565. *Decarboxylative Acylations with α-Phenylglycine.*

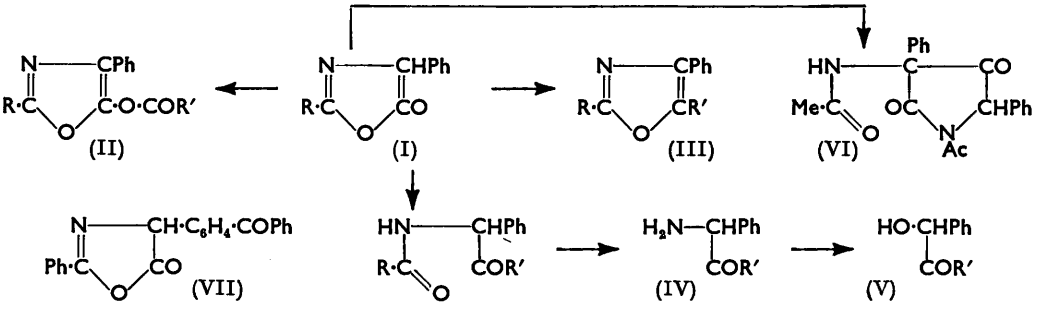
By Alexander Lawson.

5-Benzoyloxy-2 : 4-diphenyloxazole (II; R = R′ = Ph), formed as a by-product in the benzoylation of α-phenylglycine in aqueous solution, is readily formed by the action of benzoyl chloride on 2 : 4-diphenyloxazol-5-one (I; R = Ph) in pyridine. When benzoic, nicotinic, or *iso*nicotinic anhydride reacts in picoline with 2 : 4-diphenyloxazolone the main product is the corresponding oxazole (III). With *N*-acetyl-α-phenylglycine the acetamido-ketones predominate, but with nicotinic or *iso*nicotinic anhydride as acylating agent subsequent hydrolysis causes deamination and the α-hydroxybenzyl pyridyl ketones (V) are formed.

α-Phenylglycine has been used in the study of base-catalysed decarboxylative acylation by Rondestvedt, Manning, and Tabibian [1] who showed that three mols. of acetic anhydride were required for complete reaction. Searles and Cvejanovich [2] determined the rate constants for a number of pyridine-catalysed decarboxylative acylations, using among other substances *N*-acetyl- and *N*-benzoyl-α-phenylglycine with acetic anhydride. Both sets of workers described the isolation of the α-acylamino-α-phenylacetones.

King and Macmillan [3] showed that α-phenylglycine has a sufficiently active α-hydrogen atom not to need a basic catalyst for decarboxylative acetylation. They isolated α-acetamido-α-phenylacetone together with 2 : 5-dimethyl-4-phenyloxazole.

Decarboxylative acylation of amino-acids has been carried out with aromatic acid anhydrides,[4,5] and, though the reaction proceeds less readily than with a reagent such as acetic anhydride, it is possible by starting with the corresponding 2-phenyloxazolone to reduce the requirement of excess of the anhydride and to obtain products which are less readily accessible by other routes. This is the case with α-phenylglycine.



When Minovici and Thüringer [6] prepared *N*-benzoyl-α-phenylglycine they obtained also small quantities of a neutral product, m. p. 123°, $C_{22}H_{15}O_3N$ or $C_{21}H_{17}O_2N$. The substance gave what were believed to be a hydrazone and a phenylhydrazone, indicating the presence of a keto-group, and on the basis of the C_{22} formula the structure 4-*p*-benzoylphenyl-2-phenyloxazol-5-one (VII) was assigned to it. In this work small yields (4%) of the same material were obtained by the method described by Minovici *et al.* but, by action of benzoyl chloride at 0° on α-phenylglycine or on 2 : 4-diphenyloxazol-5-one in pyridine, the substance is also formed (in 80—90% yield in the latter case). Hydrolysis with 20% hydrochloric acid gives benzoic acid (two equivalents) and α-phenylglycine; with ethanolic sodium hydroxide at room temperature *N*-benzoyl-α-phenylglycine and benzoic acid are obtained. Phenylhydrazine and aniline give α-benzamido-α-*N*′-diphenylacethydrazide and α-benzamido-α-phenylacetanilide respectively. These results leave no

