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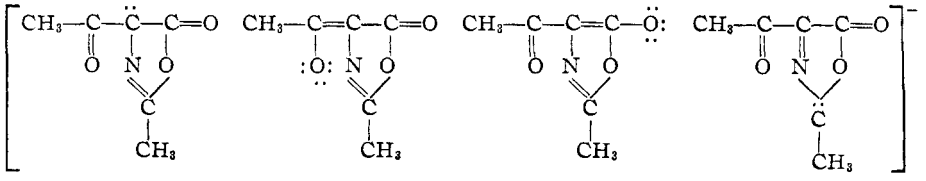
Some Observations on the Dakin–West Reaction

BY GEORGE H. CLELAND AND CARL NIEMANN

The reaction of α-amino acids with acetic anhydride in the presence of a base to give α-acetamidoalkyl methyl ketones[1,2] was recognized as an aldol reaction by Dakin and West[2] and it appears[1–3] that the over-all reaction proceeds through acetylation of the amino acid, cyclization to the azlactone, reaction of the latter compound with base to give a resonance stabilized carbanion, the reaction of this ion with acetic anhydride to give the azlactone of an α-acetamido-β-keto acid and acetate ion, and the subsequent conversion of this azlactone to the acetamido ketone and carbon dioxide. The mechanism of the last transformation is obscure though it is probable that it may be dependent upon an attack by acetate ion upon the azlactone of the α-acetamido-β-keto acid.

Although many α-acetamidoalkyl methyl ketones have been prepared *via* the Dakin–West reaction[1–5] the applicability of this reaction to the preparation of ketones other than methyl ketones has not been explored beyond Dakin and West's observation that "the homologues of acetic anhydride are much less reactive than the latter substance" and the recent report of Wiley and Borum[6] relative to the formation of 1-phenyl-1-propionamido-2-butanone from α-aminophenylacetic acid and propionic anhydride. The fact that a number of α-amino acids react smoothly in the presence of pyridine with such diverse acid anhydrides as propionic, butyric, methoxyacetic, and benzoic anhydrides to give the corresponding acylamidoalkylethyl, propyl, methoxymethyl, and phenyl ketones indicates that the reaction is generally applicable to acyclic alkyl and aryl acid anhydrides. The reaction of acetyl chloride with α-amino acids in the presence of pyridine[2] was found difficult to control and with both acetyl and benzoyl chloride the ketones were obtained in poor yield. However benzoyl fluoride was found to react smoothly in the presence of pyridine with the single α-amino acid investigated to give good yields of the corresponding acylamidoalkylphenyl ketone and it appears that the acyl fluoride may be used in lieu of the acid anhydride in the Dakin–West reaction.



The preparation of oxazoles by the dehydration of the crude reaction product obtained by treating an α-amino acid with acetic anhydride and sodium acetate[7,8] has been interpreted by Wiley[6,9] as proceeding through the intermediate α-acetamidoalkyl methyl ketone. In view of the above observations and those of Attenburrow, *et al.*,[3] it was not surprising to find that with an α-amino acid such as phenylalanine comparable yields of the α-acetamidobenzyl methyl ketone were obtained by using either pyridine or sodium acetate as a condensing agent. The difference in the behavior of pyridine and of acylate ion noted by Attenburrow, *et al.*,[3] in the case of glycine may be explained on the basis of the greater basic strength of the acylate ion favoring more complete formation of the ion, which would be expected to be more inert toward ring cleavage and subsequent decarboxylation than the corresponding acid. The difference noted by Dakin and West[2] and by Wiley and Borum[6] in the behavior of glycine and the other α-amino acids is also explainable in terms of the formation of the above resonance stabilized ion in the case of glycine and the impossibility of its formation in the case of the other α-amino acids.

