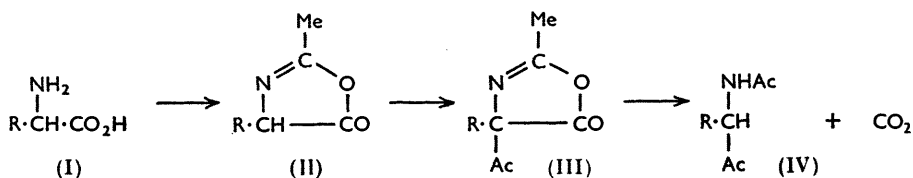


892. The Dakin-West Reaction. Part II.* Secondary Amino-acids.

By G. L. BUCHANAN, S. T. REID, R. E. S. THOMSON, and E. G. WOOD.

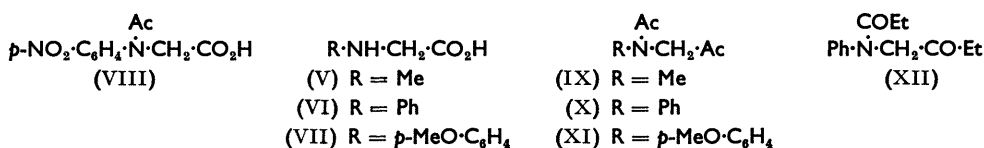
N-Phenylglycine and a number of related compounds have been converted into derivatives of anilinoacetone by boiling them with acetic anhydride. The mechanism of the reaction is discussed, and the failure of the *N*-formyl derivative to undergo the reaction reported.

It is known¹ that most primary α -amino-acids are fairly readily converted into α -acetamido-ketones by acetic anhydride and pyridine at 100° (e.g. I \rightarrow IV). The reaction is commonly held²⁻⁵ to proceed by the mechanism originally suggested by Dakin and West.⁶ Their suggestion is based on experiments with representative amino-acids, and in particular, on their claim¹ that the secondary, and the $\alpha\alpha$ -disubstituted primary α -amino-acids which



they examined, did not so react. Their mechanism accommodates all their facts and has been supported by later investigations,^{2,3,7} although it involves a final step which is not explained. The reaction has also been applied to some tertiary amino-acids,⁸ and non-amino-acids (e.g. phenylacetic¹ and *o*-chlorophenoxyacetic acid⁹) although here a different mechanism must operate.

Wiley and Borum¹⁰ have recently reported that under more drastic conditions sarcosine (V) yields the ketone (IX), and since then, other secondary amino-acids have been shown to react similarly.^{11,12} As the oxazolone mechanism is clearly inapplicable to secondary amino-acids, we have re-investigated the mechanism, basing our studies on *N*-phenylglycine (VI). This acid, or its acetyl derivative, is readily converted into the ketone (X) by boiling acetic anhydride and pyridine: the same product is obtained by the



action of acetic anhydride alone. When acetic anhydride was replaced by propionic anhydride the *N*-propionyl ethyl ketone (XII) was obtained. The presence of nuclear substituents had no obvious effect: *N*-*p*-methoxyphenylglycine (VII) and *N*-*p*-nitrophenylaceturic acid (VIII) reacted similarly, the former giving the methoxy-ketone (XI)

* The paper, *J.*, 1952, 2944, is considered to be Part I of this series.

¹ Dakin and West, *J. Biol. Chem.*, 1928, **78**, 91.

² Cleland and Niemann, *J. Amer. Chem. Soc.*, 1949, **71**, 841.

³ Attenburrow, Elliott, and Penny, *J.*, 1948, 310.

⁴ Cornforth and Elliott, *Science*, 1950, **112**, 534.

⁵ Wiley, *ibid.*, 1950, **111**, 259.

⁶ Dakin and West, *J. Biol. Chem.*, 1928, **78**, 745.

⁷ Wiley, *J. Org. Chem.*, 1947, **12**, 43.