[1] Rondestvedt, Manning, and Tabibian, *J. Amer. Chem. Soc.*, 1950, **72**, 3183.
[2] Searles and Cvejanovich, *ibid.*, p. 3200.
[3] King and Macmillan, *ibid.*, 1955, **77**, 2814.
[4] Cleland and Niemann, *ibid.*, 1949, **71**, 841.
[5] Lawson, *J.*, 1954, 3363.
[6] Minovici and Thüringer, *Bul. Chim. Soc. România*, 1920, **2**, 13.

doubt that the substance obtained by Minovici *et al.* is 5-benzoyloxy-2 : 4-diphenyloxazole (II; R = R′ = Ph) and that it is formed by the benzoylation of the enolised oxazolone. Whilst side-chain acyl derivatives of hydroxyalkylideneoxazolones are known, such direct acylation of the enolised oxazolone carbonyl group appears to be unique. Even in the most favourable cases the action of an acyl chloride on an amino-acid in the presence of a basic catalyst results in a poor yield of the corresponding acylamino-ketone.[4] Analogous acyl derivatives of enolised thiazolones are, however, readily formed.[7]

The anomalous behaviour of 2 : 4-diphenyloxazolone can no doubt be attributed to activation of the 4-hydrogen atom by the oxazolone ring and the phenyl group. Steric effects causing inhibition of hydrolysis in this case may also be involved since the corresponding acetoxyoxazole and analogous benzoyl derivatives from *N*-acetyl-α-phenylglycine and 4-ethoxycarbonyl-2-phenyloxazol-5-one (prepared from ethyl benzamidomalonate), though possibly formed, could not be isolated.

The possibility that such 5-acyloxyoxazoles might be unstable intermediates in the decarboxylative acylation of amino-acids was not supported by the behaviour of 5-benzoyloxy-2 : 4-diphenyloxazole in hot pyridine: carbon dioxide was evolved, but no oxazole or acylamino-ketone could be isolated.

Although 2-methyl-4-phenyloxazol-5-one (I; R = Me) has not been described it is no doubt formed when *N*-acetyl-α-phenylglycine is dissolved in warm acetic anhydride, since the yellow residue obtained on evaporation reacts with aniline to give α-acetamido-α-phenylacetanilide. When this yellow residue is boiled in picoline it is converted into a colourless neutral substance, $C_{20}H_{18}O_4N_2$, m. p. 230°. This is probably 3-acetamido-1-acetyl-2 : 4-dioxo-3 : 5-diphenylpyrrolidine (VI), the analogue of 3-benzamido-1-benzoyl-2 : 4-dioxopyrrolidine (Rugheimer's compound) prepared from 2-phenyloxazolone by a similar method.[8]

When 2 : 4-diphenyloxazolone (I; R = Ph) is heated in picoline with benzoic anhydride, carbon dioxide is freely evolved and 2 : 4 : 5-triphenyloxazole (III; R = R′ = Ph) and benzoyldesylamine are isolated in about 50% and 10% yield respectively. On the other hand, *N*-acetyl-α-phenylglycine and benzoic anhydride give an oil from which benzoyldesylamine dinitrophenylhydrazone is obtained in small yield and which after hydrolytic treatment gives 2 : 4 : 5-triphenyloxazole (11% yield) and desylamine hydrochloride (IV; R′ = Ph) (33% yield). It is apparent that *N*-acetyl-α-phenylglycine readily exchanges its acyl group.

Similar results are obtained with nicotinic and *iso*nicotinic anhydride. From *N*-benzoyl-α-phenylglycine the pyridyl-substituted oxazoles (III; R = Ph, R′ = C_5H_4N) are the main products. From *N*-acetyl-α-phenylglycine, however, the initial products, which did not crystallise, gave after hydrolysis α-hydroxybenzyl pyridyl ketones (V; R = C_5H_4N) corresponding to the removal of the acetyl group from, and deamination of, the corresponding acylamino-ketones.

The difference in the behaviour of the two acylamino-acids may be attributed to the more favourable conditions for ring formation resulting from the presence of the phenyl substituent, an effect which is responsible for the difference in the stability of oxazolone rings derived from acetamido- and benzamido-acids respectively.

