Some Reactions of 5-Aminolevulinic Acid with Cyclic β-Diketones†

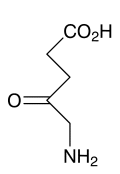
J. Chem. Research (S), 1998, 458–459†

Elaine H. Brown and Anthony R. Butler*

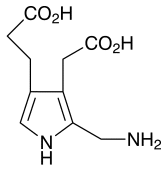
School of Chemistry, University of St Andrews, Fife KY16 9ST, UK

5-Aminolevulinic acid reacts, under acidic conditions, with cyclohexane-1,3-diones to give 3-(2′-carboxyethyl)tetrahydroindol-4-ones which were characterised, in part, by 2D NMR spectroscopy.

Although a relatively simple molecule, 5-aminolevulinic acid (**1**; 5-ALA) undergoes a number of important reactions. It is, of course, the precursor of the haem pigments and, in the presence of the enzyme porphobilinogen synthase, dimerisation occurs to give porphobilinogen **2**. The mechanism of this reaction has been studied extensively.[1] In the absence of an enzyme, dimerisation occurs to give an entirely different product, a dihydropyrazine.[2] Another reaction of 5-ALA which occurs readily is condensation with a β-diketone to give a substituted pyrrole, either a Knorr[3] or a Fischer–Fink[4] product. In a previous paper[5] we explored some features of this type of reaction using a number of diketones related to pentane-2,4-dione. In some cases only the Knorr product was obtained while, in others, there was a mixture of products. As a continuation of that work we report two examples of condensation reactions involving cyclic diketones.



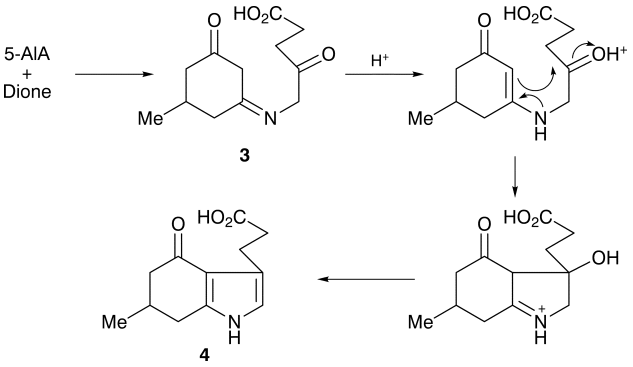
1;5-ALA



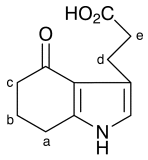
2

Reaction of 5-ALA with 5-methylcyclohexane-1,3-dione under acidic conditions gave, on standing for some days, a small quantity of a white, crystalline solid and the analytical data are consistent with formation of **4**. The mechanism proposed previously[6] for reaction with a non-cyclic diketone and shown in Scheme 1 accounts for formation of this product. The mechanism demands that one hydrogen at the 2 position of the cyclohexane moiety is sufficiently acidic for tautomerism of the imine **3** to occur. Cyclisation of **3** indicates that the steric constraints imposed by the cyclic nature of the diketone do not prevent realisation of the transition state for formation of the heterocyclic ring. However, the presence of the 5-methyl group appears to slow the reaction, for reasons which will be discussed later.

Reaction of 5-ALA with cyclohexane-1,3-dione gave some crystalline product immediately after reflux. The spectral data for the product are consistent with formation of **5** but it was not possible, from simple NMR spectra, to assign chemical shifts to the five methylene groups labelled a–e. The unambiguous assignments is an interesting exercise in the use of COSY and $^{1}H—^{13}C$ correlation NMR spectroscopy for a relatively simple molecule. In the ^{1}H NMR spectrum all signals, apart from the aromatic proton at δ 6.57 and two signals at δ 11.10 and 11.80 corresponding to NH and OH, are due to methylenes. Four signals are triplets and one at δ 2.10 is a quintet and the last must be due to CH_2-b. The signal at δ 2.40 shows a symmetrical distortion with the quintet, suggesting that they are neighbours (*i.e.* CH_2-a or CH_2-c). In the COSY spectrum (Fig. 1) the signal at δ 2.10 has cross-peaks with the signals at δ 2.37 and 2.80 and so the last two must be due to CH_2-c and CH_2-a. In the $^{1}H—^{13}C$ correlation spectrum (Fig. 2) the signal in the ^{13}C NMR spectrum for the methylene with the highest chemical shift, corresponding to CH_2-c because of the proximity of the carbonyl group, is at δ 38.2 and this correlates with a signal in the ^{1}H spectrum at δ 2.37. Thus the shifts of CH_2-a and CH_2-c are assigned.



