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The mono-(*S*)-α-methylbenzylammonium salt of (*R*)-homocitric lactone

Yunhua Jia,[a] David R. J. Palmer[a] and J. Wilson Quail[b]*

[a]Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan, Canada S7N 5C9, and [b]Saskatchewan Structural Sciences Centre, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan, Canada S7N 5C9

Correspondence e-mail: wilson.quail@usask.ca

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.004 Å
R factor = 0.042
wR factor = 0.097
Data-to-parameter ratio = 9.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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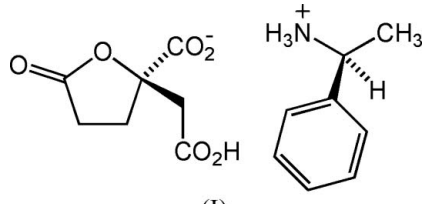
The title salt, (*S*)-α-methylbenzylammonium (*R*)-2-carboxymethyl-5-oxofuran-2-carboxylate, $C_8H_{12}N^+\cdot C_7H_7O_6^-$, was crystallized by resolution of a racemic mixture of lactones as the diastereomeric salt to separate the *R* anion, which is formed by the loss of a proton from the carboxylic acid group on the 2-position of the lactone ring. The crystal structure has a packing index of 69.5%, indicating very efficient packing.

Comment

The title compound, (I), can be hydrolyzed to (*R*)-homocitrate, which is a natural product found in the active site of nitrogenase as part of the FeMo active site (Hoover *et al.*, 1989), and is also an intermediate in the α-aminoadipate pathway of lysine biosynthesis in fungi, archaea, and in the thermophilic bacterium *Thermus thermophilis* (Andi *et al.*, 2004; Wulandari *et al.*, 2002). There have been previous reports describing the synthesis of optically active homocitric lactones (Rodriguez & Biellmann, 1996; Ancliff *et al.*, 1997) and, during the course of the present work, two more were published (Paju *et al.*, 2004; Xu *et al.*, 2005).



(I)

The crystal structure of (I) clearly shows that the anion is formed by loss of the H atom from the carboxylic acid group attached directly to the lactone ring. The carboxylic acid group separated by a methylene from the lactone ring still has an H atom, which is involved in hydrogen bonding.

Table 1 gives details of the classical and non-classical hydrogen bonds in the structure of (I). All H atoms on N and O are involved in hydrogen bonding to O atoms, and all O atoms are hydrogen-bond acceptors to O—H, N—H or C—H units. The high extent of hydrogen bonding must be significant in the stereoselective formation of the title compound. When the structure is examined with *PLATON* (Spek, 2003) using the KPI (Kitaigorodski packing index) function, the structure is found to have 0% of its volume available for solvent molecules and to have a packing index of 69.5%, well above the typical value of 65% cited in the *PLATON* documentation, indicating that the structure is very efficiently packed. Since both ions are chiral, it is unlikely that the mirror image of the anion could pack as efficiently and make use of all the potential hydrogen bonds.

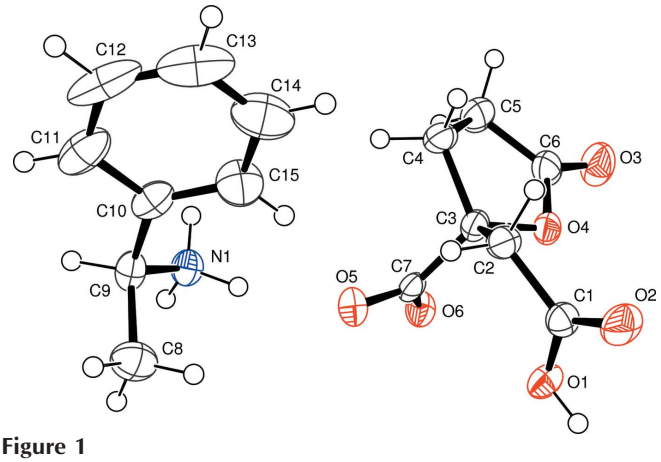


Figure 1
A view of the salt, (I), with displacement ellipsoids drawn at the 50% probability level.

