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Synthesis of *R*- and *S*-3-Oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid.

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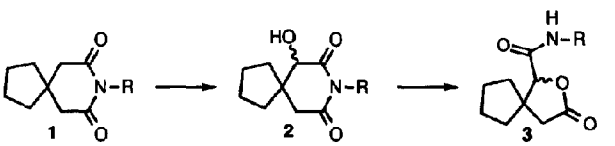
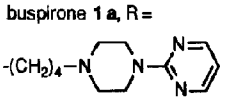
Abstract: An efficient synthesis and temperature dependent resolution of *R*- and *S*-3-Oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid are described. The assignment of absolute configuration is based on single crystal X-ray analysis of an amide derivative.

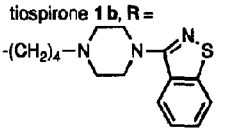
The 3,3-tetramethylene glutarimide moiety **1** is of interest in the CNS area due to drugs such as buspirone[1] **1a** and tiospirone[2] **1b** which are serotonergic anxiolytics. Recent work from Bristol-Myers Squibb has described biologically active metabolites of these compounds which involve hydroxylation in the glutarimide group **2** as well as a lactone rearrangement derivative **3**.[3] The stereochemistry at the oxygenated carbon was not defined in either case.



buspirone **1a**, R =



tiospirone **1b**, R =

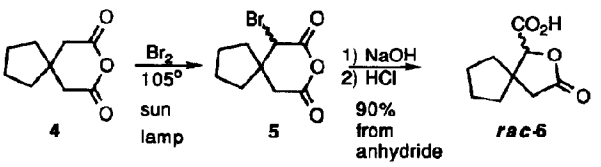


The only synthesis in the literature for these hydroxylated 3,3-tetramethylene-glutaramide analogues involved the hydroxylation of the enolates of **1a** or **1b** to provide **2a** or **2b** followed by KF-Al_2O_3 catalyzed rearrangement to obtain **3a** or **3b**.[3] In this paper we describe a simple synthesis and resolution of 3-oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid **6** as a potential precursor to these compounds.

The synthesis of the racemic lactone is shown in the Scheme and was similar to that of Ingold for the preparation of the lactone of α-hydroxyglutaric acid.[4] Anhydride **4** was melted under

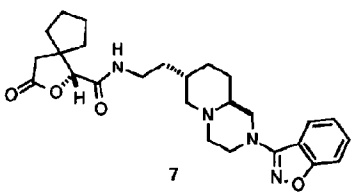
nitrogen and irradiated with a sun lamp while 1.3 equivalents of bromine were added. The crude α-bromoanhydride **5** was refluxed with excess sodium hydroxide to provide the lactone *rac*-**6** upon acidification.

Scheme

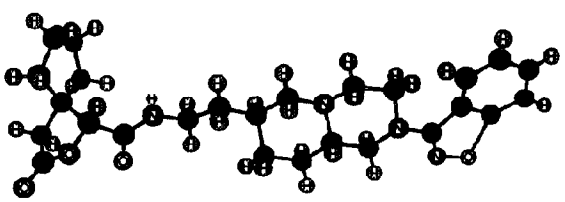


The resolution of **6** was accomplished with ephedrine from ethyl acetate and was temperature dependent. Crystallization at room temperature provided the racemic salt, while crystallization at ca. 40°C or above afforded one diastereomeric salt.[5] This type of temperature dependent resolution was classified as a double salt by Jacques et al.[6] The optical purity of the ephedrine salts was monitored by NMR in $CDCl_3$ solution with ephedrine acting as a chiral shift reagent.

The absolute configuration of **6** was determined by single crystal X-ray analysis of amide derivative **7** prepared from (−)-**6** with an optically active amine[7] of known absolute configuration. This showed that the levorotatory acid (−)-**6** (obtained with (+)-ephedrine) had the *R*- configuration while the dextrorotatory acid (+)-**6** (isolated using (−)-ephedrine) had the *S*- configuration.



7



Structure of compound **7**.[8]

Experimental:

3-Oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid ***rac*-6**.

3,3-Tetramethylene glutaric anhydride (5 g, 30 mmol) was heated to 105°C and irradiated with a sun lamp while bromine (2 mL, 38.7 mmol) was added dropwise. After the bromine color dispersed, the reaction was allowed to cool to room temperature, 2.4M NaOH (50 mL) was added and the mixture was heated to reflux for 2 h. The solution was allowed to cool to room temperature, the pH was adjusted to pH 1 with 3N HCl and the reaction was stirred in an ice water bath for 0.5 h. The precipitate (3,3-tetramethylene glutaric acid) was filtered and discarded. The filtrate was extracted three times with ethyl acetate and the combined organics were washed with brine and dried over $MgSO_4$. Evaporation yielded the title acid as a colorless oil, 5 g, 90%. NMR ($CDCl_3$, 300 MHz) δ 7.95 (broad s, OH), 4.65 (s, 1, methine) 2.61 and 2.35 (ab, 2, methylene), 1.9 - 1.45 (m, 8, tetramethylene).

(−)-3-Oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid *R*-6 and (+)-3-oxo-2-oxaspiro[4.4]-nonane-1-carboxylic acid *S*-6.