Scheme



5

The ^{1}H signals at δ 2.57 and 2.92 have cross-peaks with one another but with no other signals and must therefore correspond to CH_2-e and CH_2-d. That at δ 2.57 correlates with a signal in the ^{13}C spectrum at the high value of δ 34.5 and this must be the methylene next to the carbonyl of the carboxylic acid, *i.e.* CH_2-e, and the signal at δ 2.92 is due to CH_2-d.

There is a surprising feature in the NMR spectra. The simplicity of the ^{1}H NMR signals, with no geminal coupling, for the methylene groups at positions a, b and c indicates that ring inversion of the half-chair form of the six-membered ring must be fast on the NMR timescale. Since the solvent used for the NMR work was DMSO it was impossible to freeze out the inversion by lowering the temperature. One further interesting observation is that the methyl group at the 5 position substantially lowers the rate of cyclisation. In the transition state for cyclisation, which approximates to a half-chair structure, the methyl group could be in either the pseudo-axial or pseudo-equatorial position. From an examination of models it is clear that there is enough steric interference when in the pseudo-axial position to reduce the rate of reaction. This view was confirmed by our observation that no readily isolable product

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

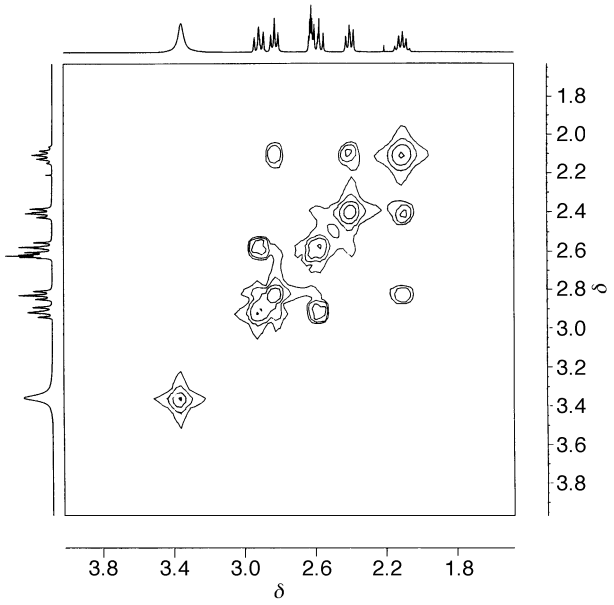


Fig. 1 COSY spectrum of **5**

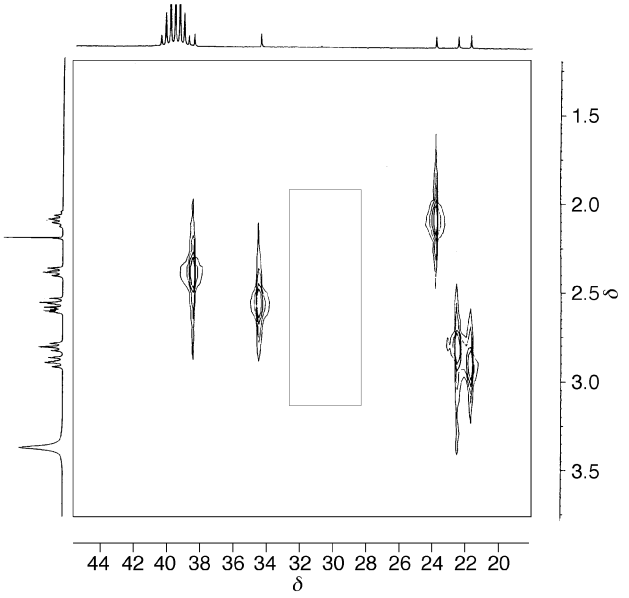


Fig. 2 ^{1}H—^{13}C correlation spectrum of **5**

resulted from the reaction, under the same conditions, of 5-ALA with dimedone.