Experimental

Because we required both enantiomers of homocitrate for our work studying the enzyme homoaconitase, we chose to synthesize racemic homocitric lactone and resolve the enantiomers as diastereomeric salts using α-methylbenzylamine as the resolving agent. Our synthesis of racemic homocitrate is more direct than the previously reported method of Ancliff *et al.* (1997), namely a Reformatsky reaction of ethyl bromoacetate with diethyl 2-oxoglutarate, followed by saponification of the resulting triester, and lactonization in acid. The use of α-methylbenzylamine to resolve similar compounds has been reported, but this is the first use of the technique on homocitric lactone itself. The overall yield of about 43% for the fractional crystallization [about 23% and 20% for the (*R*)- and (S)-lactones, respectively] is similar to that observed with related lactones. The salt is easily converted to the sodium salt of (*R*)-homocitrate by treatment with aqueous 3% NaOH and extraction of the resulting solution with CH_2Cl_2 to remove the organic amine.

To prepare racemic homocitric acid triethyl ester, activated powdered zinc (32.3 g, 0.50 mmol) was added to a 500 ml three-necked flask equipped with a 250 ml dropping funnel, a reflux condenser and a magnetic stirrer bar. The system was flushed with argon for 5 min. A solution of ethyl bromoacetate (57 ml, 0.51 mmol) and 2-oxoglutarate diethyl ester (35 g, 0.17 mmol) in dry benzene (35 ml) and absolute diethyl ether (21 ml) was added to the dropping funnel. About 5 ml of this solution was added dropwise on to the zinc powder and the flask was warmed in an oil bath (333 K) until the reaction started. The mixture was then stirred and the rest of solution was slowly added. The addition took about 1.5 h. The reaction mixture was further refluxed for 20 h in an oil bath. The flask was then cooled in an ice bath and the reaction mixture was quenched by the addition of cold 10% H_2SO_4 (175 ml) with vigorous stirring. The acid layer was drawn off and the benzene solution extracted twice with 5% H_2SO_4 (45 ml), then washed with 10% Na_2CO_3 (25 ml), 5% H_2SO_4 (25 ml) and twice with water (25 ml). The combined acid solutions were extracted twice with Et_2O (50 ml). The combined organic solutions were dried with Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by distillation under reduced pressure, resulting in a yellow oil. The oil was further purified by silica-gel flash chromatography (hexane–EtOAc–MeOH = 300:50:0.5) and 29.1 g of product was isolated as a pale-yellow oil (58% yield). Spectroscopic analysis: ^{1}H NMR (500 MHz, $CDCl_3$, δ, p.p.m.): 4.23–4.27 (2H, *m*), 4.10–4.14 (4H, *m*), 3.75 (1H, *s*), 2.93 (1H, *d*, *J* = 16 Hz), 2.67 (1H, *d*, *J* = 16 Hz), 2.50 (1H, *m*), 2.25 (1H, *m*), 2.03–2.07 (2H, *m*), 1.32 (3H, *t*, *J* = 7 Hz), 1.24 (3H, *t*, *J* = 7 Hz), 1.23 (3H, *t*, *J* = 7 Hz).

To prepare racemic homocitric lactone, homocitric acid triethyl ester (10.0 g, 0.34 mol) was added dropwise to 3% NaOH (250 ml) in an ice bath. The mixture was stirred for 2 h at room temperature and then 1*M* HCl was added, adjusting the pH to 1, and the solution concentrated at reduced pressure at 333–343 K on a rotary evaporator to yield a light-yellow solid. The crude product was extracted with acetone and insoluble NaCl was removed by filtration. The acetone solution was evaporated to yield 5.84 g of a light-yellow solid. The crude product was recrystallized from boiling EtOAc, to which hexane was added dropwise until the solution became cloudy, to give 3.6 g of white crystals (62%) (m.p. 431–433 K). ^{1}H NMR (500 MHz, D_2O, δ, p.p.m.): 3.24 (1H, *d*, *J* = 17.5 Hz), 2.92 (1H, *d*, *J* = 17.5 Hz), 2.64–2.60 (2H, *m*), 2.43 (1H, *m*), 2.32 (1H, *m*).

The homocitric lactones were resolved with α-methylbenzylamine. To racemic homocitric lactone (2.4 g, 12.8 mmol) was added absolute ethanol (100 ml) in a 250 ml round-bottomed flask. The mixture was refluxed to yield a transparent solution. The solution was concentrated to 15 ml and then (*S*)-α-methylbenzylamine (1.55 g, 12.8 mmol) was added. Several drops of Et_2O were added and crystals formed immediately. These crystals were collected and recrystallized from ethanol (25 ml), giving flattened needle crystals of (I) (882 mg, 45% yield, m.p. 457–459 K). ^{1}H NMR (500 MHz, D_2O, δ, p.p.m.): 7.42–7.35 (5H, *m*), 4.45 (1H, *q*, *J* = 7.0 Hz), 3.09 (1H, *d*, *J* = 16.5 Hz), 2.82 (1H, *d*, *J* = 16.5 Hz), 2.59–2.56 (2H, *m*), 2.35–2.22 (2H, *m*), 1.55 (3H, *d*, *J* = 7.0 Hz).

