Tetrahedron Vol 33, pp 1729 to 1732 Pergamon Press 1977 Printed in Great Britain

OXIDATION OF METHYL α-ACYLAMINOCROTONATES WITH THALLIUM(III) ACETATE

M. PAGLIALUNGA PARADISI* and G. PAGANI ZECCHINI
Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica Farmaceutica dell'Università, 00185 Rome, Italy

(*Received in the UK 26 October 1976; accepted for publication 3 February 1977*)

Abstract—The reaction of methyl α-acylaminocrotonates with thallium(III) acetate in methanol results in the formation of a mixture of diastereomeric α,β-dimethoxy derivatives. The mechanism and stereochemistry are discussed.

Although oxymetalation reactions of simple acyclic olefins have been extensively investigated, little is known of these reactions with enamines and their *N*-acyl derivatives. Two reports concern the oxidation of enamines with thallium(III) salts[1] and a third communication describes the alkoxymercuration of α-acylaminoacrylic acids.[2] We now report the results of the oxidation of methyl α-acylaminocrotonates with thallium triacetate in methanol.

The α-acylaminocrotonic acids were prepared, according to the procedure of Flaving and Slaughter (described for α-chloroacetamidocrotonic acid[3]) starting from α-ketobutyric acid and the appropriate amide. While only one α-acylaminocrotonic acid was isolated by the above-mentioned workers, we have been able to separate the other geometrical isomer as the methyl ester (by PLC on silica).

The configuration of methyl α-acylaminocrotonates has been assigned by NMR, following the work of Morgenstern,[4] on the basis of the signal of the vinyl proton which, when *cis* to the acylamino function, occurs downfield relative to the corresponding proton in the other geometrical isomer. We have thus assigned a *Z* configuration **1** to the more polar isomer obtained in higher yield, and the *E* configuration **2** to the other.

This assignment was subsequently confirmed by Srinivasan *et al.*[5] who established the stereochemistry of α-acylaminocrotonates on the basis of the shift positions of the β-methyl groups.

Preliminary analysis of the reaction mixture obtained by oxidation of **1a** with thallium triacetate in refluxing methanol (by TLC, IR and NMR) revealed, beside starting material, two new compounds in about equal amounts and in 50% overall yield. After ozonization, the separation of two unchanged reaction products (by PLC on silica) was made easier. Elemental analysis, IR and NMR spectra indicated that the compounds were probably two diastereomeric methyl α - methoxy - α - acetamido - β - methoxy - n - butyrates (**3a**: less polar isomer, **4a**: more polar isomer).

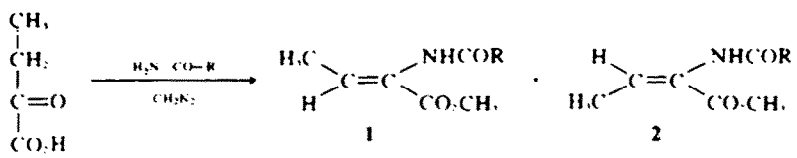
The methoxythallation reaction was extended, with similar results, to phenylacetamido **1b** and benzamido **1c** derivatives. A characteristic IR absorption pattern was shown by more polar compounds, **3a** and **3b**† in the region 1200–1100 cm^{-1}, and the less polar isomers **4a** and **4b**† also showed typical IR absorption bands in the same region.

Confirmation of the above structures was achieved by hydrogenolysis of **3a** and **4a** on palladium in acetic acid: both isomers gave a mixture of acetyl-*O*-methyl-threonine methyl ester **5a**, acetyl-*O*-methyl-allothreonine methyl ester **6a** and methyl *N* - acetyl - α - amino - n - butyrate **7a**.

Configuration assignments for diastereomeric methyl α - methoxy - α - acylamino - β - methoxy - *n* - butyrates, **3a**, **4a**, **3b** and **4b** was attempted by comparing their NMR spectra with those of acyl-*O*-methyl-threonine methyl esters, **5a** and **5b** and acyl-*O*-methyl-allothreonine methyl esters, **6a** and **6b** prepared independently. The NMR spectral parameters of these compounds are given in Table 1.