⁸ King and McMillan, *J. Amer. Chem. Soc.*, 1951, **73**, 4451.

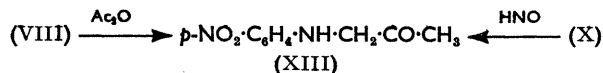
⁹ Smith, *ibid.*, 1953, **75**, 1134.

¹⁰ Wiley and Borum, *J. Amer. Chem. Soc.*, 1950, **72**, 1626.

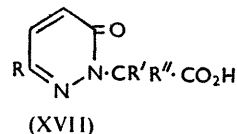
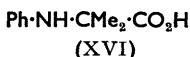
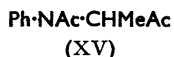
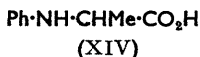
¹¹ Hinderling, Pries, and Erlenmeyer, *Helv. Chim. Acta*, 1955, **38**, 1415.

¹² D.R.P. 152,012 (*Zentr.*, 1904, **2**, 70).

and the latter, surprisingly, the deacetylated amino-ketone (XIII) whose structure was confirmed by analyses and infrared spectra, and by its identity with the product of nitration of *N*-phenylacetamidoacetone (X).

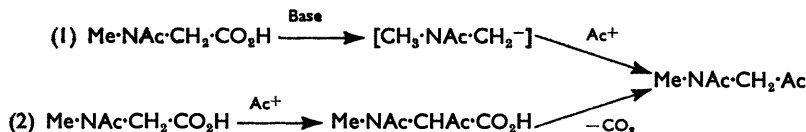


We examined the α -mono- and $\alpha\alpha$ -di-substituted *N*-phenylglycines (XIV and XVI) to discover whether the presence of a hydrogen atom on the α -carbon was vital to the reaction. King and McMillan¹³ have already demonstrated that the secondary α -acylamino-acid (XVII) is convertible into the corresponding ketone, *only* if R' or R'' is a hydrogen atom. This shows the necessity for a free α -hydrogen atom in this series, but in view of its special

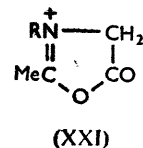
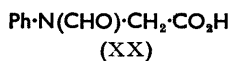
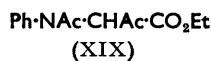
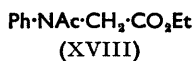


nature, it seemed advisable to examine a more conventional example. *N*-Phenylalanine (XIV) reacted with acetic anhydride, with or without pyridine, to give an oily acetamidoketone (infrared spectrum) (XV). The disubstituted acid (XVI) yielded three products, two of which were high melting and non-ketonic, and for which no consistent analytical or infrared data could be obtained; the third was acetanilide. These findings indicate that the starting acid or the reaction product is unstable under the experimental conditions, and that the high-melting products are probably polymers.

To explain the reaction with sarcosine, Wiley and Borum¹⁰ formulated two possible mechanisms. Neither of these can be considered satisfactory. The first is not consistent with our findings that the reaction, at least with *N*-phenylglycine, is not base catalyzed, and that the acid is unaffected by boiling pyridine. The second scheme requires electrophilic substitution on the methylene group, and to test this we have investigated the



reaction of acetic anhydride and pyridine on ethyl *N*-phenylaceturate (XVIII). Here the methylene grouping should be of approximately equal activity, but the reaction should stop at the intermediate β -keto-ester stage (XIX). In fact the ester (XVIII) is recovered almost quantitatively, indicating that the true mechanism involves the carboxylic acid function *per se*.



Two further mechanisms must therefore be considered. The first, due to Cornforth and Elliott,⁴ invokes the ion (XXI)¹⁴ in place of the oxazolone (II) of Dakin and West's original mechanism (*i.e.* I \rightarrow IV). Secondly, the nitrogen atom may play no part in the reaction, and in this event, the mechanism would be that which obtains for phenylacetic and *o*-chlorophenoxyacetic acid.

