Santonic acid: Zn–HCl–ether reduction and ceric ammonium nitrate oxidation

Kamlesh Pai Fondekar, Bhiwa Malik and Shashikumar Keshav Paknikar*

Department of Chemistry, Goa University, Talegaon Plateau, Goa 403206, India

(Received 19 October 2013; final version received 20 May 2014)

Reduction of santonic acid using Zn–HCl–ether yielded succinic anhydride derivatives via pinacolisation followed by rearrangement, whereas oxidation of santonic acid using ceric ammonium nitrate afforded five oxidative decarboxylation products.

Keywords: santonic acid; Zn–HCl–ether reduction; ceric ammonium nitrate oxidation; oxidative decarboxylation; bicyclo[3.3.0]octane

1. Introduction

(–)-α-Santonin (1, Figure 1), a naturally occurring sesquiterpene lactone, is an attractive starting material for the synthesis of several natural products, transformational studies and stereochemical correlations (Paknikar et al. 1994; Furtado et al. 1998; Blay et al. 2004; Natarajan et al. 2007; Arantes et al. 2009; Lamm et al. 2009; Li et al. 2010). (–)-Santonic acid (2, Figure 1), easily accessible in a single step from (–)-α-santonin (Birladeanu 2003) has, however, been explored to a very limited extent (Hortmann et al. 1968; Hortmann & Daniel 1972; Naik et al. 1987; Moyano et al. 2005; Williams et al. 2008). (–)-Santonic acid (2) appears to be a good precursor for bicyclic skeletons present among natural products.

An aim of this work was to seek entry into bicyclo[3.3.0]octane systems using Zn–HCl–ether reduction (Toda et al. 1972) to obtain pinacol (3) (Figure 1) followed by acid-catalysed molecular rearrangement. Entry into bicyclo[4.3.0]nonane skeleton has been reported (Hortmann & Daniel 1972; Naik et al. 1987), and it was our interest to explore an alternate entry into this skeleton via oxidation of 2 with ceric ammonium nitrate (CAN).

2. Results and discussion

(–)-Santonic acid (2) was subjected to reduction with the Zn–HCl–ether following reported conditions (Paquette et al. 1985), with the aim to obtain the previously prepared pinacol (3) (Hortmann & Daniel 1972) via intramolecular pinacolisation. However, under these conditions santonic acid (2) did not afford pinacol (3), but yielded a 60:40 mixture (GC–MS, 1H NMR) of succinic anhydrides 4 and 5 (Figure 2). The 13C NMR (DEPT) spectrum indicated two sets of 15 signals confirming it to be a mixture of two C15 compounds. The IR spectrum of the product revealed characteristic twin bands at 1835 and 1780 cm⁻¹ indicating the presence of substituted succinic anhydrides. It was found to be a 60:40 mixture of two isomers from its 1H NMR...
spectrum. The major compound displayed a triplet at $\delta 1.0$ ($J = 7.0$ Hz) due to a CH$_3$–CH$_2$ group, a singlet at $\delta 1.20$ and a doublet at $\delta 1.35$ ($J = 7.0$ Hz). The olefinic proton was observed as a broad singlet at $\delta 4.92$. The complete spectroscopic analysis (Section 3) led to structure 4 for the major product. The $^1$H NMR spectrum of the minor isomer (40%) exhibited a triplet at $\delta 1.0$ ($J = 7.0$ Hz, CH$_3$–CH$_2$), a singlet at $\delta 1.18$ and a doublet at $\delta 1.35$ ($J = 7.0$ Hz). The vinyl protons of these minor isomers exhibited broader resonances compared to the major isomer. The vinyl proton resonances of the minor isomer exhibited a triplet at $\delta 4.10$ with a $J$ value of 7.0 Hz, a singlet at $\delta 1.18$ and a doublet at $\delta 1.35$ with a $J$ value of 7.0 Hz. The vinyl resonances in these minor isomers showed broader and more complex patterns compared to the major isomer.
hydrogen was observed as a singlet at δ 5.09. Structure 5 was, therefore, assigned to the minor isomer. It is clear that the reaction proceeds via pinacol (3), which under acidic conditions undergoes further rearrangement resulting in the cleavage of the C5–C6 bond to yield succinic anhydrides 4 and 5. Thus, the action of zinc in ether saturated with dry hydrogen chloride on santonic acid (2) resulted in pinacolisation followed by cationic rearrangement to afford a mixture of 4 and 5 with rigid cis-bicyclo[3.3.0]octane skeletons in a single step.

CAN is another interesting oxidising agent (Ho 1973; Hwu & King 2001) which catalyses Baeyer–Villiger oxidation of carbonyl compounds (Goswami et al. 2004) and more interestingly regiospecific Baeyer–Villiger oxidation of conformationally constrained polycyclic ketones (Mehta et al. 1976). It was our interest to evaluate the reaction of CAN with santonic acid since we envisaged the insertion of oxygen between C5 and C6 if it undergoes regiospecific Baeyer–Villiger oxidation. However, oxidation of 2 with CAN yielded products derived exclusively by oxidative decarboxylation (Figure 3). Column chromatography and

Figure 3. Oxidative decarboxylation products of santonic acid 2 with CAN. Number of atoms in 6–10 are based in those of 2.
preparative TLC yielded 6, 7, an unseparated mixture of 8 + 9 (60:40) and 10. All five products were characterised mainly by using NMR spectral analysis.