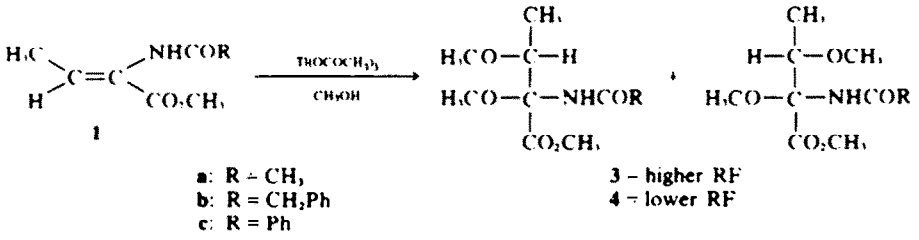
The coupling constants of the two vicinal protons (CH – CH) of acyl - *O* - methyl - threonine methyl esters **5a** and **5b** and those of acyl-*O*-methyl-allothreonine methyl esters **6a** and **6b** are low. This, in agreement with Karplus' rule, emphasizes a predominant contribution to the conformational equilibrium of *gauche*, rather than *trans*, rotational conformers of both *threo* and *erythro*

†The diastereomeric α,β-dimethoxy derivatives **3c** and **4c** derived from **1c** were not separated; their composition (by NMR, after ozonization) was equimolar.

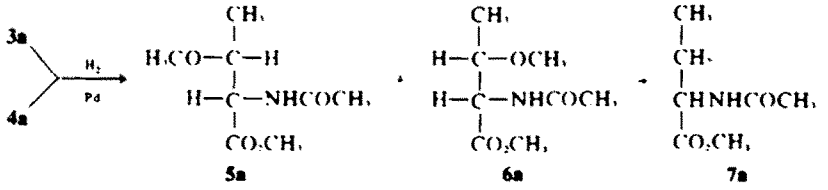


a: R = CH_3
b: R = CH_2Ph
c: R = Ph

Scheme 1.



Scheme 2. One of the enantiomers only shown.



Scheme 3.

Table 1. NMR data† of methyl α - methoxy - α - acylamino - β - methoxy - n - butyrates, acyl-*O*-methyl-threonine methyl esters and acyl-*O*-methyl-allothreonine methyl esters

Compound†	δ (ppm)							J		
	β-CH_3	OCH_3 (α, β)	CO_2CH_3	β-CH	α-CH	NH	COR	CH–CH	CH–CH_3	CHNH
3a	1.14d	3.42s	3.76s	3.67q	—	6.76bs	2.06s	—	6.3	—
4a	1.25d	3.29s 3.35s	3.80s	3.96q	—	6.70bs	2.08s	—	6.3	—
3b	1.06d	3.15s 3.33s	3.74s	3.51q	—	6.65bs	3.59s 7.27s	—	6.3	—
4b	1.14d	3.19s 3.22s	3.74s	3.89q	—	6.60bs	3.59s 7.27s	—	6.3	—
5a	1.18d	3.28s	3.75s	3.95o	4.64dd	6.21bd	2.08s	2.4	6.3	9
6a	1.23d	3.35s	3.75s	3.66o	4.72dd	6.38bd	2.05s	3.6	6.3	8.5
5b	1.09d	3.20s	3.70s	3.88o	4.60dd	6.13bd	3.62s 7.28s	2.4	6.3	9
6b	1.14d	3.25s	3.70s	3.57o	4.73dd	6.24bd	3.61s 7.31s	3.6	6.3	8.2

