded the pure compound, m. p. 95—96°, $[\alpha]_D^{20}$—220° ± 1° (c, 1.78 in benzene).

Anal. 11.71 mg. subst.: 28.73 mg. CO_2, 5.65 mg. H_2O
$C_{22}H_{21}NO_6$ (395.40) calc'd.: C 66.82; H 5.35%
found: C 66.95; H 5.40%

The *benzylidene derivative* IV of L-1-(p-methoxphenyl)-2-phthalimido-4-carboethoxybutan-3-one was obtained from the compound II (0.39 g.) and benzaldehyde, with piperidine as catalyst, at 0°. The crude reaction product was steam-distilled and the undistilled residue extracted with benzene, the solvent evaporated, and the residue heated in propionic acid with traces of sulphuric acid. The acids were removed, and the crude *benzylidene derivative* of L-*1-(p-methoxyphenyl)-2-phthalimido-4-carboethoxybutan-3-one* (0.22 g.) chromatographed on alumina from benzene. From the first fraction, after evaporation of the solvent, the pure compound was obtained (0.12 g.). Recrystallization from ethanol gave colourless prisms, m. p. 142—143°.

Anal. 10.61 mg. subst.: 28.01 mg. CO_2, 5.00 mg. H_2O
$C_{29}H_{26}NO_6$ (483.50) calc'd.: C 72.04; H 5.21%
found: C 72.04; H 5.27%

Acknowledgment. The author thanks Professor K. Balenović for his interest in this work, and Dr. L. Filipović for the microanalyses.

REFERENCES

1. H. Erlenmeyer and H. Kühne, *Helv. Chim. Acta* **32** (1949) 370.
2. F. E. Lehmann, A. Bretscher, H. Kühne, E. Sorkin, M. Erne and H. Erlenmeyer, *Helv. Chim. Acta* **33** (1950) 1217.
3. F. E. Lehmann and A. Bretscher, *Helv. Physiol. et Pharmakol. Acta* **10** (1952) 20.
4. K. Balenović and V. Thaller, *J. Org. Chem.* (in press).
5. K. Balenović, V. Thaller and L. Filipović, *Helv. Chim Acta* **32** (1949) 745.
6. P. A. Levene and R. E. Steiger, *J. Biol. Chem.* **79** (1928) 95.
7. H. D. Dakin and R. West, *J. Biol. Chem* **78** (1928) 91; **78** (1928) 745.
8. S. Gabriel and J. Colman, *Ber.* **35** (1902) 3805.
9. R. E. Bowman, *J. Chem. Soc.* **1950**, 322.

IZVOD

O nekim derivatima tirozina. Aminokiseline XXX

V. Thaller

Opisuje se nova sinteza DL-1-(p-oksifenil)-2-aminobutan-2-ona (Ia). Iz L-tirozina priređen je optički aktivni β-keto derivat L-1-(p-metoksifenil)-2-ftalimido-4-karboetoksibutan-3-on (III) kao i racemički benzilidenski derivat IV spoja III.

KEMIJSKI INSTITUT
PRIRODOSLOVNO-MATEMATIČKOG FAKULTETA
ZAGREB
I
INSTITUT »RUĐER BOŠKOVIĆ«
BIOKEMIJSKI ODJEL
ZAGREB

Primljeno 25. novembra 1955.