¹³ King and McMillan, *J. Amer. Chem. Soc.*, 1952, **74**, 3222.

¹⁴ See also Lawson and Searle, *J.*, 1957, 1556.

Neither of these mechanisms adequately explains our observation that when *N*-formyl-*N*-phenylglycine (XX) was treated under standard conditions with acetic anhydride and pyridine, the starting material was recovered in 90% yield and no ketonic material could be detected.

EXPERIMENTAL

Dakin-West Reaction.—*N*-Phenylglycine ¹⁵ (20 g., 0.15 mole) and acetic anhydride (150 ml., 1.7 mole) were heated under reflux for 6 hr., the excess of acetic anhydride removed at reduced pressure, and the product distilled, forming a fraction (17.1 g., 67.6%), b. p. ca. 115°/0.15 mm. or ca. 135°/1 mm. This formed needles, m. p. 79—80° (from petroleum). The *p*-nitrophenylhydrazone had m. p. 182° (from alcohol). Mixtures with authentic materials ¹⁶ have the same m. p.s.

In replicate experiments reflux times of $\frac{1}{2}$, 1, 4, and 8 hr. were used. In the first case the yield was 40% and some *N*-phenylaceturic acid was recovered; in the others the yields (crude) were 53, 61, and 67%, respectively. One experiment, in which the purified *N*-acetyl derivative was refluxed for 1 hr., gave a crude yield of 65%: in another, in which pyridine (0.6 mole) was included, the same product was obtained.

After being boiled under reflux for 7 hr. with an excess of pyridine, *N*-phenylglycine was recovered in 90% yield.

1-(*N*-phenylpropionamido)butan-2-one (XII). *N*-Phenylglycine (10 g.) and propionic anhydride (90 ml.) were boiled under reflux for 4 hr. yielding the ethyl ketone (7.0 g., 55%), b. p. 125—130°/0.4 mm.; ν (thin film) 1723 and 1660 cm^{-1} [*oxime*, m. p. 125° (from ethanol) (Found: C, 66.4; H, 7.4; N, 12.0. $\text{C}_{13}\text{H}_{18}\text{O}_2\text{N}_2$ requires C, 66.6; H, 7.7; N, 12.0%)].

N-*p*-Methoxyphenylacetamidoacetone (XI). *N*-*p*-Methoxyphenylglycine ¹⁷ (12 g.) and acetic anhydride (75 ml.) were refluxed for 1 hr., giving the *acetamido-ketone* (45%), b. p. 136—138°/0.1 mm.; ν (thin film) 1715 and 1660 cm^{-1} [*oxime*, m. p. 118—119° (from water) (Found: C, 61.1; H, 6.7; N, 11.4. $\text{C}_{12}\text{H}_{16}\text{O}_3\text{N}_2$ requires C, 61.0; H, 6.8; N, 11.9%)].

N-*p*-Nitrophenylaceturic acid (VIII). *N*-Phenylaceturic acid (7.2 g.) in concentrated sulphuric acid (10 ml.) was cooled in ice, and concentrated nitric acid (2 ml.)—concentrated sulphuric acid (1.5 ml.) was added at <10°. After 40 min. at room temperature the solution was poured on ice. The solid product (90%) (from acetic acid) had m. p. 191° (lit., ¹² m. p. 191—192°).

N-*p*-Nitroanilinoacetone (XIII). (a) *N*-*p*-Nitrophenylaceturic acid (20.7 g.) and acetic anhydride (110 ml.) were refluxed for 1 hr., yielding the *ketone* (3.7 g., 22%), b. p. 130—135°/0.3 mm., m. p. 151° (from ethanol); ν (Nujol) 3350 (N-H) and 1715 (C=O) cm^{-1} , no amide C=O absorption (Found: C, 55.9; H, 5.1; N, 14.6. $\text{C}_9\text{H}_{10}\text{O}_3\text{N}_2$ requires C, 55.7; H, 5.15; N, 14.4%).

