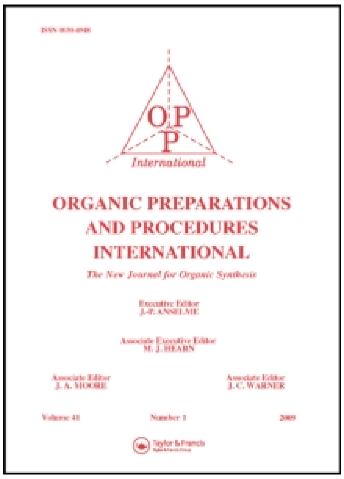

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γ-ARYL-γ-AMINO ACIDS

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γ-ARYL-γ-AMINO ACIDS

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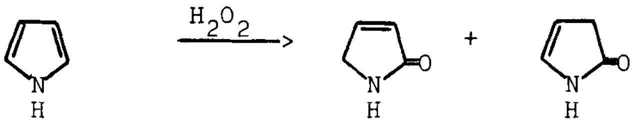
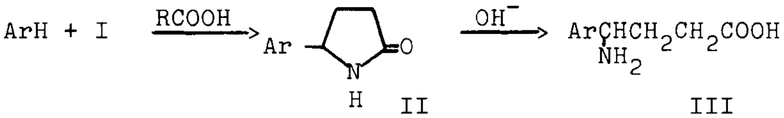
The oxidation of a dilute aqueous solution of pyrrole with hydrogen peroxide gave a 30% yield of a liquid mixture of 3- and 4-pyrrolin-2-ones (Ia and Ib).



Ia Ib

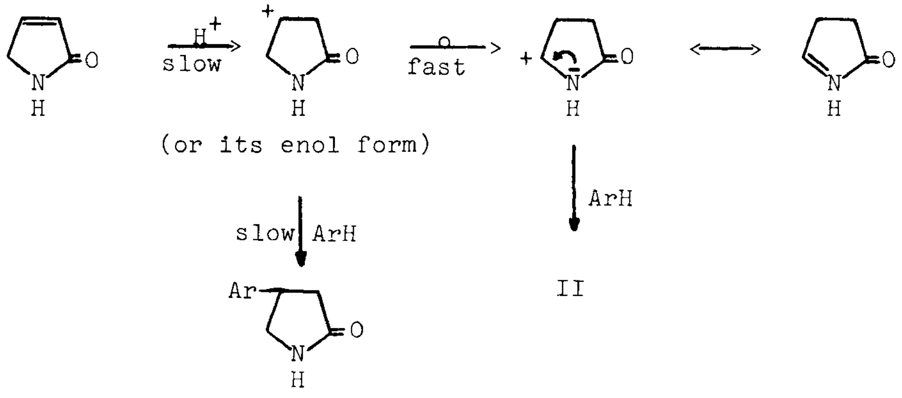
In saturated liquid aliphatic acids this mixture reacted readily with strongly nucleophilic aromatic or heteroaromatic compounds, such as phenol, dimethylaniline, furan and indole, to give 5-aryl-2-pyrrolidinones (II) in good yields.



II III

These saturated lactams were cleaved with mineral bases to the corresponding γ-aryl-γ-aminobutanoic acids (III)(DL).

It is reasonable to assume that, after protonation of Ia at O or 3-position, a hydride transfer takes place to give a carbonium ion at the 5-position as shown below. This would explain the formation of 5-aryl-2-pyrrolidinones as the major products of the reaction.



Experimental

Separation and purification of all compounds were accomplished or monitored by thin layer chromatography; spots were developed by drying the plate, treating for 1 min. with gaseous chlorine and spraying after 30 min. with iodine-potassium iodide starch solution (Rydon's reagent[1]). Melting points were determined by the open capillary method and are uncorrected. Infrared spectra were determined as KBr disks on a Perkin-Elmer Model 137 Infracord spectrophotometer. Ultraviolet spectra (95% ethanol as solvent) were obtained with an Unicam SP 500 spectrophotometer. Proton nmr spectra were recorded with a Varian HA-60 spectrometer; chemical shifts are reported in ppm (δ) from TMS as internal standard.