Experimental

5-Benzoyloxy-2 : 4-diphenyloxazole (II; R = R′ = Ph).—This substance was obtained in 4% yield by the action of benzoyl chloride on α-phenylglycine in presence of excess of sodium hydrogen carbonate as described by Minovici *et al.*[6] Alternatively *N*-benzoyl-α-phenylglycine (2 g.) was dissolved in acetic anhydride (10 ml.) on the steam-bath, the solution evaporated to dryness under reduced pressure, and again after the addition of xylene to remove the acetic anhydride, the residue of 2 : 4-diphenyloxazolone dissolved in dry pyridine (4 ml.) and cooled in ice, and benzoyl chloride (1·2 ml.) added slowly with stirring. Water and crushed ice were added and the precipitated oxazole was filtered off, and washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Recrystallisation from ethyl acetate gave

[7] Jepson, Lawson, and Lawton, *J.*, 1955, 1791.
[8] Bullerwell and Lawson, *J.*, 1952, 1350.

prisms, m. p. 128° (Minovici *et al.* gave 123°) (80—90% yield) (Found : C, 77·5; H, 4·8; N, 4·3. $C_{22}H_{15}O_3N$ requires C, 77·4; H, 4·4; N, 4·3%). The *oxazole* (1·4 g.) was boiled with 20% hydrochloric acid (30 ml.) for 2 hr. On cooling, benzoic acid (0·96 g., 1·9 equivs.) was filtered off and concentration of the filtrate, followed by neutralisation with sodium carbonate, gave α-phenylglycine (0·45 g.). Hydrolysis of the oxazole with 0·5N-ethanolic sodium hydroxide at room temperature followed by acidification gave benzoic acid and *N*-benzoyl-α-phenylglycine, separated by fractional crystallisation from aqueous ethanol. The oxazole, warmed in aqueous acetic acid with phenylhydrazine, gave benzoic acid and α-benzamido-α-*N'*-diphenylacethydrazide (also prepared directly from 2 : 4-diphenyloxazolone), m. p. 191° (needles from aqueous acetic acid). The oxazole also gave α-benzamido-α-phenylacetanilide, needles, m. p. 210° (from ethanol), when warmed with an excess of aniline.

3-*Acetamido*-1-*acetyl*-2 : 4-*dioxo*-3 : 5-*diphenylpyrrolidine*.—*N*-Acetyl-α-phenylglycine (1 g.) was dissolved in warm acetic anhydride (10 ml.) and the solution evaporated to dryness under reduced pressure, traces of acetic anhydride being removed by repeated distillation with xylene. The yellow residue of oxazolone gave, on treatment with aniline, α-*acetamido*-α-*phenylacetanilide* (from ethanol), m. p. 218° (Found : C, 71·1; H, 6·0. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0%). The oxazolone was boiled in 2-picoline (5 ml.) for 30 min. under reflux; on removal of the picoline by steam-distillation (benzaldehyde was identified in the distillate), the insoluble material was extracted with benzene which was shaken with aqueous sodium hydrogen carbonate and then with dilute hydrochloric acid. The residue left on evaporation of the benzene was crystallised from ethanol, to give 3-*acetamido*-1-*acetyl*-2 : 4-*dioxo*-3 : 5-*diphenylpyrrolidine* (20%), prisms, m. p. 230° (Found : C, 68·3; H, 5·3; N, 7·8%; *M*, 334. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1; N, 8·0%; *M*, 350). Heating this product in aqueous ethanol at pH 8 or with ethanolic 2N-hydrochloric acid caused hydrolysis to 3-*acetamido*-2 : 4-*dioxo*-3 : 5-*diphenylpyrrolidine*, m. p. 249°, plates from aqueous ethanol (Found : C, 69·8; H, 5·2; N, 8·9. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%).

2 : 4 : 5-*Triphenyloxazole*.—2 : 4-Diphenyloxazolone (2·3 g.) and benzoic anhydride (6 g.) were heated in dry 2-picoline (20 ml.) at 135—140° for 2 hr.; evolution of carbon dioxide had then ceased. The picoline was removed under reduced pressure and the residue refluxed with dry methanol and again distilled. The residue, dissolved in chloroform, was shaken with aqueous sodium hydrogen carbonate, and after evaporation under reduced pressure the residual oil was crystallised from ethanol, to give the oxazole (1·4 g.), m. p. 114°. Addition of a little water to the mother-liquor gave 0·3 g. of impure benzoyldesylamine, purified by recrystallisation (m. p. 137—139°).

