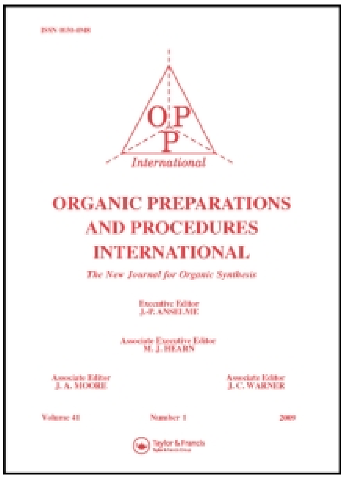

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R,S-4-(4'-METHOXYBENZYLIDENEAMINO) PHENYLALANINE AND R,S-4-(2'-METHYL-4'-NITROPHENYLAZO) PHENYLALANINE

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OPPI BRIEFS

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R,S-4-(4'-METHOXYBENZYLIDENEAMINO)PHENYLALANINE AND R,S-4-(2'-METHYL-4'-NITROPHENYLAZO)PHENYLALANINE

Submitted by (5/12/75)

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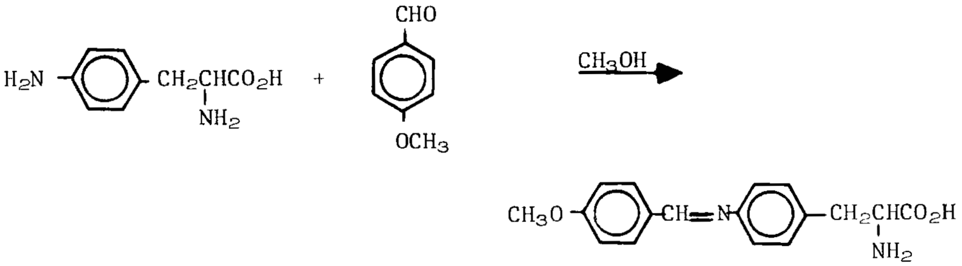
p-Imino and p-azo derivatives of phenylalanine are unusual compounds. Apparently, the only reported example of this type of compound is S-p-(phenylazo)phenylalanine.[1] The preparation of two new examples of this class of compounds is described.



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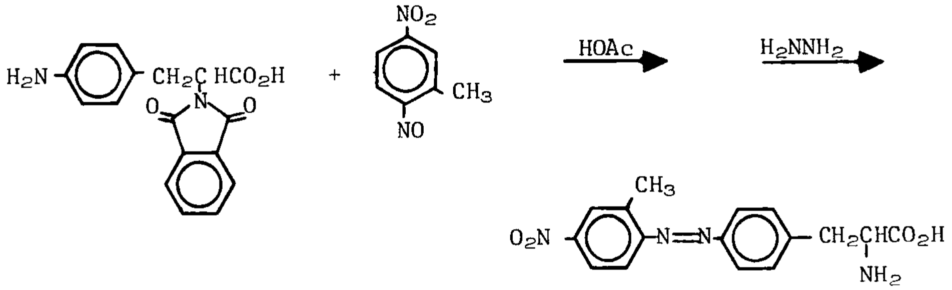

II

EXPERIMENTAL[2]

R,S-4-Aminophenylalanine. - R,S-4-Nitrophenylalanine[3] was catalytically hydrogenated according to a published procedure.[4] The product was obtained in 84% yield; mp. 260°, lit.[4] mp. 264° (dec.). The overall yield of R.S-4-aminophenylalanine from 4-nitrobenzyl chloride was 43%.

R,S-4-(4'-Methoxybenzylineamino)phenylalanine(I).- R,S-4-Aminophenylalanine, 0.7 g (3.97 mmole), and 1 ml (1.12 g, 8.23 mmole) of *p*-anisaldehyde were mixed in 50 ml of CH_3OH. The resultant suspension was stirred at ambient temperature in a flask which was protected with a Drierite-filled drying tube. The solid dissolved and then a colorless solid precipitated. After two hours, the precipitate was collected by filtration, washed with hot water, CH_3OH, and finally ether. The white crystals weighed 1.0 g (84%); mp. 208-209° (dec.); ir (Nujol) 1635 (-C=N-).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.38.
Found: C, 68.29; H, 6.24; N, 9.40.

R,S-4-Nitro-N-phthaloylphenylalanine. - R,S-4-Nitrophenylalanine[3] was treated with phthalic anhydride and pyridine following the published procedure.[5] The product was obtained in 88% yield; mp. 180-183°, lit.[5] mp. 180-181°.

R,S-4-Amino-N-phthaloylphenylalanine. - R,S-4-Nitro-N-phthaloylphenylalanine, 2.6 g (7.64 mmole), was dissolved in 200 ml of ethanol and 0.37 g of 5% Pd-C was added. The mixture was shaken at 50 psi of H_2 for 3 hrs. at room temperature. The catalyst was removed by filtration through a layer of Celite and the solvent was distilled under reduced pressure. The residue was recrystallized from aqueous ethanol to afford 0.8 g of white crystals (34%), mp. 185.5-187.5°; tlc R_f 0.14 (60 ml of $CHCl_3$, 40 ml of C_6H_6, and 10 drops of HOAc); ir (Nujol) 3540-3430 (NH_2), 1780, 1725 (imide and carboxyl C=O), 1622 (NH_2); nmr (DMSO-d_6 + D_2O) 3.25 (d, 2, CH_2) 4.9 (q, 1, CH), 6.78-7.23 and 7.80 (q, 4 and s, 4, aromatic H).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.02.
Found: C, 65.97; H, 4.65; N, 8.91.