Oxidation of Pyrrole. Formation of 1a and 1b. A solution of 10 g (0.15 mole) of pyrrole and 14.5 g (13 ml, 0.15 mole) of 36% hydrogen peroxide in 900 ml. of water was gently refluxed for 4 hr. in the presence of 3 g of barium carbonate (to neutralize acidic by-products). The excess hydrogen peroxide was destroyed by the slow addition of small amounts of finely ground lead dioxide to the hot reaction mixture. The filtered aqueous solution was concentrated by distillation under reduced pressure (the temperature should be kept under 50°), and the viscous residue was treated with dioxane, filtered and concentrated again to a viscous, red oil, which was distilled at 100-130° (air bath) (0.5 mm), yielding a light yellow, liquid mixture of isomers (I) (3.7 g, 30%) (67% based on reacted pyrrole). Further data on I have been reported elsewhere.[2]

5-(*o*-Hydroxyphenyl)-2-pyrrolidinone (IIa). A solution of I (1 g, 12 mmole) and phenol (3.38 g, 36 mmole) in 20 ml. of acetic acid was refluxed under a nitrogen atmosphere for 3 hr. Excess acid was removed by distillation under reduced pressure and the residue was chromatographed on 50 g of SiO_2 (Merck, 0.05-0.2 mm), eluting with $CHCl_3$ to eliminate unreacted phenol, and then with ethyl acetate. From the eluate, IIa (1.23 g, 58%) was obtained and crystallized from water as white needles, mp 202°; ir: broad band at 3150 cm^{-1} (OH and NH), 1670 cm^{-1} (CO); nmr: (DMSO-d6) δ 1.5-2.5 (m, 4H) (CH_2CH_2), 4.9 (t, 1H) ($C\underline{H}N$), 6.7-7.3 (m, 4H) (aromatic protons), 7.9 (s, 1H) (NH), 8.8 (s, 1H) (OH).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.52; H, 6.34; N, 8.07.

Oxidative degradation of IIa with alkaline potassium permanganate according to the procedure used for 5-(2-pyrrolyl)-2-pyrrolidinone[3] afforded salicylic acid as the major product (undepressed mp with an authentic sample).

4-Amino-4-(o-hydroxyphenyl)-butanoic acid (IIIa). A solution of 0.4 g (2.26 mmole) of IIa in 2N sodium hydroxide (20 ml., 40 mmole) was refluxed for 4-5 hr., i.e., until the spot due to IIa disappeared (tlc). The cold reaction mixture was neutralized with 2N hydrochloric acid and diluted with water (30 ml). The product was chromatographed on 50 g of Amberlite IR 120 H and was eluted with 3N ammonium hydroxide. Concentration of the eluate and crystallization of the residue from a little water gave 0.36 g (70%) of IIIa, in dihydric form, mp 195-196°. The ir spectrum pattern was characteristic for an aminoacid; nmr: (D_2O) δ 2.0-2.5 (m, 4H) (CH_2CH_2), 3.9 (5, 1H) (C<u>H</u>N), 6.8-7.5 (m, 4H) (aromatic protons).

Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41. Found: C, 51.86; H, 7.39.

5-(p-Dimethylaminophenyl)-2-pyrrolidinone (IIb). A solution of I (1 g, 12 mmole) and dimethylaniline (1.95 g, 16 mmole) in acetic acid (15 ml.) was refluxed for 3 hr. Acetic acid and unreacted dimethylaniline were removed by distillation under reduced pressure and the residue was suspended in cold 50% ethanol (6 ml), filtered and washed with ether. Sublimation at 125° (0.5 mm) afforded pure IIb as light, white needles (2.04 g, 83%), mp 157-158°; ir: 3290 cm^{-1} (NH), 1700 cm^{-1} (CO); nmr: ($CDCl_3 + D_2O$) δ 1.8-2.5 (m, 4H) (CH_2CH_2) 2.9 (s, 6H) (CH_3NCH_3), 4.6 (t, 1H) (C<u>H</u>N), 6.5-7.3 (m, 4H) (aromatic protons). The pattern of the multiplet due to the aromatic protons was characteristic for para-disubstituted benzenes, showing two perturbed doublets; the multiplicity and the relative intensity of the lines were identical with those of p-bromophenetole.[4]

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 17.71. Found: C, 70.52; H, 8.05; N, 17.55.