From Dakin and West's observations[2] one would expect that a dipeptide would react with acetic anhydride in the presence of a base to give one equivalent of carbon dioxide and that the corresponding diketopiperazine would not react at all. These expectations have been realized and it may be concluded that all evidence is consistent with the previously stated proposition[2] that only those α-amino acids or their derivatives which are capable of forming azlactones containing an active α-hydrogen atom will undergo the Dakin-West reaction. Complicating competitive reactions are to be found in the case of the β-hydroxy-α-amino acids where the base catalyzed intermolecular dehydration reaction takes obvious precedence over the intramolecular carbonyl addition reaction and in the case of glutamic acid where pyrrolidone carboxylic acid formation limits azlactone formation.[2]

(1) Levene and Steiger, *J. Biol. Chem.*, **74**, 689 (1927); **79**, 95 (1928).
(2) Dakin and West, *ibid.*, **78**, 91, 745, 757 (1928).
(3) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948).
(4) Wood and du Vigneaud, THIS JOURNAL, **67**, 210 (1945).
(5) Wiley, *J. Org. Chem.*, **12**, 43 (1947).
(6) Wiley and Borum, THIS JOURNAL, **70**, 2005 (1948).
(7) Wrede and Keil, *Z. physiol. Chem.*, **203**, 279 (1931).
(8) Wrede and Feurerriegel, *ibid.*, **218**, 129 (1933).
(9) Wiley, *Chem. Rev.*, **37**, 401 (1945).

Experimental[10]

1-Phenyl-2-acetamido-3-butanone.[2]—(A) A mixture of 12.4 g. (0.075 mole) of DL-phenylalanine, 39.3 g. (0.5 mole) of pyridine and 65.2 g. (0.64 mole) of acetic anhydride was heated on a steam-bath for five hours, steam distilled until free of pyridine, the residue treated with an excess of aqueous sodium bicarbonate, and extracted with six 100-ml. portions of ether. The ethereal extract was dried, the solvent removed and the waxy orange-yellow solid recrystallized twice from xylene to give 12.1 g. (79%) of 1-phenyl-2-acetamido-3-butanone,[2] colorless needles, m. p. 98–99° (cor.).

(B) A mixture of 1.65 g. (0.01 mole) of DL-phenylalanine, 4 g. (0.05 mole) of anhydrous sodium acetate and 10.8 g. (0.11 mole) of acetic anhydride was heated with stirring for thirty minutes at 130–135°, and the reaction product worked up substantially as described in (A) to give 0.94 g. (46%) of acetamidoketone, colorless needles, m.p. 98–99° (cor.).

(C) A mixture of 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine and 8.8 g. (0.11 mole) of acetyl chloride was heated with stirring for one hour at 60° and the reaction mixture worked up as described previously to give 0.15 g. (8%) of 1-phenyl-2-acetamido-3-butanone, colorless needles, m. p. 97–99° (cor.) after one recrystallization from xylene.

1-Phenyl-2-propionamido-3-pentanone.—A mixture of 3.3 g. (0.02 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 26 g. (0.2 mole) of propionic anhydride was refluxed at 140–145° for thirty minutes, the solution concentrated *in vacuo*, treated with an excess of aqueous sodium bicarbonate, extracted successively with two 100-ml. portions of ether and of chloroform, the non-aqueous phases combined, dried, and the solvents evaporated to give approx. 5 g. of a light-orange oil. The oil was taken up in hot ligroin, b. p. 90–130°, filtered, the volume reduced to 25 ml., and the solution stored at 5° overnight. The colorless needles so obtained were recrystallized first from ligroin and then from aqueous-acetone to give 1.7 g. (36%) of 1-phenyl-2-propionamido-3-pentanone, colorless needles, m. p. 67–68° (cor.). In a second experiment the reaction mixture resulting from heating 5 g. (0.03 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 26 g. (0.2 mole) of propionic anhydride at 135° for one and one-half hours was fractionally distilled to give 2.9 g. (41%) of 1-phenyl-2-propionamido-3-pentanone, colorless needles, m. p. 67–68° (cor.).

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.9; H, 8.2; N, 5.9.

The oxime, colorless needles, m. p. 152–153° (cor.), was recrystallized from 95% ethanol.

Anal. Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.7; H, 8.1; N, 11.3. Found: C, 67.6; H, 8.4; N, 11.1.

The 2,4-dinitrophenylhydrazone, yellow needles, m. p. 153–154° (cor.), was recrystallized alternately from ethyl acetate and 95% ethanol.

