945. *The Conversion of Certain αα-Disubstituted* N-*Phenylglycines into 4-Oxo-1-phenyl-Δ²-pyrrolines.*

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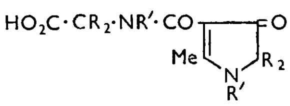
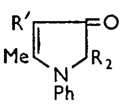
αα-Dialkyl-substituted *N*-phenylglycines (I) are converted by hot acetyl chloride into complex derivatives of type (III; R′ = Ph) which yield, on hydrolysis, basic 2-methyl-4-oxo-1-phenyl-Δ²-pyrrolines (IV; R′ = H).

Whereas *N*-phenylglycine is converted, under the conditions of the Dakin–West reaction, into *N*-phenylacetamidoacetone, the αα-disubstituted compound, α-anilino-α-methylpropionic acid (I; R = Me), is reported[1] to yield a mixture of complex products. We have examined the behaviour of several compounds of type (I; R = alkyl) towards hot acetyl chloride, which converts *N*-phenylglycine into the *N*-acetyldipeptide[2] (II). With the αα-disubstituted glycines no evidence of dipeptide formation has been obtained; the products, isolated in good yield, are believed to be 4-oxo-1-phenyl-Δ²-pyrroline derivatives of type (III; R′ = Ph). In each case investigated the product, on acid hydrolysis, gave equivalent amounts of the original amino-acid and a basic oxopyrroline (IV; R′ = H), presumably formed by decarboxylation of an intermediate β-keto-acid (IV; R′ = CO_2H).

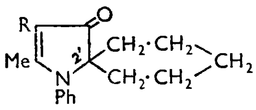
(I) $Ph{\cdot}NH{\cdot}CR_2{\cdot}CO_2H$ $Ac{\cdot}NPh{\cdot}CH_2{\cdot}CO{\cdot}NPh{\cdot}CH_2{\cdot}CO_2H$ (II)



(III)



(IV)



(V)

Thus 1-anilino*cyclo*hexanecarboxylic acid, after treatment with acetyl chloride and hydrolysis of the product, gave the spiran (V; R = H). This structure was assigned on the basis of the following observations: the compound reacts slowly with hydroxylamine in hot pyridine forming a monoxime; it contains one *C*-methyl group, readily yields a yellow monopiperonylidene derivative, and is oxidised by acid potassium permanganate to 1-acetanilido*cyclo*hexanecarboxylic acid. The analogous base derived from α-anilino-α-methylpropionic acid has been shown to be 2 : 5 : 5-trimethyl-4-oxo-1-phenyl-Δ²-pyrroline

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[1] Buchanan, Reid, Thomson, and West, *J.*, 1957, 4427.

[2] Southwick, Dimond, and Stansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 1608.

(IV; R = Me, R′ = H) by an independent synthesis. The method developed by Benary *et al.*[3] for the synthesis of 3-hydroxypyrroles was used, ethyl β-anilinocrotonate being condensed with α-bromo-α-methylpropionyl bromide and the resulting oxopyrroline ester (IV; R = Me, R′ = CO_2Et) hydrolysed to the acid which was decarboxylated smoothly at its melting point, giving the expected trimethyloxopyrroline. The ultra-violet absorption spectra of the spiran ($\lambda_{max.}$ in alcohol 316 mμ, ε 15,350) and the trimethyl-oxopyrroline ($\lambda_{max.}$ 316 mμ, ε 16,500; shoulder at 244 mμ, ε 1330) show the expected similarity to those recorded by Davoll[4] for various β-oxopyrrolines; 2 : 5-dimethyl-4-oxo-1-phenyl-Δ^2-pyrroline, for example, has absorption maxima at 246·5 (ε 2800) and 324·5 mμ (ε 16,200).

The heterocyclic nucleus of the spiran (V; R = H) has some of the properties of an activated aromatic system. Thus it is attacked rapidly in the cold by bromine in acetic acid, giving a monobromo-derivative which must have structure (V; R = Br) since it is oxidised by potassium permanganate to 1-acetanilido*cyclo*hexanecarboxylic acid. With excess of bromine, further substitution occurs. Treatment with nitrous acid yields a weakly basic, turquoise nitroso-compound which, by analogy with the bromo-derivative, is probably represented by formula (V; R = NO). The non-basic monoacetyl derivative, slowly formed from the oxopyrroline by the action of hot acetic anhydride and sodium acetate, is similarly formulated as (V; R = Ac).

Structure (III) for the products of the acetyl chloride reaction explains the observed results of hydrolysis, and such compounds could be formed by combination of two molecules of the acetylated amino-acids. It is possible that the reaction proceeds through the corresponding acid chloride since the same product (III; R = Me, R′ = Ph) was obtained from α-acetanilido-α-methylpropionic acid with acetyl chloride and with phosphorus pentachloride in hot benzene.

