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THE RESOLUTION OF RACEMIC 2-ALKYL-1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACIDS

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Abstract: Practical procedures for the resolution of racemic modification of (1R, 2S)- and (1S, 2R)-1-amino-2-ethylcyclopropane-1-carboxylic acid 1a,b ,(1R, 2S)- and (1S, 2R)-1-amino-2-methylcyclopropane-1-carboxylic acid 2a,b, and (1R, 2R)- and (1S, 2S)-1-amino-2-methylcyclopropane-1-carboxylic acid 3a,b are described; the structures as 1a,2a, and 3a were confirmed by X-ray crystallographic methods.

In the preceding paper[1] we described a convenient synthesis of the racemic forms of 2-alkylated-1-aminocyclopropane-1-carboxylic acids 1a,b, 2a,b, and 3a,b. In order to develop our studies on ethylene biosynthesis[2,3] we required reliable[4] methods for the resolution of these amino-acids so that they may be tested as substrates or competitive inhibitors of the ethylene synthetase system found in apple tissue.

Initially, the racemates 1a,b, 2a,b, and 3a,b were converted to their N-chloroacetyl derivatives and tested as substrates for Porcine Kidney Acylase I[5]. By following the reaction by N.M.R. spectroscopy it was shown that only 4b was selectively hydrolysed by this enzyme.[6] Standard work up of the crude product from 4a,b gave (1S, 2S)-3b, $[\alpha]^{20}_{D}$+44° (C = 1.0, H_2O), δH(300MHz, D_2O) as described[1], and unreacted 4a. Acidic hydrolysis (6M HCl, reflux, 6h.) of 4a and purification by ion-exchange [Dowex 50W X 8(H)] gave (1R, 2R)-3a, $[\alpha]^{20}_{D}$ -42° (C = 1.4, H_2O), δH(300MHz, D_2O) as described.[1] The structure of the chloroacetyl derivative as (1R, 2R)-4a was confirmed by X-ray crystallographic analysis of the crystals from ethylacetate/hexane (figure 1).

Crystal Data: $C_7H_{10}NO_3Cl$, m = 200.0, Monoclinic, space group $P2_1$, a = 5.961(1) b = 10.066(4), c = 7.424(1) Å, β = 90.35(1)°, U = 445.2 Å^3, Z = 2,D_C = 1.43 cm^{-1}. 1568 independent reflections (0 < 2θ < 55°) gave 1461 observed reflections (I > 3 σ(I)). The structure was solved by Patterson and electron density methods. The Final R value is 0.030 (R_w 0.038). All data were measured on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.71069 Å). Refinement was by full matrix least squares in all cases.[7] The absolute configuration in 4a was determined by including a polarity parameter[8] in the refinement which converged to 0.97(13), thus showing that the molecule illustrated in Fig.1

to have the correct absolute configuration. This was confirmed by the careful measurement of 22 Friedel pairs followed by the application of Bijvoet's method.[9]