Desylamine.—*N*-Acetyl-α-phenylglycine (2 g.) and benzoic anhydride (10 g.) in 2-picoline (20 ml.) were treated as above. The oil obtained on removal of the chloroform did not crystallise, but afforded *benzoyldesylamine* 2 : 4-*dinitrophenylhydrazone*, m. p. 196° (from ethanol–toluene) (Found : C, 65·7; H, 4·4. $C_{27}H_{21}O_5N_5$ requires C, 65·5; H, 4·2%). The oil, on treatment with boiling concentrated hydrochloric acid for 2 hr., partially dissolved and the insoluble portion on recrystallisation from ethanol gave 2 : 4 : 5-triphenyloxazole (0·3 g.); the acid solution was evaporated under reduced pressure and the residue, recrystallised from aqueous ethanol, consisted of desylamine hydrochloride (0·8 g.), m. p. 233° (decomp.) (Found : C, 67·5; H, 5·8. Calc. for $C_{14}H_{13}ON,HCl$: C, 67·8; H, 5·7%); the picrate had m. p. 175° (Found : C, 54·5; H, 3·7. Calc. for $C_{20}H_{16}O_8N_4$: C, 54·5; H, 3·6%).

Action of Pyridinecarboxylic Anhydrides on 2 : 4-*Diphenyloxazolone*.—2 : 4-Diphenyloxazolone (1·85 g.) was heated at 135—140° with nicotinic anhydride (6·0 g.) in 2-picoline (10 ml.) for 1 hr. The picoline was removed by steam-distillation, the solution made alkaline with sodium hydrogen carbonate, and the insoluble gum dissolved in benzene. The benzene was extracted with dilute hydrochloric acid which was in turn extracted with chloroform. The chloroform on evaporation left 2 : 4-*diphenyl*-5-3'-*pyridyloxazole hydrochloride* which crystallised from aqueous ethanol as pale yellow needles, m. p. 219° (0·9 g.) (Found : C, 68·6; H, 4·8; N, 7·9. $C_{20}H_{14}ON_2,HCl,H_2O$ requires C, 68·2; H, 4·8; N, 7·9%). The free *base* obtained by treatment with sodium hydrogen carbonate crystallised from ethanol in colourless needles, m. p. 120° (Found : C, 80·7; H, 4·7; N, 9·2. $C_{20}H_{14}ON_2$ requires C, 80·6; H, 4·7; N, 9·4%). In a similar manner *iso*nicotinic anhydride [9] and 2 : 4-diphenyloxazolone gave 2 : 4-*diphenyl*-5-4'-*pyridyloxazole hydrochloride* (34%), m. p. 222° (from aqueous ethanol) (Found : C, 68·2; H, 4·8. $C_{20}H_{14}ON_2,HCl,H_2O$ requires C, 68·2; H, 4·8%). The free *base*, needles, had m. p. 126° (from ethanol) (Found : C, 80·8; H, 4·5%).

[9] Schrecker and Maury, *J. Amer. Chem. Soc.*, 1954, **76**, 5803.

Action of Pyridinecarboxylic Anhydrides on N-*Acetyl-α-phenylglycine.*—*N*-Acetyl-α-phenylglycine (2 g.) was heated in 2-picoline (10 ml.) with nicotinic anhydride (8 g.) at 135—140° for 45 min. After removal of the picoline in steam and the nicotinic acid in aqueous sodium hydrogen carbonate, a benzene solution of the residue was extracted with dilute hydrochloric acid. The residue left after evaporation of the benzene gave 3-acetamido-1-acetyl-2 : 4-dioxo-3 : 5-diphenylpyrrolidine (above) (0·15 g.). The dilute hydrochloric acid solution was boiled for 1 hr. and made alkaline with sodium carbonate. The precipitated base was extracted with ether from which, after drying, *α-hydroxybenzyl 3-pyridyl ketone hydrochloride* (as V; R′ = C_5H_4N) was precipitated with anhydrous hydrogen chloride. Crystallisation from ethanol gave colourless needles (0·4 g.), m. p. 165° (Found : C, 62·0; H, 4·7; N, 5·3. $C_{13}H_{11}O_2N$,HCl requires C, 62·2; H, 4·8; N, 5·6%). The free *base*, liberated by sodium hydrogen carbonate, formed prisms (from ethanol), m. p. 86° (Found : C, 73·2; H, 5·1; N, 6·8. $C_{13}H_{11}O_2N$ requires C, 73·2; H, 5·2; N, 6·6%). In a similar way *iso*nicotinic anhydride gave *α-hydroxybenzyl 4-pyridyl ketone* (V; R′ = C_5H_4N) (20%), prisms (from ethanol), m. p. 147° (Found : C, 72·6; H, 5·2; N, 6·7%). The *phenylhydrazone*, yellow prisms (from ethanol), had m. p. 233° (Found : C, 75·0; H, 5·4. $C_{19}H_{17}ON_3$ requires C, 75·2; H, 5·6%).

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