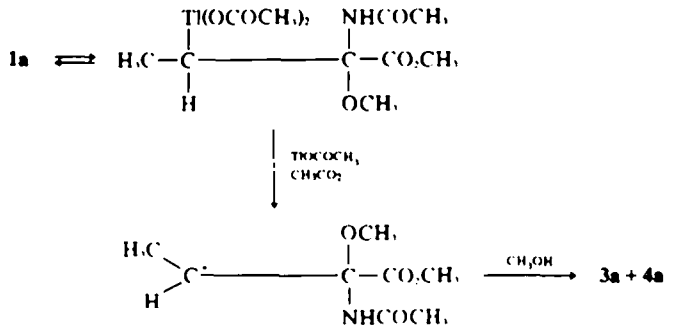
†a: R = CH_3, b: R = CH_2Ph.

‡δ(ppm) values relative to TMS as internal standard; coupling constants in Hz. Intensities of the signals in accordance with the number of protons; s: singlet, d: doublet, dd: double doublet, q: quartet, o: octet, b: broad.

derivatives. The higher coupling constant of allothreonine derivatives ($J_{\alpha\beta}$ 3.6 Hz), than that observed in corresponding threonine derivatives ($J_{\alpha\beta}$ 2.4 Hz) could be due to the increase in steric hindrance in the *trans* forms of the latter compounds.[6] The different preferential distribution of conformers affects the shifts of protons of threonine and allothreonine derivatives. The more remarkable difference in shifts between the two sets of diastereoisomers concerns the β-proton, which in threonine derivatives absorbs downfield relative to the corresponding isomers [$\Delta\delta_{H\beta} = 0.29$ ppm in the acetyl derivatives **5a–6a**; $\Delta\delta_{H\beta} = 0.31$ in the phenylacetyl derivatives **5b–6b**].

Substitution of the β-proton by a methoxyl group should not cause substantial change in conformational equilibria, on the assumption that a methoxyl group is (like the β-proton) the smallest of the groups bonded to the α-carbon. Furthermore, the effect of diamagnetic anisotropy of the oxygen atom in ethers and alcohols seems to be less important than that of carbonyl groups.[6] In agreement with this, we found an identical $\Delta\delta_{H\beta}$ (0.29 ppm) between the β-protons of **4a** and **3a**. In addition, the $\Delta\delta_{H\beta}$ (0.38 ppm) observed between **4b** and **3b** is similar to that between **5b** and **6b** (0.31 ppm). In view of these results, it seems probable that the configuration of the less polar isomers **3a** and **3b** may arise from **6a** and **6b** by replacing the β-proton by a methoxyl; as a consequence, the configuration of **4a** and **4b** would be that deriving from **5a** and **5b**.

It is noteworthy that the only products observed in this oxidation were α,β-dimethoxy derivatives. In the first stage of the reaction (the formation of the adduct) it is likely that thallium attack occurs on the β-carbon atom with uptake of methanol at α–C. This is supported by the results of Gallina *et al.*[3] and by the lack of both acetoxy substituted products (which would have been expected for a concerted addition) and geminal dimethoxy derivatives (arising from a possible shift of the β-hydrogen).[7] As concerns the decomposition step, the lack of acetylated products excludes an S_Ni process,[7] the nearly equimolecular rate of two α,β-dimethoxy derivatives obtained, suggests that the reaction step proceeds *via* an ionic mechanism (S_N1) but cannot exclude some anchimeric assistance to heterolysis of carbon–metal bond by the α-methoxy substituent. To obtain further mechanistic information, we have carried out the reaction



Scheme 4. One of the enantiomers only shown.

with the *E* geometrical isomer **2a**. The reaction mixture (analysed by NMR) was formed of **3a** and **4a** (in a similar ratio to that obtained by oxidation of **1a**) and by the same **1a**.

This result, together with lack of isomerization of **2a** under similar reaction conditions, but in the presence of CH_3COOH instead of thallium triacetate, allows us to conclude that the formation of adduct is reversible but does not exclude some participation of anchimeric assistance to the reaction mechanism.