As the enzymic method failed for the resolution of the racemates 1a,b and 2a,b an alternative chemical method was sought. Thus the racemate 1a,b was converted to its amine hydrochloride methyl ester (MeOH, HCl(g), 50°, 18h.) which was coupled with S-(+)-2-hydroxy-2-phenylacetic acid [N-Ethoxycarbonyl-2-ethoxy-1,2 dihydroquinoline (EEDQ) (2 equivs.)[10], triethylamine (1 equiv.), dichloromethane, 18h.] to the diastereoisomeric derivatives 5a,b (75% from 1a,b), δH(300MHz, C^2HCl_3)[11] 3.62, 3.64 p.p.m. (2x3H, 2xs, $2xCO_2Me$). Double recrystallisation (from ethyl acetate/hexane) gave the essentially pure diastereoisomer 5a, m.p. 153-4°, $[\alpha]_D^{20}$ +113° (C = 1.5, EtOH), δH(300MHz, C^2HCl_3) 0.94-1.00(1H, m, 3-H), 0.98(3H, t, J 8Hz, $2\text{-}CH_2\underline{CH_3}$), 1.10-1.25(1H, m, $2\text{-}C\underline{H_2}CH_3$), 1.31(3H, t, J 7Hz, $OCH_2\underline{CH_3}$), 1.44-1.55(1H, m, $2\text{-}C\underline{H_2}CH_3$), 1.70-1.78(2H, m, 2,3-H), 3.64(3H, s, CO_2Me), 4.19-4.27(2H, ca dq, $OC\underline{H_2}CH_3$), 6.00(1H, s, CHPh), 6.66(1H, s, NH), and 7.36-7.53(5H, m, Ph-H), m/e (ammonium chemical ionisation) 336(MH^+, 100%), which upon acid hydrolysis and ion-exchange gave[12] 1R,2S-1a $[\alpha]_D^{20}$ +65° (C = 1.3, H_2O), δH(300MHz, D_2O) as described.[1] The structure as 5a was confirmed by X-ray crystallographic methods (Figure 2).

Crystal Data: $C_{18}H_{23}NO_6$, m = 349.4, Orthorhombic, space group $P2_12_12_1$, a = 9.895(2), b = 10.381(3), c = 18.405(5) Å, U = 1890.6 Å^3, Z = 4, D_c = 1.23g cm^{-3}. 1904 independent reflections ($0 < 2\theta < 50°$) gave 1448 observed reflections ($I > 2\ \sigma(I)$). The structure was solved by direct methods[13] and the final R value is 0.034(R_w 0.041).

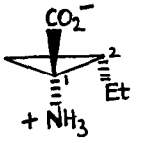
By similar means, the amine hydrochloride methyl ester from 1a,b was coupled with R-(-)-2-hydroxy-2-phenylacetic acid to yield 6a,b (79% from 1a,b). Double recrystallisation gave the essentially pure diastereoisomer 6b m.p. 154-5°, $[\alpha]_D^{20}$ -109° (C = 1.8, EtOH), which upon acidic hydrolysis and ion-exchange gave (1S, 2R)-1b, $[\alpha]_D^{20}$ -67° (C = 1.5, H_2O), δH(300MHz, D_2O) as described.[1]

An identical operation was used to resolve the racemate 2a,b. Thus 2a,b was converted to its amine hydrochloride methyl ester form which was coupled, as before, with S-(+)-2-hydroxy-2-phenylacetic acid to the diastereoisomeric derivatives 7a,b (85% from 2a,b) δH(300MHz, C^2HCl_3) 1.06(3H, d, J 6Hz, 2-Me) 1.155(3H, d, J 6Hz, 2-Me), 3.62, 3.64(2x3H, 2xs, $2xCO_2Me$). Double recrystallisation (from ethyl acetate/hexane) gave the essentially pure diastereoisomer isomer 7a, m.p. 139-40°, $[\alpha]_D^{20}$ +106° (C = 3.1, EtOH), δH(300MHz, C^2HCl_3) 0.88(1H, dd, J 5,7Hz, 3-H), 1.06(3H, d, J 6Hz, 2-Me), 1.31(3H, t, J 7Hz, $OCH_2\underline{CH_3}$), 1.69-1.83(2H, m, 2,3-H), 3.64(3H, s, CO_2Me), 4.18-4.26(2H, ca dq, $OC\underline{H_2}CH_3$), 6.00(1H, s, CHPh), 6.70(1H, s, NH) and 7.36-7.39, 7.49-7.52 (5H, m, Ph-H), m/e (ammonium desorption chemical ionisation) 350(MH^+, 100%), which upon acidic hydrolysis and ion-exchange gave (1R, 2S)-2a, $[\alpha]_D^{20}$ +73.5 (C = 0.4, H_2O), δH(300MHz, D_2O) as described.[1] The structure as 7a was confirmed by X-ray crystallographic methods (Figure 3).