(b) *N*-Phenylacetamidoacetone (7.2 g.) in acetic acid (5 ml.) and concentrated sulphuric acid (10 ml.) was nitrated with concentrated nitric acid (2 ml.)—concentrated sulphuric acid (1.5 ml.) at <10°. The solution was kept for 40 min. at room temperature and poured on ice. The product, m. p. 151° (from ethanol), was identical (mixed m. p. and infrared spectrum) with that described above.

2-*N*-Phenylacetamidobutan-3-one (XV). *N*-Phenylalanine ¹⁸ (5.5 g.), acetic anhydride (37 ml.), and pyridine (37 ml.) were refluxed for 1 hr., yielding the *acetamido-ketone* (13%), b. p. 128—132°/0.2 mm.; ν (thin film) 1715 and 1660 cm^{-1} [*oxime*, m. p. 180—181° (from water) (Found: C, 65.8; H, 7.1; N, 12.6. $\text{C}_{15}\text{H}_{16}\text{O}_2\text{N}_2$ requires C, 65.45; H, 7.3; N, 12.7%)]. The same product was obtained when the pyridine was omitted.

Dakin-West Reaction with α -Anilino- α -methylpropionic Acid.—The acid ⁸ (20 g.) and acetic anhydride (140 ml.) were boiled under reflux for 4 hr. On cooling, a solid product separated and more was precipitated by the addition of ether (300 ml.). This product (in all 3 g.) was separated by hot acetic acid into a soluble fraction which had m. p. 285° (from acetic acid) (Found: C, 79.4, 78.7; H, 6.1, 6.0; N, 6.4, 6.5%), and insoluble material, m. p. 330° (from nitrobenzene (Found: C, 76.0, 79.1; H, 5.6, 7.4; N, 7.1, 6.4%). Neither gave ketonic derivatives.

¹⁵ de Moulpiéd, *J.*, 1905, **87**, 435.

¹⁶ Wolf, *Annalen*, 1952, **578**, 83.

¹⁷ Coghill and Johnson, *J. Amer. Chem. Soc.*, 1925, **47**, 184.

¹⁸ Nastvogel, *Ber.*, 1889, **22**, 1793.

Concentration of the mother-liquor afforded acetanilide, m. p. and mixed m. p. 113°. An intractable resin was left in the distillation flask.

Reaction with the *N*-acetyl derivative (see below) gave the same mixture.

α-Methyl-*α*-(*N*-phenylacetamido)propionic Acid. *α*-Anilino-*α*-methylpropionic acid⁸ was dissolved in the minimum amount of warm acetic anhydride. Excess of water was then added; the acetyl derivative, m. p. 175—176° (from water), slowly separated (Found: C, 65.3; H, 6.9; N, 6.5. C₁₂H₁₅O₃N requires C, 65.2; H, 6.8; N, 6.3%).

Action of Acetic Anhydride and Pyridine on Ethyl N-Phenylaceturate.—The ester (40 g.), acetic anhydride (200 ml.), and pyridine (85 ml.) were refluxed for 6 hr., and low-boiling material was then distilled off at reduced pressure. The residue gave starting material (38 g.).

Action of Acetic Anhydride and Pyridine on N-Formyl-N-phenylglycine (XXII).—The acid¹⁹ (15 g.), acetic anhydride (75 ml.), and pyridine (75 ml.) were boiled under reflux for 4 hr. and distilled. Starting material (13.5 g.), m. p. and mixed m. p. 125°, was recovered.

The authors thank Dr. V. Wolff for authentic samples of *N*-phenylacetamidoacetone and its derivatives. They are also indebted to Mr. J. M. L. Cameron and his staff for micro-analyses and to Dr. G. Eglinton and his staff for infrared spectra.

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¹⁹ Vorländer and Mumme, *Ber.*, 1901, **34**, 1647.