One compound which is probably of type (III) has been previously described. Accordinto to Steiger,[5] α-methyl-α-methylaminopropionic acid is converted in low yield, by acetic anhydride in hot acetic acid, into an oxopyrroline formulated as (III; R = R′ = Me). This compound is apparently hydrolysed slowly by boiling water to the original acid. A second hydrolysis product, believed to be a tetramethyloxopyrroline, was not obtained pure.

EXPERIMENTAL

Light petroleum used had b. p. 60—80°.

*5′-Methyl-3′-oxo-1′-phenyl*cyclo*hexane*spiro*-2′-Δ^4-pyrroline* (V; R = H).—1-Anilino*cyclo*hexanecarboxylic acid [6] (6·0 g.) and acetyl chloride (30 ml.) were heated under reflux until a yellow solid separated (40—60 min.). This product was washed with a little acetyl chloride and then decomposed with hot water, giving a colourless *acid* (4·0 g.), m. p. *ca.* 214° (decomp.), which crystallised from alcohol in colourless prisms, m. p. 215° (Found, in a sample dried *in vacuo* at 100°: C, 74·0; H, 7·1; N, 5·8. $C_{30}H_{34}O_4N_2$ requires C, 74·1; H, 7·0; N, 5·8%). A suspension of the crude acid (2·0 g.) in concentrated hydrochloric acid (20 ml.) was heated on the steam-bath for 30 min., then diluted with water (40 ml.). The crystalline hydrochloride of 1-anilino*cyclo*hexanecarboxylic acid was collected and the filtrate made alkaline with 2N-aqueous sodium hydroxide, *5′-methyl-3′-oxo-1′-phenyl*cyclo*hexane*spiro*-2′-Δ^4-pyrroline* (0·93 g.), m. p. 130—131°, being precipitated. This base crystallised from light petroleum in flat needles, m. p. 131—132° (Found: C, 79·9; H, 8·1; N, 5·9. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9; N, 5·8%).

1-Anilino*cyclo*pentanecarboxylic acid [6] (1·0 g.) was similarly converted into an *acid* (0·60 g.), plates (from aqueous alcohol), m. p. 225—256° (decomp.) (Found: C, 73·5; H, 6·6; N, 6·0. $C_{28}H_{30}O_4N_2$ requires C, 73·4; H, 6·5; N, 6·1%), which was converted by hydrochloric acid into

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[3] Benary and Silbermann, *Ber.*, 1913, **46**, 1363; Benary and Konrad, *Ber.*, 1923, **56**, 44.
[4] Davoll, *J.*, 1953, 3802.
[5] Steiger, *Helv. Chim. Acta*, 1934, **17**, 555.
[6] Bain and Ritchie, *J.*, 1955, 4411.

*5'-methyl-3'-oxo-1'-phenyl*cyclo*pentane*spiro-*2'-Δ⁴-pyrroline*, irregular plates (0·21 g.), m. p. 96° (from light petroleum) (Found: C, 79·2; H, 7·4; N, 6·2. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%).

α-Anilino-α-methylpropionic acid[7] (5·0 g.) with acetyl chloride yielded an *acid* which crystallised from aqueous alcohol in almost colourless prisms (3·1 g.), m. p. 235° (decomp.) (Found: C, 70·6; H, 6·7; N, 6·9. $C_{24}H_{26}O_4N_2$ requires C, 70·9; H, 6·5; N, 6·9%). The same product was obtained by the action of hot acetyl chloride or phosphorus pentachloride in hot benzene on α-acetanilido-α-methylpropionic acid.[1] Hydrolysis with hydrochloric acid gave 2 : 5 : *5-trimethyl-4-oxo-1-phenyl-Δ²-pyrroline* (IV; R = Me, R' = H), prisms (from light petroleum), m. p. 88° (Found: C, 77·4; H, 7·5; N, 6·9. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%), $\lambda_{max.}$ 316 mμ (ε 16500), $\nu_{max.}$ (C=O) 1640 cm.⁻¹.

*Reactions of 5'-Methyl-3'-oxo-1'-phenyl*cyclo*hexane*spiro-*2'-Δ⁴-pyrroline.*—The spiran, dissolved in ice-cold dilute hydrochloric acid, gave with nitrous acid a crystalline yellow hydrochloride, converted by the action of water, or more rapidly by sodium hydroxide, into the green *nitroso-compound* which crystallised from ethyl acetate–alcohol in turquoise needles, m. p. *ca.* 210° (after decomp.) (Found: N, 10·2. $C_{16}H_{18}O_2N_2$ requires N, 10·4%).