4-Amino-4-(p-dimethylaminophenyl)-butanoic acid (IIIb). A suspension of IIb (0.3 g, 1.5 mmole) in 2 N sodium hydroxide (20 ml., 40 mmole) was refluxed for 2 hr. The solution was neutralized with 2N hydrochloric acid, and chromatographed on 50 g of Amberlite IR 120 H. The column was washed with water and the aminoacid eluted with 3N ammonium hydroxide. Ammonia and water were removed from the eluate under reduced pressure and the residue was washed with ethanol; IIIb (monohydrate) was obtained as a white solid (0.270 g, 74%), mp 163-164° (dec), very soluble in water; the ir spectrum pattern was characteristic for an aminoacid.

Anal. Calcd. for $C_{12}H_{20}N_2O_3$: C, 59.84; H, 8.39; N, 11.66. Found: C, 59.47; H, 8.20; N, 11.40.

5-(2-Furyl)-2-pyrrolidinone (IIc). A solution of I (1 g, 12 mmole) and furan (4.4 ml., 60 mmole) in a 1:1 mixture of formic and acetic acids (20 ml.) was refluxed under nitrogen atmosphere for 3 hr. The excess of furan and of the organic acids was removed at reduced pressure. The residue was treated with ethyl acetate (30 ml.), filtered and the filtrate evaporated to a white residue. Sublimation at 100° (0.5 mm), gave IIc as white prisms (1.56 g, 86%), mp 82°; uv: λ_{max} 215 mμ (ε 21,700); ir: 3180 cm^{-1} (NH), 1690 cm^{-1} (CO); nmr: ($CDCl_3$) δ 2.2-2.6 (m, 4H) (CH_2CH_2), 4.8 (t, 1H) (C<u>H</u>N), 6.25 (m, 2H) and 7.35 (q, 1H) (furanic protons).

<u>Anal</u>. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27.
Found: C, 63.65; H, 6.07; N, 9.27.

<u>4-Amino-4-(2-furyl)-butanoic acid (IIIc)</u>. A solution of IIc (0.5 g, 3.3 mmole) in 2N sodium hydroxide (20 ml, 40 mmole) was refluxed for 10 min. under nitrogen atmosphere, neutralized with 2N hydrochloric acid and chromatographed on Amberlite IR 120 H (50 g). The column was washed with water and the aminoacid eluted with 3 N ammonium hydroxide. Ammonia and water were removed from the eluate under reduced pressure, giving IIIc (0.5 g, 95%) as white solid, mp 160°, very soluble in water.

The ir spectrum pattern was characteristic for an aminoacid; nmr: (DMSO-d6) δ 1.7-2.2 (m, 4H) (CH_2CH_2); 4.0 (broad, 1H) ($CH\overset{+}{N}H_3$); 6.1-6.4 (m, 2H) and 7.5 (q, 1H) (furanic protons).

<u>Anal</u>. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28.
Found: C, 56.62; H, 6.67; N, 8.07.

<u>5-(3-Indolyl)-2-pyrrolidinone (IId)</u>. A solution of I (1 g, 12 mmole) and indole (1.4 g, 12 mmole) in acetic acid (5 ml.) was refluxed for 1 hr. under a nitrogen atmosphere. Excess acetic acid was removed at reduced pressure and the

residue treated with 9:1 water-ethanol (10 ml.), filtered and washed with a little cold 50% ethanol, giving IId (2 g, 83%) as white solid, mp 176-177° (from ethanol), lit.[5]: mp 176-177°; uv: λ_{max} 220 mμ (ε 35,500), 280 (6,100), 287 (5,000) (sh); ir: 3215 cm^{-1} (broad, NH groups), 1685 (CO); nmr: (DMSO-d6) δ 2.0-2.7 (m, 4H) (CH_2CH_2), 5.05 (t, 1H) (Ind C$\underline{H}$N), 7.0-7.7 (m, 5H) (indolic protons); addition of D_2O caused the major peak at δ 7.2, due to the indolic proton in the 2-position, to appear as singlet (decoupled from indolic NH).

This material was shown to be identical (ir and mixture melting point) with the product obtained according to the method of Masmaev and Rodina.[5]

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 71.87; H, 5.97; N, 13.93.

4-Amino-4-(3-indolyl)-butanoic acid (IIId). Various attempts to hydrolyze IId, both in alkaline and acidic medium under a nitrogen atmosphere, failed.

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