CONCLUSION

In agreement with the referee's suggestion we could conclude the discussion as it follows: Our results of the methoxythallation of methyl α-acylaminocrotonates are quite different from those previously reported[14,15] concerning the oxidation of enamines with thallium salts. The formation of α-acetoxyketones was observed after the oxidation of morpholine enamine derivatives of several ketones with thallium(III) acetate in acetic acid[16]; α-methoxy ketones and α-diketones were isolated after hydrolytic work up of the reaction mixture arising from the oxidation of tautomeric imines with thallium (III) nitrate in methanol.[16]

EXPERIMENTAL

Thallium triacetate was prepared by the method of Kochi and Bethea.[8] M.ps were determined with a Büchi oil bath apparatus; IR spectra were recorded on a Perkin-Elmer 521 spectrophotometer in CCl_4 solutions. NMR spectra were measured for $CDCl_3$ solutions (TMS as internal standard) with a Jeol C-60 HL spectrometer. Preparative layer chromatography (PLC) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick). Light petroleum refers to the fraction with b.p. 40–60°.

Methyl α-acetamidocrotonates **1a** *and* **2a**

A mixture of α-ketobutyric acid (20 g) and acetamide (6 g) in trichloroethylene (250 ml) was refluxed for 26 h, using a Soxhlet condenser filled with molecular sieve type 4 Å (Merck). After cooling at 4° overnight, the crude precipitate (12.27 g) was collected and crystallised from acetone, giving pure (*Z*)-α-acetamidocrotonic acid (5.7 g), m.p. 160–1° (lit.[9] 159–60°). Esterification of this acid with ether diazomethane yielded methyl (*Z*)-α-acetamidocrotonate **1a**, m.p. 59–60° (from ether-light petroleum); ν_{max} 3400, 1730, 1700, 1658 and 1265 cm^{-1}; δ 1.75 (3H, d, J6.7 Hz, β-Me), 2.08 (3H, s, COMe), 3.68 (3H, s, CO_2Me), 6.66 (1H, q, J6.7 Hz, vinylic), 7.04 (1H, s broad, NH). (Found: C, 53.31; H, 6.93; N, 8.93. $C_7H_{11}NO_3$ requires: C, 53.49; H, 7.05; N, 8.91%).

The mother liquors from this reaction were evaporated under reduced pressure to yield an oily residue (~10 g). This residue (3.5 g) was esterified with ether-diazomethane and chromatographed on a column of silica (1:30). Elution with ethyl acetate and ethyl acetate—methanol (8:2) gave a nearly pure product (0.36 g), which, rechromatographed on silica (PLC) [benzene-ethyl acetate (1:1) as eluent] finally yielded pure methyl (*E*)-α-acetamidocrotonate **2a**, m.p. 48–49° (from ether–light petroleum); ν_{max} 3440 (w), 3400, 1730, 1680 and 1260 cm^{-1}; δ 2.07 (3H, d, J7.5 Hz, β-Me), 2.08 (3H, s, COMe), 3.82 (3H, s, CO_2Me), 7.05 (1H, q, J7.5 Hz, vinylic), 7.48 (1H, s broad, NH). (Found: C, 53.36; H, 6.92; N, 8.70. $C_7H_{11}NO_3$ requires: C, 53.49; H, 7.05; N, 8.91%).

Methyl α-phenylacetamidocrotonates **1b** *and* **2b**

α-ketobutyric acid (20 g) and phenylacetamide (13.5 g) in trichloroethylene (250 ml) gave, after conventional work-up, a solid precipitate (m.p. 188–89°) (11 g), which, after crystallisation from acetone, afforded (*Z*)-α-phenylacetamidocrotonic acid, m.p. 195–96° (5.5 g). Esterification with ether-diazomethane yielded methyl (*Z*)-α-phenylacetamidocrotonate **1b**, m.p. 80–81° (from ether-light petroleum); ν_{max} 3400, 1715, 1695, 1658, 1275 and 700 cm^{-1}; δ 1.71 (3H, d, J7.1 Hz, β-Me), 3.67 (2H, s, CH_2-Ph), 3.69 (3H, s, CO_2Me), 6.70 (1H, q, J7.1 Hz, vinylic), 6.87 (1H, s broad, NH), 7.30 (5H, aromatic). (Found: C, 66.92; H, 6.46; N, 5.94. $C_{13}H_{15}NO_3$ requires: C, 66.93; H, 6.48; N, 6.01%).

