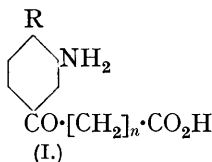


253. The ω -3-Amino-4-methoxy- and -ethoxy-benzoyl Derivatives of Propionic, Butyric, and Valeric Acid.

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STEREOCHEMICAL considerations (Plant, J., 1933, 1586) indicate that δ -*m*-aminobenzoyl-valeric acid (I; R = H; $n = 4$) might yield a compound containing a cyclic structure attached in the meta-positions by loss of water, but preliminary experiments have shown that, since the nitration of δ -benzoylvaleric acid leads to a mixture of products, the preparation of relatively large quantities of the amino-acid is difficult. Attention has therefore been given to the production of amino-acids (I; R = OMe and OEt; $n = 4$) in which the substitution process is simplified without affecting the suitability of the substances for the purposes of cyclisation. Friedel-Crafts reactions between adipic anhydride and anisole or phenetole give respectively a mixture of δ -anisoylvaleric acid with $\alpha\delta$ -dianisoylbutane, and the analogous *phenetoyl* compounds. The formation of these derivatives is further evidence of the polymeric character of adipic anhydride (Hill, *J. Amer. Chem. Soc.*, 1930, **52**, 4110). Nitration of δ -anisoyl- and δ -phenetoyl-valeric acid proceeded smoothly, and the *nitro-acids*, the constitutions of which were established by oxidation to 3-nitro-4-methoxy- and 3-nitro-4-ethoxy-benzoic acid respectively, readily gave the *amino-acids* (I; R = OMe and OEt; $n = 4$) on reduction.



The replacement of the amino-group in these acids by other radicals such as OH, CO₂H, NH·CH₂·CO₂H, and O·CH₂·CO₂H would lead to substances which might undergo cyclisation through the meta-positions, and in certain cases derivatives simpler than those of valeric acid could be employed. β -Anisoyl- and β -phenetoyl-propionic acids have therefore been similarly converted into the *amino-acids* (I; R = OMe and OEt; $n = 2$), and γ -anisoyl- and γ -phenetoyl-butyric acids into the *amino-acids* (I; R = OMe and OEt; $n = 3$), but attempts to effect simple cyclisation in the valeric acid derivatives have been unsuccessful, and efforts to convert the various amino-acids into other substances along the lines mentioned have indicated their general unsuitability for the object in view. The recent preparation by Ziegler and Lüttringhaus (*Annalen*, 1934, **511**, 1) and Spanagel and Carothers (*J. Amer. Chem. Soc.*, 1935, **57**, 935) of several compounds containing a ring system in the meta-positions illustrates the theoretical deductions referred to, and makes a continuation of the present experiments unnecessary.

EXPERIMENTAL.

δ -Anisoylvaleric Acid and $\alpha\delta$ -Dianisoylbutane.—Crude adipic anhydride, prepared by refluxing the acid with an excess of acetic anhydride for 6 hours and removing the volatile material under reduced pressure at 100° (compare Hill, *loc. cit.*), proved to be entirely satisfactory for the following experiments. A mixture of the anhydride (40 g.), anisole (60 c.c.), and carbon disulphide (100 c.c.) was treated gradually with aluminium chloride (60 g.) and then refluxed for 3 hours. The solvent was allowed to evaporate, the residue treated with ice-dilute hydrochloric acid, and excess of anisole removed in steam. When the product, which solidified on cooling, was extracted with warm aqueous sodium carbonate, $\alpha\delta$ -dianisoylbutane (compare Fuson, Kuykendall, and Wilhelm, *J. Amer. Chem. Soc.*, 1931, **53**, 4187), colourless prisms, m. p. 144°, from alcohol, remained, while acidification of the filtered solution precipitated δ -anisoylvaleric acid (*idem, ibid.*), colourless plates, m. p. 127°, from alcohol. The yields of both substances were good, but varied in different experiments. In a typical case the diketone amounted to 14 g., and the acid to 16 g.

The diketone (24 g.) was shaken with amalgamated granulated zinc (400 g.) and a little concentrated hydrochloric acid, and the mixture left over-night. After the addition of more hydrochloric acid, the whole was refluxed for 12 hours, and the product then extracted with ether. When the extract had been well washed with water, dried, and evaporated, the residue gave $\alpha\zeta$ -*di-p-anisylhexane*, colourless plates (9.5 g.), m. p. 69–71°, from alcohol, on distillation (b. p. 250–260°/23 mm.) (Found: C, 80.5; H, 8.8. C₂₀H₂₆O₂ requires C, 80.5; H, 8.7%).

When reduced similarly, δ -anisoylvaleric acid (35 g.) gave ε -*p-anisylhexoic acid* (24 g.), m. p. 47–49° (Found: C, 70.2; H, 8.1. C₁₃H₁₈O₃ requires C, 70.3; H, 8.1%), the crude product

being purified by solution in aqueous sodium carbonate, reprecipitation, and distillation (b. p. 208—210°/14 mm.).

δ-3-Amino-4-methoxybenzoylvaleric Acid.—Potassium nitrate (6.6 g.) was added gradually to a solution of *δ*-anisoylvaleric acid (15 g.) in concentrated sulphuric acid (90 c.c.) at between —5° and 0°, and the product precipitated by pouring on ice. *δ*-3-Nitro-4-methoxybenzoylvaleric acid, pale yellow plates, m. p. 107—109°, was then obtained (12.5 g.) on crystallisation from benzene (Found : C, 55.3; H, 5.2. C₁₃H₁₅O₆N requires C, 55.5; H, 5.3%). When a solution of this acid in nitric acid (*d* 1.42) was boiled for 5 minutes, oxides of nitrogen were evolved, and the product, m. p. 190°, obtained by dilution with water was shown by mixed m. p. with an authentic specimen to be 3-nitro-4-methoxybenzoic acid.