Heated on the steam-bath for 5 hr. with hydroxylamine hydrochloride in pyridine, the spiran yielded the *oxime*, needles (from light petroleum), m. p. 116—117° (Found: N, 10·7. $C_{16}H_{20}ON_2$ requires N, 10·9%).

With boiling acetic anhydride in the presence of sodium acetate the spiran was slowy converted into a non-basic *monoacetyl derivative*, needles (from benzene–light petroleum), m. p. 194° (Found: C, 76·9; H, 7·4; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 4·9%).

The *piperonylidene derivative*, prepared in alcohol containing a trace of sodium ethoxide, formed orange-yellow plates, m. p. 202—203°, from aqueous alcohol (Found: N, 3·6. $C_{24}H_{23}O_3N$ requires N, 3·7%).

Gradual addition of bromine (0·3 g.) in acetic acid (5 ml.) to a solution of the spiran (0·48 g.) in the same solvent (10 ml.) and dilution with water gave the *monobromo-derivative* (0·40 g.), prisms (from benzene–light petroleum), m. p. 156° (Found: C, 60·5; H, 5·9; N, 4·3. $C_{16}H_{18}ONBr$ requires C, 60·0; H, 5·6; N, 4·4%). With two mols. of bromine the spiran yielded a *dibromo-derivative*, yellow needles, m. p. 141° (from benzene–light petroleum) (Found: N, 3·5; Br, 40·8. $C_{16}H_{17}ONBr_2$ requires N, 3·5; Br, 40·1%). When three mols. of bromine were used, the product was a *tribromo-derivative*, yellow plates (from light petroleum), m. p. 136—137° (Found: N, 3·0; Br, 50·2. $C_{16}H_{16}ONBr_3$ requires N, 2·9; Br, 50·2%).

1% Aqueous potassium permanganate (100 ml.) was added slowly to a stirred solution of the spiran (1·0 g.) in 2N-sulphuric acid (50 ml.), and the following morning the resinous dark precipitate was collected, dried, and triturated with cold benzene. The residue, crystallised from benzene, formed colourless needles (80 mg.), m. p. 200—201°, undepressed on admixture with *1-acetanilido*cyclo*hexanecarboxylic acid*, m. p. 200—201° (Found: N, 5·4. $C_{15}H_{19}O_3N$ requires N, 5·4%), which was prepared from the anilino-acid with acetic anhydride in pyridine. The acetanilido-acid (0·25 g.) was also obtained by a similar oxidation (in acetone) of the monobromopyrroline (1·0 g.).

Ethyl 2 : 5 : *5-Trimethyl-4-oxo-1-phenyl-Δ²-pyrroline-3-carboxylate* (IV; R = Me, R' = CO_2Et).—α-Bromo-α-methylpropionyl bromide (5·6 g.) in ether (10 ml.) was added slowly with stirring to a cooled solution of ethyl β-anilinocrotonate (5·1 g.) and dry pyridine (2·0 g.) in ether (30 ml.). The mixture was kept at room temperature for 30 min. and the ether then removed by distillation. Two days later, the pasty yellow residue was treated with water, and the resulting orange-red oil (9·7 g.) isolated with ether. To a solution of this product in ice-cold methanol (20 ml.), potassium hydroxide (4·0 g.) dissolved in methanol (10 ml.) was added during 10 min. Stirring was continued for a further 15 min. with cooling and then for 30 min. at room temperature. After filtration, to remove potassium bromide, the methanol was evaporated and the residue treated with water and extracted with ether. The product, recrystallised from benzene–light petroleum, gave *ethyl* 2 : 5 : *5-trimethyl-4-oxo-1-phenyl-Δ²-pyrroline-3-carboxylate* as colourless plates (1·2 g.), m. p. 138° (Found: C, 69·9; H, 6·8; N, 5·4; OEt, 17·1. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1; OEt, 16·5%).

2 : 5 : *5-Trimethyl-4-oxo-1-phenyl-Δ²-pyrroline-3-carboxylic Acid* (IV; R = Me, R' = CO_2H).—The foregoing ester (0·50 g.) was heated under reflux with potassium hydroxide (1·25 g.) in ethanol (12·5 ml.) and water (12·5 ml.) for 3 hr. The ethanol was removed and the oxypyrroline

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[7] Bucherer and Grolée, *Ber.*, 1906, **39**, 986.

acid (0·43 g.) precipitated with dilute hydrochloric acid. Crystallised from ethanol, it formed needles, m. p. *ca.* 220° (gas) (Found: C, 68·9; H, 6·0; N, 5·7. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%). This acid (0·30 g.), heated to its m. p. *in vacuo* (15 min.), gave in almost quantitative yield 2 : 5 : 5-trimethyl-4-oxo-1-phenyl-Δ^2-pyrroline, m. p. and mixed m. p. 88° (Found: C, 77·8; H, 7·7; N, 6·9%).

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