Anal. Calcd. for $C_{20}H_{23}O_6N_5$: N, 16.9. Found: N, 16.8.

1-Phenyl-2-butyramido-3-hexanone.—A mixture of 3.3 g. (0.02 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 40 g. (0.25 mole) of butyric anhydride was heated for three hours at 145–150°, and the reaction product worked up as described for the preceding preparation to give a light-orange oil which crystallized upon standing at 5°. This product was recrystallized successively from xylene and ligroin, 30–60°, to give 1.4 g. (27%) of 1-phenyl-2-butyramido-3-hexanone, colorless needles, m. p. 59–60° (cor.).

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.6; H, 8.7; N, 5.4.

The oxime, colorless needles, m. p. 145–146° (cor.) was recrystallized twice from water.

Anal. Calcd. for $C_{16}H_{24}O_2N_3$: C, 69.5; H, 8.8; N, 10.1. Found: C, 69.3; H, 8.7; N, 10.1.

The 2,4-dinitrophenylhydrazone, bright yellow needles, m. p. 173–174° (cor.) was obtained after successive recrystallization from ethanol and ethyl acetate.

Anal. Calcd. for $C_{22}H_{27}O_5N_5$: C, 59.9; H, 6.2; N, 15.9. Found: C, 60.1; H, 6.4; N, 16.0.

1-Methoxy-3-methoxyacetamido-4-phenyl-2-butanone.—A mixture of 5 g. (0.03 mole) of DL-phenylalanine, 12 g. (0.15 mole) of pyridine and 24 g. (0.15 mole) of methoxyacetic anhydride[11] was heated with stirring at 115° for one hour, the solution evaporated *in vacuo*, the residue treated with an excess of aqueous sodium bicarbonate, extracted successively with two 100-ml. portions of ether and of chloroform, the non-aqueous phases combined, dried, the solvents removed, the residual oil taken up in 60% ethanol, the solution treated with Norite, filtered, and the solvents evaporated to give 6.2 g. (78%) of a neutral light-yellow oil which could not be induced to crystallize. A portion of the oil was treated with *p*-nitrophenylhydrazine to give a *p*-nitrophenylhydrazone, stout orange rhombs, m. p. 179–181° (cor.) after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{20}H_{24}O_5N_4$: C, 60.0; H, 6.0; N, 14.0. Found: C, 60.2; H, 6.1; N, 14.1.

The 2,4-dinitrophenylhydrazone was obtained as light-yellow needles, m. p. 168–169° (cor.) after two recrystallizations from chloroform.

Anal. Calcd. for $C_{20}H_{23}O_7N_5$: C, 53.9; H, 5.2; N, 15.7. Found: C, 53.8; H, 5.2; N, 15.8.

The semicarbazone, rosettes of colorless needles, m. p. 116–117° (cor.), was recrystallized twice from water.

Anal. Calcd. for $C_{15}H_{22}O_4N_4$: C, 55.9; H, 6.9; N, 17.4. Found: C, 55.7; H, 7.0; N, 17.5.

α-Benzamidopropiophenone.—A mixture of 3 g. (0.034 mole) of DL-alanine, 12 g. (0.15 mole) of pyridine and 34 g. (0.15 mole) of benzoic anhydride[12] was heated with stirring at 130–135° for two and one-half hours, and the reaction product worked up as previously described. The solid obtained was recrystallized once from ligroin and twice from aqueous ethanol to give 3.6 g. (42%) of α-benzamidopropiophenone, colorless prisms, m. p. 104–105° (cor.). α-Benzamidopropiophenone has been reported to have a m. p. of 103°[13] and 104–105°.[14]

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.9; H, 6.0; N, 5.5. Found: C, 76.0; H, 6.0; N, 5.4.

The oxime, rosettes of colorless needles, m. p. 157–158° (cor.), was recrystallized twice from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.9; H, 6.2; N, 10.3.