The mother liquors from the reaction were evaporated under vacuum to give an oily residue (16.7 g). This residue (1.15 g) was esterified and chromatographed on silica (PLC) [benzene–ethyl acetate (8:2) as eluent] to give methyl (*E*)-α-phenylacetamidocrotonate **2b** (0.13 g), m.p. 66–66.5° (from ether–light petroleum); ν_{max} 3400, 3365, 1722, 1702, 1680, 1265 and 695 cm^{-1}; δ 2.05 (3H, d, J7.5 Hz, β-Me), 3.62 (2H, s, CH_2Ph), 3.71 (3H, s, CO_2Me), 7.13 (1H, q, J7.5 Hz, vinylic), 7.03 (6H, aromatic, NH). (Found: C, 66.99; H, 6.56; N, 5.99. $C_{13}H_{15}NO_3$ requires: C, 66.93; H, 6.48; N, 6.01%).

Methyl α-benzamidocrotonates **1c** *and* **2c**

α-ketobutyric acid (10 g), benzamide (5.86 g) and trichloroethylene (125 ml) gave, after usual work-up, a solid precipitate, m.p. 181–85° (5.68 g), which, after crystallisation from acetone, gave (*Z*)-α-benzamidocrotonic acid, m.p. 192–3° (1.31 g) (lit.[10] 193–5°,[11] 192–3°). Esterification with ether diazomethane yielded methyl (*Z*)-α-benzamidocrotonate **1c**, m.p. 78–9° (from ether–light petroleum) (lit.[12] m.p. 80°,[13] 78–79°); ν_{max} 3400, 1713, 1688, 1660, 1280 and 700 cm^{-1}; δ 1.84 (3H, d, J7.1 Hz, β-Me), 3.76 (3H, s, CO_2Me), 6.88 (1H, q, J7.1 Hz, vinylic), 7.30–8 (6H, aromatic, NH).

From the mother liquors (4.4 g), after esterification with ether-diazomethane and chromatography on silica (PLC) [benzene-ethyl acetate (8:2) as eluent] methyl (*E*)-α-benzamidocrotonate **2c** was recovered, m.p. 107.5–108° (from ether–light petroleum) (0.5 g); ν_{max} 3440 (w), 3400, 1735, 1700, 1670, 1265 and 700 cm^{-1}; δ 2.13 (3H, d, J7.4 Hz, β-Me), 3.86 (3H, s, CO_2Me), 7.20–7.92 (6H, aromatic superimposed on vinylic signal), 8.22 (1H, s, NH). (Found: C, 65.71; H, 6.09; N, 6.31. $C_{12}H_{13}NO_3$ requires: C, 65.74; H, 5.98; N, 6.39%).

General procedure for oxidation of methyl α-acylaminocrotonates

To a solution of methyl α-acylaminocrotonate in methanol (1.25 g/100 ml) was added thallium triacetate (molar ratio 1:3). The mixture was refluxed for three days, cooled, filtered and evaporated under vacuum. The residue was extracted several times with hot ethyl acetate; the hot slurry was filtered each time

and the combined organic solutions were concentrated and then passed through a column of silica (10 g per 1 g of crotonate); the elution (ethyl acetate) was continued until the combined fractions gave, after evaporation, a residue of constant weight. The oily residue was examined by TLC, IR and NMR, then dissolved in methylene chloride (20 ml for 1 g of crotonate), cooled to about −30° in a Dewar flask containing dry-ice and acetone and ozonised until a blue colour appeared. Zinc dust and acetic acid (4 g in 3 ml per 1 g of crotonate) were added to the solution; after stirring for 90 min, the mixture was filtered, evaporated under vacuum and chromatographed on silica (PLC).