R,S-4-(2'-Methyl-4'-nitrophenylazo)-N-phthaloylphenylalanine. - R,S-4-Amino-N-phthaloylphenylalanine, 3.10 g (10.0 mmole), was mixed with 100 ml of abs. ethanol and 100 ml of glacial HOAc and 1.66 g (10.0 mmole) of 5-nitro-2-nitrosotoluene (Eastman Organic Chemicals) was then added. The reaction mixture (a suspension) was stirred for 21 hrs. at room temperature after which time most of the insoluble material dissolved. The filtrate was concentrated by distillation under reduced pressure to yield a rust-colored solid residue (weight, 7.3 g). This was extracted with about 150 ml of boiling benzene and the resultant mixture was filtered. The filtrate was stored for about 20 hrs. at room temperature. A crystalline red solid precipitated during this period and was collected and dried to give 1.33 g, mp. 192.5-195.0°; tlc (60 ml of $CHCl_3$, 40 ml of C_6H_6, and 10 drops of HOAc) $R_f \sim 0.4$, one rust-colored zone; ir (Nujol) 1780, 1725 (C=O), 1600 (N=N), 1520, 1340 (NO_2); nmr (d_6-DMSO) 2.7 (s, 3H), 3.65 (m, 2H), 5.3 (m, 1H), 7.4 (s, 2H, benzene solvate), and 7.5-8.4 (m, 11-12H).

Anal. Calcd. for $(C_{24}H_{18}N_4O_6)_3 \cdot C_6H_6$: C 64.46, H 4.16, N 11.56
Found: C 64.56, H 4.24, N 11.66

Another crop of crystals was obtained by dilution of the benzene filtrate with petroleum ether (bp. 30-60°), weight 1.03 g, mp. 183.5-188.5°. This material behaved identically to the first crop in a thin layer chromatogram. The total yield of product (two fractions) was 51%. A mixture of the two crops of product was used in the preparation of II (see below).

R,S-4-(2'-Methyl-4'-nitrophenylazo)phenylalanine (II). - R,S-4-(2'-Methyl-4'-nitrophenylazo)phthaloylphenylalanine, 2.27 g (5.0 mmole), 500 ml of abs. ethanol, and 1.70 ml (1.75 g, 35.0 mmole) of 85% hydrazine hydrate was stirred at room temperature. The original red solution became turbid after 3.5 hrs. and a precipitate separated after 5.0 hrs. The mixture was filtered after 5.5 hrs. and 0.41 g of a dark red solid was collected. The filtrate was stored for 2.5 days, during which time a second crop of solid which weighed 0.41 g separated. These two dark red fractions were recrystallized from glacial HOAc to afford a by-product which decomposed at 216.5°. The ir spectrum included an unionized carboxyl carbonyl band at 1700. This by-product probably formed by partial opening of the phthaloyl ring.

The filtrate from the second fraction was distilled under reduced pressure. The crystalline red residue weighed 3.3 g. It was recrystallized from boiling HOAc. After storage for several days at room temperature, 0.54 g of red crystals of II were collected, mp. 212° (dec.); tlc (60 ml of $CHCl_3$, 40 ml of benzene, and 10 drops of HOAc) R_f 0.01, one red zone; ir (Nujol) 2200-2800 (amino acid) 1585-1645 (amino acid C=O and N=N), 1510 and 1335 (NO_2).

Anal. Calcd. for $C_{16}H_{16}N_4O_4$(II): C, 58.53; H, 4.91; N, 17.06
Found: C, 58.68; H, 4.10; N, 17.09

A second crop of crystals, 0.43 g, was obtained when the HOAc filtrate from the first crop was diluted with water, mp. 202.5-206.0° (dec.); tlc identical with that of the first crop; ir (Nujol) identical with that above. Total yield of product II (two fractions) was 59%.

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2. Thin layer chromatograms (tlc) were performed on microscope slides (75 x 25 mm) which were coated with a 0.01-inch layer of silica gel (J. T. Baker, 7GF). The coated slides were activated at 110° for 1 hr. Capillary pipettes were used for applying 0.5-1.0 µl of a 1% solution to the plates. The zones were detected as yellow

areas on a purple background after spraying with a 0.5% aqueous $KMnO_4$ solution, sometimes followed with heating. Amino acid-containing zones were detected as colored spots on a white background after spraying with ninhydrin reagent (0.8 g of ninhydrin, 5 ml of collidine, 95 ml of n-BuOH). Sometimes iodine vapor was used to render the zones visible. Cited R_f values are approximate. Melting points were determined in a capillary suspended in a stirred oil bath and are corrected. Infrared spectra were obtained with a Perkin-Elmer Infracord Model 137, Perkin-Elmer Spectrophotometer Model 521, or Beckman Accu-Lab 3. Band positions are reported in cm^{-1}. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60A spectrometer. Tetramethylsilane was used as an internal standard. Resonances are reported as ppm on the δ scale. Elemental analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, West Germany, or by Bristol Laboratories, Syracuse, New York.

3. Prepared in 65% yield (mp. 222°) using the procedure of J. H. Burckhalter and V. C. Stephens, J. Am. Chem. Soc., 73, 56 (1951).
4. P. Block, Jr., J. Org. Chem., 21, 1237 (1956).
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