The ketone (3 g.) in 3 ml. of cold concd. sulfuric acid was diluted with ice water, the solid collected, washed with water and recrystallized twice from ligroin to give 2,5-diphenyl-4-methyl-oxazole, prisms, m. p. 81–82° (cor.). Lister and Robinson[14] give a m. p. of 82°.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.6; N, 6.0. Found: C, 81.8; H, 5.7; N, 5.8.

α-Benzamido-β-phenyl-propiophenone.—(A) A stirred mixture of 2.5 g. (0.015 mole) of DL-phenylalanine, 8 g. (0.10 mole) of pyridine, and 22.5 g. of benzoic anhydride (0.10 mole) was heated at 140–145° for two hours. The reaction mixture was worked up as described for α-benzamidopropiophenone to give 2.2 g. (44%) of α-benzamido-β-phenyl-propiophenone, long colorless needles, m. p. 146–147° (cor.) after two recrystallizations from aqueous-ethanol.

Anal. Calcd. for $C_{22}H_{19}O_2N$: C, 80.2; H, 5.8; N, 4.3. Found: C, 80.3; H, 5.8; N, 4.3.

(10) In the following experiments no attempt has been made to determine the conditions leading to maximum yields.

(11) Prepared by a method similar to that described by Allen, *et al.*, "Organic Syntheses," **26**, 1 (1946).

(12) Clarke, *et al.*, "Organic Syntheses," Coll. Vol. **1**, 91 (1941).

(13) Behr-Bregowski, *Ber.*, **30**, 1515 (1897).

(14) Lister and Robinson, *J. Chem. Soc.*, **101**, 1297 (1912).

The oxime was obtained after two recrystallizations from 95% ethanol as colorless needles, m. p. 188–189° (cor.).

Anal. Calcd. for $C_{22}H_{20}O_2N_2$: C, 76.7; H, 5.8; N, 8.1. Found: C, 76.7; H, 6.0; N, 8.0.

A solution of 0.4 g. of α-benzamido-β-phenyl-propiophenone in 30 ml. of 6 *N* hydrochloric acid and 10 ml. of ethanol was refluxed for three hours, the solvents removed, the residue extracted with ether, and dissolved in 10 ml. of ethanol. The addition of 25 ml. of ether gave the hydrochloride of α-amino-β-phenylpropiophenone, lustrous needles, m. p. > 200° with decomposition.

Anal. Calcd. for $C_{15}H_{16}ONCl$: C, 68.8; H, 6.2; N, 5.4; Cl,13.6. Found: C, 68.6; H, 6.4; N, 5.2; Cl, 13.8.

(B) A mixture of 2.7 g. (0.01 mole) of N-benzoyl-DL-phenylalanine, 5.9 g. (0.075 mole) of pyridine and 11.3 g. (0.05 mole) of benzoic anhydride heated at 135–140° for two hours with stirring when treated as described above gave 1.2 g. (36%) of α-benzamido-β-phenylpropiophenone, colorless needles, m. p. 146–147° (cor.).

(C) When 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine, and 17 g. (0.12 mole) of benzoyl chloride was heated for one hour at 135–140°, 39–42% of the anticipated quantity of carbon dioxide was evolved but on working up the dark tarry reaction product only 0.36 g. (9%) of α-benzamido-β-phenyl-propiophenone, m. p. 146–147° (cor.), was obtained.

(D) A mixture of 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine and 12.5 g. (0.1 mole) of benzoyl fluoride[15] was heated for two hours at 135–140° with stirring and from the reaction mixture there was obtained 1.55 g. (39%) of α-benzamido-β-phenylpropiophenone, m. p. 146–147° (cor.).

(15) Meslans and Girardet, *Bull. soc. chim.*, [3] **15**, 877 (1896).

Studies Based upon Evolution of Carbon Dioxide.—A mechanically stirred mixture of 0.7 g. (0.0044 mole) of DL-alanylalanine, 3.6 g. (0.045 mole) of pyridine, and 4.6 g. (0.045 mole) of acetic anhydride heated for two hours at 110–115° gave 0.004 mole of carbon dioxide. In a second experiment heating for one and one-half hours at 115° gave 92% of the anticipated amount of carbon dioxide (one equivalent) and when the reaction mixture was refluxed with 6 *N* hydrochloric acid no more carbon dioxide was obtained.