Oxidation of methyl (Z)-α-acetamidocrotonate **1a**

1 g of methyl (*Z*)-α-acetamidocrotonate **1a** and thallium triacetate (7.3 g) in methanol (80 ml) gave, after conventional work-up, an oil which was chromatographed on silica (PLC) [benzene–ethyl acetate (1:1) as eluent], to yield the less polar methyl α - methoxy - *R,S* - α - acetamido - β - methoxy - *n* - butyrate **3a** (0.26 g), m.p. 76–77° (from ether–light petroleum), ν_{max} 3418, 1758, 1735, 1692, 1170 and 1100 cm^{-1}; and the more polar diastereoisomer **4a** (0.22 g), m.p. 71–72° (from ether–light petroleum); ν_{max} 3410, 1747, 1731 and 1120 cm^{-1}. (Found **3a**: C, 49.33; H, 7.73; N, 6.46; **4a**: C, 49.41; H, 7.82; N, 6.35. $C_9H_{17}NO_5$ requires: C, 49.30; H, 7.82; N, 6.39%).

Oxidation of methyl (Z) - α - phenylacetamidocrotonate **1b**

0.5 g of methyl (*Z*) - α - phenylacetamidocrotonate **1b** and thallium triacetate (2.45 g) in methanol (40 ml) gave, after the usual work-up, an oil, which was chromatographed on silica (PLC) [benzene–ethyl acetate (8:2) as eluent] to yield the less polar methyl α - methoxy - *R,S* - α - phenylacetamido - β - methoxy - *n* - butyrate **3b** (0.24 g), m.p. 64–65° (from ether–light petroleum), ν_{max} 3410 (shoulder), 3385, 1760, 1735, 1685, 1170, 1100 and 697 cm^{-1}, and the more polar diastereoisomer **4b** (0.22 g), m.p. 80–81° (from ether–light petroleum); ν_{max} 3402, 3380 (shoulder), 1747, 1732, 1685, 1115 and 696 cm^{-1}. (Found **3b**: C, 61.09; H, 7.24; N, 4.76; **4b**: C, 61.09; H, 7.12; N, 4.65. $C_{15}H_{21}NO_5$ requires: C, 61.00; H, 7.17; N, 4.74%).

Oxidation of methyl (Z) - α - benzamidocrotonate **1c**

1 g of methyl (*Z*) - α - benzamidocrotonate **1c** and thallium triacetate (5.22 g) in methanol (80 ml) gave, after the usual work-up, an oil, which was chromatographed on silica (PLC) to afford the mixture (0.53 g) of diastereomeric methyl α - methoxy - *R,S* - α - benzamido - β - methoxy - *n* - butyrates, in 54% and 46% relative amounts (by NMR on the basis of the signals of β-methyl protons, δ 1.21 and 1.34, *J* 7.0 Hz). (Found: C, 59.74; H, 6.83; N, 4.90. $C_{14}H_{19}NO_5$ requires: C, 59.77; H, 6.81; N, 4.98%).

Acetyl-O-methyl-R,S-threonine methyl ester **5a**

Methylation with ether diazomethane of acetyl - *O* - methyl - *R,S* - threonine, prepared according to the procedure of Winitz *et al.*[14] yielded the methyl ester **5a**, m.p. 58–59° (from ether–light petroleum); ν_{max} 3440, 1747, 1680, 1200, 1160 and 1095 cm^{-1}. (Found: C, 50.59; H, 7.87; N, 7.48. $C_8H_{15}NO_4$ requires: C, 50.78; H, 7.99; N, 7.40%).