A hot solution of the nitro-acid (12.5 g.) in dilute ammonia was added in portions to a boiling solution of ferrous sulphate (90 g.) to which an excess of ammonia (*d* 0.88) had been added. The whole was boiled for 10 minutes with frequent shaking, filtered, and the filtrate concentrated on the steam-bath. *δ*-3-Amino-4-methoxybenzoylvaleric acid, brown plates, (4.6 g.), m. p. 116°, from alcohol, gradually separated as an oil which solidified on cooling (Found : C, 62.1; H, 6.7. C₁₃H₁₇O₄N requires C, 62.1; H, 6.8%). The amino-acid was readily dissolved by dilute sulphuric acid and by dilute aqueous sodium carbonate.

δ-Phenetoxyvaleric Acid Derivatives.—The following were prepared from phenetole by methods similar to those described above for the corresponding methoxy-compounds: *αδ*-diphenetoylbutane, colourless plates, m. p. 127°, from alcohol (Found : C, 74.6; H, 7.5. C₂₂H₂₆O₄ requires C, 74.6; H, 7.3%); *δ*-phenetoxyvaleric acid, colourless plates, m. p. 110°, from benzene (Found : C, 67.2; H, 7.1. C₁₄H₁₈O₄ requires C, 67.2; H, 7.2%); *αζ*-di-*p*-phenetylhexane, colourless plates, m. p. 69—70°, from alcohol (Found : C, 80.9; H, 9.2. C₂₂H₃₀O₂ requires C, 81.0; H, 9.2%); *ε*-*p*-phenetylhexoic acid, colourless plates, m. p. 57°, from petroleum (Found : C, 71.2; H, 8.4. C₁₄H₂₀O₃ requires C, 71.2; H, 8.4%); *δ*-3-nitro-4-ethoxybenzoylvaleric acid, colourless prisms, m. p. 110°, from benzene (Found : N, 4.9. C₁₄H₁₇O₆N requires N, 4.7%); *δ*-3-amino-4-ethoxybenzoylvaleric acid, pink plates, m. p. 102°, from benzene (Found : C, 63.6; H, 7.0. C₁₄H₁₉O₄N requires C, 63.4; H, 7.2%).

A solution of *δ*-3-nitro-4-ethoxybenzoylvaleric acid (2 g.) in nitric acid (20 c.c., *d* 1.42) was warmed on the steam-bath until oxides of nitrogen ceased to be evolved, and poured on ice. The solution of the precipitated solid in ammonia was extracted with ether, and 3-nitro-4-ethoxybenzoic acid, colourless plates, m. p. 198°, from alcohol, then recovered by the addition of hydrochloric acid. Its identity was established by mixed m. p. with an authentic specimen (King and Murch, J., 1925, 127, 2632).

Derivatives of β-Benzoylpropionic Acid.—*β*-3-Nitro-4-methoxybenzoylpropionic acid, obtained from *β*-anisoylpropionic acid (prepared as described by Bargellini and Giua, *Chem. Zentr.*, 1912, i, 1555), by nitration as above gave 3-nitro-4-methoxybenzoic acid (mixed m. p.) on oxidation with boiling nitric acid (*d* 1.42). It separated from alcohol in pale yellow prisms, but was difficult to obtain pure. Nevertheless, it readily gave *β*-3-amino-4-methoxybenzoylpropionic acid, colourless needles, m. p. 138°, from water, on reduction as above (Found : N, 6.3. C₁₁H₁₃O₄N requires N, 6.3%).

β-3-Nitro-4-ethoxybenzoylpropionic acid, colourless needles, m. p. 153°, from alcohol (Found : N, 5.1. C₁₂H₁₃O₆N requires N, 5.2%), and *β*-3-amino-4-ethoxybenzoylpropionic acid, colourless plates, m. p. 144—146°, from water (charcoal) (Found : C, 60.7; H, 6.5. C₁₂H₁₅O₄N requires C, 60.7; H, 6.3%), were similarly prepared from *β*-phenetoxypropionic acid (previously described by Gabriel and Colman, *Ber.*, 1899, 32, 395), and the former oxidised to 3-nitro-4-ethoxybenzoic acid (identified by mixed m. p.).

Derivatives of γ-Benzoylbutyric Acid.—The following were prepared from *γ*-anisoyl- and *γ*-phenetoxybutyric acid (Plant and Tomlinson, this vol., p. 856) by processes similar to those used for the corresponding derivatives of *β*-benzoylpropionic acid: *γ*-3-nitro-4-methoxybenzoylbutyric acid, colourless prisms, m. p. 145°, from alcohol (Found : N, 4.9. C₁₂H₁₃O₆N requires N, 5.2%), oxidised to 3-nitro-4-methoxybenzoic acid; *γ*-3-amino-4-methoxybenzoylbutyric acid, pale brown needles, m. p. 162—164°, from alcohol (Found : C, 60.8; H, 6.4. C₁₂H₁₅O₄N requires C, 60.7; H, 6.3%); *γ*-3-nitro-4-ethoxybenzoylbutyric acid, colourless plates, m. p. 127°, from benzene (Found : N, 5.1. C₁₃H₁₅O₆N requires N, 5.0%), oxidised to 3-nitro-4-ethoxybenzoic acid; *γ*-3-amino-4-ethoxybenzoylbutyric acid, almost colourless plates, m. p. 176—178°, from alcohol (Found : C, 62.1; H, 6.9. C₁₃H₁₇O₄N requires C, 62.1; H, 6.8%).

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