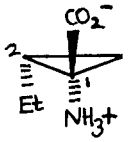
Crystal Data: $C_{17}H_{21}NO_6$, m = 335.4, orthorhombic, space group $P2_12_12_1$ a = 9.765(6) b = 10.140(2), c = 18.482(4) Å, U = 1830.0 Å^3, Z = 4, D_c = 1.22g cm^{-3}. 1845 independent reflections ($0 < 2\theta < 50°$) gave 1225 observed reflections ($I > 2\ \sigma(I)$). The structure was solved by direct methods[13]. The current R value is 0.050(R_w = 0.060).

When the amine hydrochloride methyl ester from 2a,b was coupled with R-(-)-2-hydroxy-2-phenylacetic acid, a mixture of 8a,b (89% from 2a,b) was formed. Double recrystallisation gave the essentially pure diasteroisomer 8b, m.p. 139-40°, $[\alpha]_D^{20}$ -104° (C = 3.0 in EtOH), which upon acidic hydrolysis and ion-exchange gave (1S, 2R)-2b, $[\alpha]_D^{20}$ -69° (C = 0.3, H_2O), δH(300MHz, D_2O) as described.[1]

We wish to thank the S.E.R.C. for support (to B.J.R.).



1a (1R,2S)



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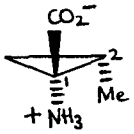
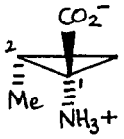
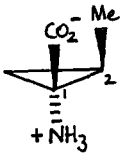


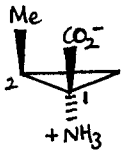
2a (1R,2S)



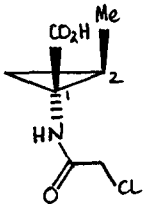
2b (1S,2R)



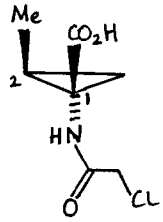
3a (1R,2R)



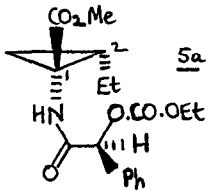
3b (1S,2S)



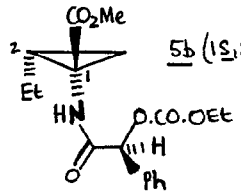
4a (1R,2R)



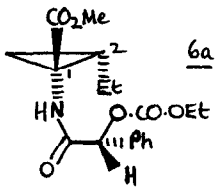
4b (1S,2S)



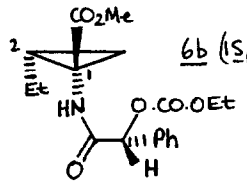
5a (1R,2S)



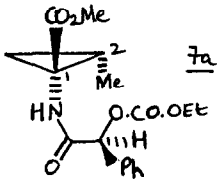
5b (1S,2R)



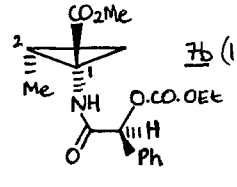
6a (1R,2S)



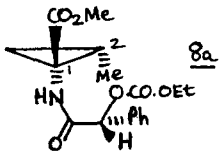
6b (1S,2R)



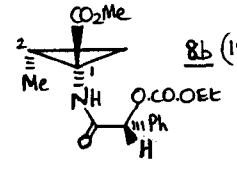
7a (1R,2S)



7b (1S,2R)



8a (1R,2S)



8b (1S,2R)

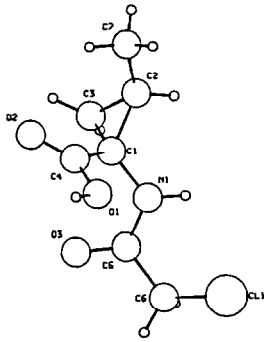


Figure 1.