A mixture of 0.44 g. (0.004 mole) dimethyldiketopiperazine, 2 g. (0.025 mole) of pyridine and 3.6 g. (0.035 mole) of acetic anhydride was heated with stirring at 120° for two hours. No carbon dioxide was evolved during this period nor after refluxing with 6 *N* hydrochloric acid.

Summary

The Dakin–West reaction has been shown to be applicable to the synthesis of α-acylamidoalkyl aryl ketones as well as to the synthesis of α-acylamidoalkyl alkyl ketones other than methyl ketones. It has been found that acetate ion may be used in lieu of pyridine as a condensing agent and that the acid anhydride may be replaced by the corresponding acyl fluoride. The nature of the base catalyzed reaction involving a dipeptide and an acid anhydride has been considered in a preliminary manner.

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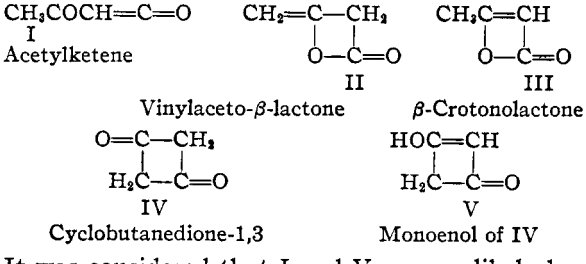
The Use of Carbon-14 in the Determination of the Structures of Aldoketene Dimers[1,2]

BY JOHN D. ROBERTS, ROSE ARMSTRONG, R. F. TRIMBLE, JR., AND MARION BURG

The structures of aldoketene dimers prepared by the dehydrohalogenation of acyl halides have not been conclusively established. Recent infrared spectroscopic studies by Miller and Koch[3] indicate that the parent compound, diketene, is probably an equilibrium mixture of compounds having structures II and III although IV could not be excluded as a component of the mixture by the infrared data.



It was considered that I and V were unlikely because of the absence of absorption at the characteristic hydroxyl and C=C=O frequencies.

(1) Assisted by the joint program of the Office of Naval Research and the Atomic Energy Commission.

(2) Presented at the St. Louis Meeting of the American Chemical Society, September 7, 1948.

(3) Miller and Koch, THIS JOURNAL, **70**, 1890 (1948).

The higher aldoketene dimers prepared from acyl halides by the Wedekind procedure[4,5,6,7] have chemical and physical properties which are generally similar to those of diketene and presumably present a similar structural problem.[8] It is apparently agreed that the dimers of dialkyl-substituted ketenes (ketoketene dimers) have tetraalkylcyclobutanedione-1,3 structures.[6]

In the present investigation the isotopic tracer

(4) Wedekind, *Ber.*, **34**, 2070 (1901); *Ann.*, **323**, 246 (1902); **378**, 261 (1910); Wedekind and Haeussermann, *Ber.*, **41**, 2297 (1908).

(5) Hill, Ph.D. Thesis, Cornell University, 1941.

(6) Hanford and Sauer, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1947, pp. 127 ff.

(7) Sauer, U. S. Patent 2,369,919; THIS JOURNAL, **69**, 2444 (1947).

(8) Two seemingly isomeric forms have been reported for methylketene dimer. A liquid, b. p. 50–52° (9 mm.), has been prepared from the dehydrohalogenation of propionyl chloride[5,7] having properties similar to those of diketene and a solid form, m. p. 140°, has been obtained from the polymerization of methylketene prepared from the debromination of α-bromopropionyl bromide with zinc by Staudinger and Klever, *Ber.*, **41**, 906 (1908); Staudinger, *ibid.*, **44**, 533 (1911). The solid compound has also been synthesized by Schroeter, *ibid.*, **49**, 2697 (1916); **53**, 1917 (1920); **59**, 977 (1926), from diethyl α,α′-dimethylacetonedicarboxylate. The structure, 1,3-dimethylcyclobutene-2-ol-4-one was assigned to the solid compound by Staudinger on the basis of its pronounced enolic properties. However, this assignment can only be regarded as tentative in the absence of a molecular weight determination.