Experimental

NMR spectra were recorded on a Brucker 300 spectrometer (300 and 75 MHz), mass spectra at the EPSRC National Mass Spectrometer Centre, Swansea.

Reaction of 5-*ALA with* 5-*Methylcyclohexane*-1,3-*dione*.—5-ALA (0.89 g, 5.3 mmol) and the dione (0.67 g, 5.3 mmol) were refluxed in acetate buffer (pH 4.57, 50 cm^3) for 30 min and the mixture allowed to stand in a refrigerator for 2 weeks. A small quantity of white, crystalline material was obtained and recrystallised from ethanol to give 3-(2′-*carboxyethyl*)-6-*methyl*-4,5,6,7-*tetrahydroindol*-4-*one* **4**. Yield 6%; mp 198 °C (decomp.); δ_H ([$^2H_6$]DMSO) 1.10 (d, 3 H, methyl), 2.00–2.30 (m, 5 H), 2.50 (t, 2 H, methylene), 2.80 (d, 2 H, methylene), 6.50 (s, 1 H, aromatic), 11.00 (br s, 1 H, NH or OH); δ_C ([$^2H_6$]DMSO) 20.9, 21.9, 28.6, 30.8, 31.7, 34.6, 116.2, 117.1, 121.1, 143.7, 174.6, 193.5; *m*/*z* 221 (M^+) (Found: 221.1052. $C_{12}H_{15}NO_3$ requires 221.1052).

Reaction of 5-*ALA with cyclohexane*-1,3-*dione*.—5-ALA (1 g, 6 mmol) and the dione (0.67 g, 6 mmol) in acetate buffer (pH 4.57, 20 cm^3) were refluxed for 30 min and then allowed to stand overnight. The yellow precipitate was recrystallised from ethanol to give 3-(2′-*carboxyethyl*)-4,5,6,7-*tetrahydroindol*-4-*one* **5**. Yield 10%; mp 194–196 °C; δ_H ([$^2H_6$]DMSO) 2.10 (quintet, 2 H, CH_2-b), 2.40 (t, 2 H, CH_2-c), 2.57 (t, 2 H, CH_2-e), 2.80 (t, 2 H, CH_2-a), 2.92 (t, 2 H, CH_2-d), 6.57 (s, 1 H, aromatic), 11.10 (s, 1 H, NH), 11.80 (br s, 1 H, OH); δ_C ([$^2H_6$]DMSO) 22.0 (CH_2-a), 23.0 (CH_2-d), 24.0 (CH_2-b), 34.5 (CH_2-e), 38.2 (CH_2-c), 116.0 (CH), 118.0, 122.0 144.0, 174.0 and 195.0 (quaternary); *m*/*z* 207 (M^+) (Found: C, 63.5; H, 6.5; N, 6.7. $C_{11}H_{13}NO_3$ requires C, 63.7; H, 6.3; N, 6.8%).

Received, 15th April 1998; Accepted, 28th April 1998
Paper E/8/02819B

References

1 E. K. Jaffe, G. D. Markham and J. S. Rajagopalan, *Biochemistry*, 1990, **29**, 8345.
2 E. K. Jaffe and J. S. Rajagopalan, *Bioorg. Chem.*, 1990, **18**, 381.
3 L. Knorr, *Liebigs Ann. Chem.*, 1886, **236**, 290.
4 H. Fischer and E. Fink, *Hoppe-Seyler's Z. Physiol. Chem.*, 1944, **280**, 123.
5 A. R. Butler and S. D. George, *Tetrahedron*, 1993, **49**, 7017.
6 A. R. Butler and S. D. George, *J. Chem. Soc., Perkin Trans. 2*, 1994, 315.