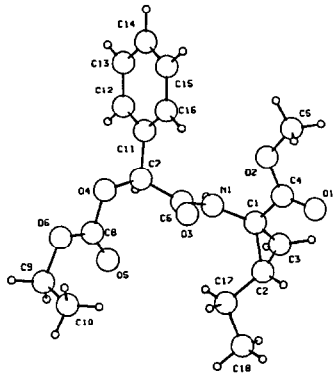


Figure 2.

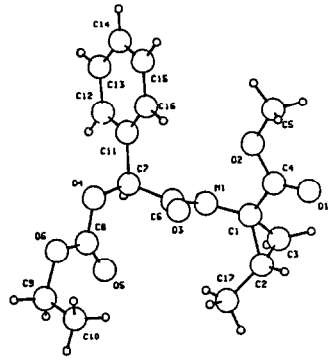


Figure 3.

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1. J. E. Baldwin, R. M. Adlington, and B. J. Rawlings, Tetrahedron Lett., preceding paper.

2. R. M. Adlington, R. T. Aplin, J. E. Baldwin, B. J. Rawlings, and D. Osborne, J.Chem. Soc.,Chem.Commun, 1982, 1086.

3. R. M. Adlington, J. E. Baldwin, and B. J. Rawlings, J.Chem.Soc.,Chem.Commun., 1983, 290.

4. A report of the resolution of (±) allocoronamic acid (1a,b) into its (+) (1S, 2R) $[\alpha]_D^{23}$ +65.0° (C = 1.83, H_2O) and (-)(1R, 2S) $[\alpha]_D^{21}$ -68.4° (C =1.15, H_2O) forms [A. Ichihara et al, Agric.Biol.Chem., 1977, 41, 2497] in which the absolute configurations were assigned "by application of the sector rule in ORD" was subsequently reversed by the same author (A. Ichihara et al, Tetrahedron Lett., 1979, 365). However conclusive proof of the correct absolute configuration by X-ray crystallographic methods was not reported.

5. Obtained from Sigma Chemical Company, Poole, Dorset, BH17 7NH, England, order number A 3010, Acylase 1, grade 1, Activity 2,000-3,000 units per mg protein.

6. The chloroacetyl derivatives were incubated with Acylase 1 at pH 7-7.5, 37°, for 12h. Direct n.m.r. analysis (500MHz, D_2O) showed the presence of 3b δH 0.97(3H, d, J 6Hz, 2-Me) and unreacted 4a, δH 0.92(3H, d, J 6Hz, 2-Me) ratio ca 1:1. The chloroacetyl derivatives of 1a,b and 2a,b were not substrates for this enzyme. Hence in these cases, the C(2) alkyl group which is cis- to the amide function must seriously retard the enzymatic rate of amide hydrolysis. The selective enzymatic hydrolysis of 4b over 4a was expected as this entantiomer contains the 1S-aminoacid configuration.

7. D. J. Watkin, and J. R. Carruthers, CRYSTAL Manual, Chemical Crystallography Laboratory, University of Oxford, 1981.

8. D. Rodgers, Acta.Cryst., 1981, A37, 734

9. J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, Nature, 1951, 168, 271.

10. EEDQ (2 equivs.) was used both to form the amide bond and to convert the free hydroxy function to an ethyl carbonate group.

11. N.M.R. shifts in deuteriochloroform are referenced to $CHCl_3$ = 7.27 p.p.m.

12. S-(+)-2-Hydroxy-2-phenylacetic acid was recovered after hydrolysis with identical ^1H n.m.r. spectrum and optical rotation $[\alpha]_D^{20}$ +146 (C = 2.5, EtOH) to that initially used $[\alpha]_D^{20}$ +150 (C = 1.5,EtOH) to form 5a,b.

13. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declerq, and M. M. Woolfson, MULTAN 80, A system of computer programs for the solution of crystal structures from X-ray diffraction data, Department of Physics, University of York, England, 1980. The atomic co-ordinates for Figure 1,2,3 are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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