The racemic acid (6.65 g, 36.1 mmol) and d-(+)-ephedrine (6.03 g, 36.2 mmol) in ethyl acetate (175 mL) were heated at 40-50°C with an oil bath until crystallization occurred; crystallization at room temperature gave the racemic mixture. After crystallization at >40°C, the reaction was stirred for 0.5 h while cooling to room temperature and the precipitated salt was filtered; 2.65 g, 21% yield; mp 161-3°C; $[\alpha]_D$ −6.47 (c = 0.51, MeOH). NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 5), 5.33 (s, 1), 4.63 (s, 1), 3.40 (m, 1), 2.80 (s, 3), 2.53 and 2.32 (ab, 2), 2.02 - 1.40 (m, 8), 1.09 (d, 3). Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.19; H, 7.78; N, 4.01. The optical purity of the salt was determined from its proton nmr spectrum. The mixture of diastereomeric salts with ephedrine showed two singlets at δ 4.63 and 4.70 and two ab patterns centered at δ 2.45. In the resolved salt isolated above, only one singlet and one ab group were observed indicating < 2% of the diastereomeric salt was present.

The d-(+)-ephedrine salt of the levorotatory acid (1.6 g, 4.6 mmol) was dissolved in water (10 mL) and the pH lowered to pH 2 with 2N HCl. The acid solution was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to provide the levorotatory acid *R*-6 as a colorless oil; 0.84 g, 100% yield. $[\alpha]_D$ −30.76 (c = 0.998, $CHCl_3$). NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1), 4.69 (s, 1, methine), 2.64 and 2.39 (ab, 2, methylene), 1.94 - 1.55 (m, 8).

Racemic acid (4.81 g, 26 mmol) recovered from the filtrate from the first resolution and l-(−)-ephedrine (4.3 g, 26 mmol) in 125 mL ethyl acetate at 40-50°C as above provided the (−)-ephedrine salt of the (+)-acid *S*-6; 3.24 g, 36% yield. mp 160-3°C; $[\alpha]_D$ +4.96 (c = 0.565, $CHCl_3$). Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.39; H, 7.64; N, 4.06.

The salt (1.65 g, 4.73 mmol) was treated as described for the enantiomer to afford ***S*-6** in quantitative yield as an oil; $[\alpha]_D$ +29.63 (c = 0.999, $CHCl_3$).

(–)-3-Oxo-N-[2-[7-(2-(3-(1,2-benzisoxazolyl))-2,3,4,6,7*S*,8,9,(9a*S*)-octahydro-1H-pyrido[1,2-a]pyrazinyl)]-ethyl]2-oxaspiro-[4,4]-nonane-1*R*-carboxamide **7.**

Acid ***R*-6** (190 mg, 1.03 mmol) and (–)-(7*S*,9a*S*)-7-(2-aminoethyl)-2-(benzo[d]isoxazol-3-yl)-perhydro-1H-pyrido[1,2-a]pyrazine[7] (316 mg, 1.05 mmol) were combined in methylene chloride (10 mL) with N-methylmorpholine (0.16 mL, 1.46 mmol). To the resulting suspension was added n-propanephosphoric acid cyclic anhydride (1.28 g, 2 mmol, 50% by weight in methylene chloride). After stirring at room temperature overnight, the reaction was washed with water, with brine and was dried over $MgSO_4$. The crude product was purified by chromatography over silica gel with ethyl acetate as eluant followed by crystallization from isopropanol. The yield was 0.25 g, 48%. mp 128-9°C; $[\alpha]_D$ – 14.76 (c = 0.42, CH_2Cl_2). ^{13}CMR ($CDCl_3$, 300 MHz) δ 174.503, 167.348, 163.971, 161.061, 129.512, 122.270, 122.146, 116.128, 110.479, 83.586, 61.316, 60.087, 54.126, 53.692, 50.861, 48.225, 43.000, 36.528, 36.415, 34.254, 33.788, 32.600, 30.282, 29.250, 24.024, 23.429.

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References and Notes:

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3 Buspirone: Jajoo, H. K.; Mayol, R.F.; LaBudde, J. A.; Blair, I. A. *Drug Metabolism and Disposition*, **1989**, *17*, 634. Tiospirone: Cipollina, J. A..; Ruediger, E. H.; New, J.S.; Wire, M. E.; Shepherd, T. A.; Smith, D. W.; Yevich, J. P. *J. Med. Chem.*, **1991**, *34*, 3316.
4 Ingold, C. K. *J. Chem. Soc.*, **1921**, *119-T1*, 305.
5 The exact transition temperature for this resolution has not been determined. When the acid *rac*-6 and ephedrine were dissolved in ethyl acetate at room temperature the racemic salt precipitated. This mixture was heated to 40-50°C which redissolved the racemic salt followed by crystallization of the resolved salt.
6 Jacques, J.; Collet, A. ;Wilen, S. A. Enantiomers, Racemates and Resolutions, John Wiley and Sons., N.Y., **1981**, p 295 -299.
7 Bright, G. M.; Desai, K. A.; Seeger, T. F.; Smolarek, T. A. World Patent Appl. WO 9306101-A1 (**1993**).
8 The structure of compound **7** was drawn in CSC Chem3D Plus™ with the experimentally determined X-ray coordinates. The X-ray data has been submitted to the Cambridge Crystallographic Data Centre.

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