Acetyl-O-methyl-R,S-allothreonine methyl ester **6a**

O-Methyl-*R,S*-allothreonine was prepared from crotonic acid according to the procedure of West *et al.*[15] and subsequently acetylated, as described previously.[14] Acetyl - *O* - methyl - *R,S* - allothreonine (m.p. 141°) was esterified with ether-diazomethane to afford the methyl ester **6a** as an oil, which failed to crystallise; ν_{max} 3435, 1738, 1680, 1200 and 1086 cm^{-1}. (Found: C, 50.82; H, 8.01; N, 7.59. $C_8H_{15}NO_4$ requires: C, 50.78; H, 7.99; N, 7.40%).

Phenylacetyl-O-methyl-R,S-threonine methyl ester **5b**

Phenylacetyl-*O*-methyl-*R,S*-threonine methyl ester **5b** was prepared in a manner analogous to that employed for **5a**, except that sodium hydroxide was used as the base and phenylacetyl chloride as the acylating agent. The methyl ester crystallised from ether, m.p. 82–83°, ν_{max} 3425, 1748, 1675, 1163, 1092 and 693 cm^{-1}. (Found: C, 63.28; H, 7.17; N, 5.18. $C_{14}H_{19}NO_4$ requires: C, 63.38; H, 7.22; N, 5.28%).

Phenylacetyl-O-methyl-R,S-allothreonine methyl ester **6b**

Phenylacetyl-*O*-methyl-*R,S*-allothreonine methyl ester **6b** was prepared as described above for **6a**, using phenylacetyl chloride and sodium hydroxide. **6b** was obtained as an oil which failed to crystallise; ν_{max} 3422, 1739, 1675, 1200, 1075 and 696 cm^{-1}. (Found: C, 63.20; H, 7.37; N, 5.31. $C_{14}H_{19}NO_4$ requires: C, 63.38; H, 7.22; N, 5.28%).

Methyl acetyl-R,S-α-amino-n-butyrate **7a**

(*Z*)-α-acetamidocrotonic acid (0.3 g) in methanol (30 ml) was hydrogenated over 10% palladium catalyst on C (600 mg) under a pressure of hydrogen slightly greater than one atmosphere and at room temperature, until the absorption corresponded to one molar proportion. The catalyst was removed and the solution evaporated under reduced pressure, to yield acetyl - *R,S* - α - amino - *n* - butyric acid, m.p. 129–31° (from acetone) (lit.[16] m.p. 129–31°). The acid was methylated with ether–diazomethane to give methyl acetyl - *R,S* - α - amino - *n* - butyrate **7a**, m.p. 44–45° (from di-isopropyl ether); ν_{max} 3422, 3330 (broad), 1731, 1678, 1200 and 1150 cm^{-1}; δ 0.91 (3H, t, *J* 7.1 Hz, β-Me), 1.8 (2H, m, CH_2), 2.02 (3H, s, CO-Me), 3.68 (3H, s, CO_2Me), 4.5 (1H, m, CH), 6.43 (1H, broad signal, NH). (Found: C, 49.84; H, 8.42; N, 8.27. $C_7H_{13}NO_3\frac{1}{2}H_2O$ requires: C, 49.94; H, 8.32; N, 8.32%).

Hydrogenolyses of **3a** *and* **4a**

Hydrogenolyses of **3a** and **4a** were effected by dissolving the dimethoxy compounds (0.3 g) in acetic acid (50 ml), using 10% Pd on C as catalyst (0.6 g) at 60° and under 46 p.s.i., for one day in a Parr apparatus. The catalyst was filtered and the solutions evaporated under vacuum. The residues were chromatographed on silica (PLC). Two fractions were eluted with (1:1) benzene–ethyl acetate and examined by NMR and IR spectra. The less polar fraction (0.11 g from **3a**, 0.12 g from **4a**) was a mixture of **7a** and **5a** (molar ratio 3:1); the more polar fraction (0.09 g from **3a**, 0.04 g from **4a**) resulted to be fairly pure **4a**.

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