A New Synthesis of α-Amino Acids. Amidoalkylation of Active Methylene Compounds with Glyoxylic Acid Derivatives[1]

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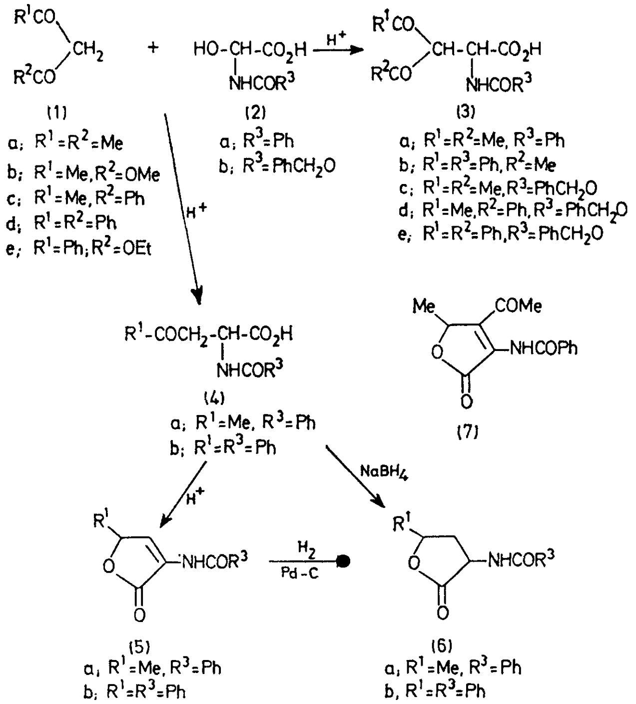
Summary The synthesis of *N*-acyl derivatives of α-amino-γ-keto acids (**3**,**4**) by the amidoalkylation of 1,3-dicarbonyl compounds (**1**) with glyoxylic acid–amide adducts (**2**) is described; the γ-ketoacids (**4**) were further converted to the corresponding butenolide (**5**) or α-acylaminobutyrolactone (**6**).

α-Amino-γ-ketoacids and α-amino-γ-hydroxyacids are natural occurring amino acids.[2] The γ-ketoacids can easily be converted to the hydroxy acids, which are more stable in the γ-butyrolactone form (**6**), to αγ-diamino acids on reductive amination, or to heterocyclic derivatives on treatment with hydrazine.


(1) a; $R^1=R^2=Me$ b; $R^1=Me, R^2=OMe$ c; $R^1=Me, R^2=Ph$ d; $R^1=R^2=Ph$ e; $R^1=Ph; R^2=OEt$

(2) a; $R^3=Ph$ b; $R^3=PhCH_2O$

(3) a; $R^1=R^2=Me, R^3=Ph$ b; $R^1=R^3=Ph, R^2=Me$ c; $R^1=R^2=Me, R^3=PhCH_2O$ d; $R^1=Me, R^2=Ph, R^3=PhCH_2O$ e; $R^1=R^2=Ph, R^3=PhCH_2O$

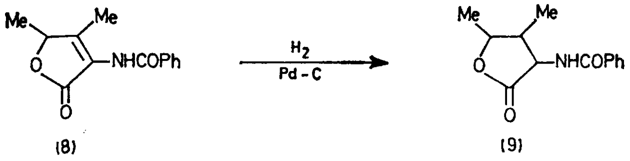
(4) a; $R^1=Me, R^3=Ph$ b; $R^1=R^3=Ph$

(5) a, $R^1=Me, R^3=Ph$ b; $R^1=R^3=Ph$

(6) a, $R^1=Me, R^3=Ph$ b, $R^1=R^3=Ph$

(7)

We now report a new, direct synthesis of *N*-acyl derivatives of α-amino-γ-keto acids using 1,3-diketones (**1a**, **1c**, **1d**) or β-ketoesters (**1b**, **1e**) and glyoxylic acid-amide adducts (**2**)[3] as starting materials.


(8) (9)

Treatment of acetylacetone with α-hydroxyhippuric acid[3] (**2a**) in concentrated sulphuric acid at room temperature gave compound (**3a**) (m.p. 145 °C) in 62% yield. Under the same experimental conditions methyl acetoacetate and ethyl benzoyl acetate gave α-benzamidolevulinic acid (**4a**) (m.p. 125 °C, 71%) and *N*-benzoyl-β-benzoylalanine (**4b**) (m.p. 181 °C, 65%). Benzoylacetone gave either compound (**3b**) (m.p. 192 °C, 48%) or the β-benzoylalanine derivative (**4b**) (54%) depending on the reaction conditions. In concentrated sulphuric acid *N*-benzoyl-β-benzoylalanine (**4b**) was obtained while in 10% (v/v) sulphuric–acetic acid the product isolated was compound (**3b**). Dibenzoylmethane reacted with α-hydroxyhippuric acid in concentrated sulphuric acid to give *N*-benzoyl-β-benzoylalanine (**4b**) in 42% yield.

α-Hydroxy-*N*-benzyloxycarbonylglycine[3] (**2b**) which is unstable in concentrated sulphuric acid, was found to react with acetylacetone, benzoylacetone and dibenzoylmethane in 10% sulphuric–acetic acid to give products of type (**3**) in 35—55% yield. Compound (**3c**) melted at 126 °C, (**3d**) at 123 °C and (**3e**) at 165 °C after crystallization from ethyl acetate–light petroleum (b.p. 40—60 °C).

The γ-ketoacids (**4a**) and (**4b**) cyclized in the presence of an acid catalyst or acetic anhydride to the corresponding $\Delta^{\alpha,\beta}$-butenolides (**5a**) (m.p. 61 °C, 52%) and (**5b**) (m.p. 125 °C, 49%). The butenolide (**5a**) was catalytically hydrogenated to the corresponding α-benzamido-5-methylbutyrolactone (**6a**) (m.p. 140 °C).[4] Only one isomer was obtained in the catalytic hydrogenation while treatment of the γ-ketoacids (**4a**) and (**4b**) with sodium borohydride afforded a mixture of two isomeric lactones. Compound (**3a**) afforded the keto-butenolide (**7**) on treatment with a sulphonic acid in boiling 1,2-dichloroethane (m.p. 138 °C).

Reaction of ethyl α-methylacetoacetate with α-hydroxyhippuric acid in concentrated sulphuric acid at room temperature gave α-benzamido-$\beta\gamma$-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**8**) (m.p. 144 °C, 44%) together with the corresponding acid (m.p. 139 °C, 8%). The unsaturated lactone (**8**) gave, according to the n.m.r. spectrum, only one of the possible isomeric butyrolactones (**9**) (m.p. 125 °C) on catalytic hydrogenation.

All products had satisfactory elemental analyses and i.r. and n.m.r. spectra.

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[1] For previous papers in this series see D. Ben-Ishai, I. Sataty, and Z. Berler, *J.C.S. Chem. Comm.*, 1975, 349.

[2] 'Handbook of Biochemistry,' 2nd edn., ed. H. A. Seber, C.R.C., 1970, B-12; H. Faulshich, J. Dolling, K. Michl, and T. Wieland, *Annalen*, 1973, 560, and references therein; O. Wiss and H. Fuchs, *Helv. Chim. Acta*, 1952, **35**, 407.

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[4] H. L. Goering, S. J. Cristol, and K. Dittmer, *J. Amer. Chem. Soc.*, 1948, **70**, 3310.