The combined mother liquor was concentrated and refluxed to give a saturated solution. On standing, very fine crystals were formed, which were enriched in the (*S*,*S*)-diastereomer. This process was repeated several times to obtain as much solid as possible. The combined solid (1.24 g, 4 mmol) was treated with 3% NaOH (16 ml, 3 equivalents) and extracted with dichloromethane. The aqueous solution was titrated with 1*M* HCl until the pH was 1 and then concentrated on a rotary evaporator at 338–343 K to give a residue [lactone, (*S*)-isomer enriched]. The residue was dissolved in acetone and filtered to remove NaCl, and then concentrated to dryness (0.75 g, 3.99 mmol). This (*S*)-enriched lactone was completely dissolved in absolute ethanol (10 ml) and then (*R*)-α-methylbenzylamine (0.48 g, 3.97 mmol) was added. On standing, flattened needle crystals of the mono-(*R*)-α-methylbenzylammonium (*S*)-homocitrate salt were formed (810 mg, 20.5%, m.p. 459–461 K). The overall yield of the resolution was 43% (both enantiomers).

Crystal data

$C_8H_{12}N^+\cdot C_7H_7O_6^-$
M_r = 309.31
Orthorhombic, $P2_12_12_1$
a = 7.4654 (2) Å
b = 9.9907 (3) Å
c = 20.3404 (5) Å
V = 1517.01 (7) Å^3
Z = 4
D_x = 1.354 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 1979 reflections
θ = 1.0–27.5°
μ = 0.11 mm^{-1}
T = 173 (2) K
Plate, colourless
0.20 × 0.10 × 0.02 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans and ω scans with κ offsets
Absorption correction: none
21123 measured reflections
1998 independent reflections
1666 reflections with $I > 2\sigma(I)$
R_{int} = 0.098
θ_{max} = 27.5°
h = −9 → 9
k = −12 → 12
l = −26 → 26

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0389P)^2 + 0.3713P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.097$	$\Delta\rho_{max} = 0.17$ e Å^{-3}
$S = 1.10$	$\Delta\rho_{min} = -0.19$ e Å^{-3}
1998 reflections	
202 parameters	
H-atom parameters constrained	

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···O6^{i}	0.84	1.76	2.600 (2)	173
N1—H1A···O2^{ii}	0.91	2.43	2.965 (3)	118
N1—H1A···O3^{iii}	0.91	2.12	2.887 (3)	142
N1—H1B···O6^{iv}	0.91	1.94	2.815 (3)	160
N1—H1C···O5	0.91	1.94	2.839 (3)	170
C2—H2B···O5	0.99	2.52	2.867 (3)	100
C4—H4A···O3^{iii}	0.99	2.53	3.404 (3)	147
C5—H5A···O4^{iii}	0.99	2.43	3.315 (3)	149
C12—H12···O6^{v}	0.95	2.59	3.496 (3)	159
C13—H13···O1^{vi}	0.95	2.56	3.334 (4)	139
C15—H15···O5	0.95	2.31	3.226 (3)	163

Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $x, y+1, z$; (iii) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (v) $-x+\frac{1}{2}, -y+1, z-\frac{1}{2}$; (vi) $x-\frac{1}{2}, -y+\frac{1}{2}, -z$.

The absolute configuration of the α-methylbenzylamine was known. The data were collected with Mo radiation and there are no atoms with atomic number greater than eight in the compound. Thus, all Friedel pairs were averaged in processing the data. All H atoms, including the $-NH_3^+$ and –OH H atoms, were found in difference Fourier maps. They were placed in calculated positions, with C—H distances in the range 0.95–0.99 Å, N—H distances of 0.91 Å and an O—H distance of 0.84 Å, and included in the refinement in the riding-model approximation, with $U_{iso}(H) = 1.2U_{eq}$ of the carrier atom for aromatic H and $1.5U_{eq}$ of the carrier atom for all other H.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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