The most distinctive feature of the 1H NMR spectrum of compound 6 is the 1:3:3:1 quartet \((J = 6.4 \text{ Hz})\) at \(\delta = 5.29\) due to C11–H. This downfield shift is due to the replacement of the carboxyl group by an \(-\text{ONO}_2\) group. The C13 protons were observed as a doublet \((J = 6.4 \text{ Hz})\) at \(\delta = 1.45\). The total proton count indicated 19 hydrogen atoms and confirmed the presence of 1 nitrogen atom giving molecular formula \(\text{C}_{14}\text{H}_{19}\text{NO}_5 (M^+ 281)\). The chemical shifts and the splitting pattern of the protons indicated that the tricyclic skeleton and the two ketonic carbonyls remained intact. Based on these data, structure 6 is assigned to the first product.

Compound 7, the third product isolated from the column revealed 1H NMR data very similar to 6 except the C11–CH\(_3\) doublet was at \(\delta = 1.35\) instead of \(\delta = 1.45\).

Compounds 6 and 7 are thus stereoisomeric, differing only in the configuration at C11.

Although the second product isolated by column chromatography appeared as a single spot on TLC, the 1H NMR spectrum indicated it to be a mixture of 8 and 9 (60:40) and revealed strong similarities to the spectrum of 6. Signals for only two methyl groups (C4–CH\(_3\) and C10–CH\(_3\)) could be seen in the region \(\delta 1.0–2.0 \text{ ppm}\). The olefinic region contained a four-line pattern at \(\delta 5.70\) (1H, dd, \(J = 17.3\) and 11.0 Hz) and the AB part of an ABX system at \(\delta 5.31\) (1H, d, \(J = 11.0\) Hz) and \(\delta 5.42\) (1H, d, \(J = 17.3\) Hz), characteristic of a vinyl group attached to a quaternary carbon. The ratio of the integration under the olefinic proton region and the methyl groups indicated that the major component (60%) contained a vinyl group and has structure 8. Structure 9 is assigned to the other component (40%) on the basis of a sharp signal at \(\delta 2.33\) due to an acetyl group. Interestingly, 8 was obtained earlier by lead tetraacetate oxidation of santonic acid (Naik 1987). A sample prepared using the reported procedure displayed identical behaviour on TLC. Efforts to separate 8 and 9 using column chromatography were unsuccessful.

Compound 10 was obtained as a crystalline solid, mp. 182\(^\circ\)C. The 1H NMR spectrum displayed a sharp singlet at \(\delta = 1.45\) (3H, C10–CH\(_3\)) and two methyls at \(\delta = 1.27\) (d, \(J = 6.3\) Hz, C11–CH\(_3\)) and \(\delta = 1.09\) (d, \(J = 6.8\) Hz, C4–CH\(_3\)). C\(_{11}\)–H afforded a quartet at \(\delta = 4.01\) (\(J = 6.3\) Hz). The upfield shift of this methine compared with the corresponding methines of diketo-nitrates 6 and 7 can be accounted for if the hydroxyl group is attached to C11. Structure 10 was assigned to this product.

All the products are derived by Ce\(^{4+}\) oxidation at the carboxyl group; the ketonic carbonyls of 2 were unaffected. Mechanisms which account for all five products formed in this reaction are presented in Figure 3. These proposed mechanisms are in agreement with the earlier observations of oxidative decarboxylations of substituted phenylacetic acids (Trahanovsky et al. 1974) which proceed via the radical generated by loss of CO\(_2\) which undergoes oxidation with Ce\(^{4+}\) to give a carbocation which reacts with nitrate and hydroxide ions or deprotonates to afford products such as 6–10.

3. Experimental

3.1. General experimental procedures

Melting points are uncorrected. IR spectra (neat film/KBr) were recorded on a Perkin-Elmer IR 298 spectrometer (Perkin Elmer Corporation, USA). NMR spectra were recorded either on Bruker 360 MHz (1H) or 90 MHz (13C) for 4 and 5 (Bruker Corporation, USA). A Bruker 500 MHz (1H NMR) was used for 6–10, and a Bruker 125 MHz (13C) for 7 and Bruker 90 MHz (1H) for the remaining compounds in CDCl\(_3\) with TMS as an internal standard. HRMS were recorded on QSTAR\(_{XL}\) MS/MS Applied Biosystem instrument (Applied Biosystem Instruments, USA). All yields refer to pure isolated products. Activation of zinc was performed by washing zinc dust with HCl (2%) followed by water, ethanol, acetone, dry ether and heating at 100\(^\circ\)C for 5 min just before use.
3.2. Santonic acid (2)
Santonic acid (2) was prepared from santonin (1) following the procedures described in the literature (Woodward et al. 1948).

3.3. Reaction of santonic acid (2) with Zn–HCl–ether
Santonic acid (2, 0.54 g, 0.002 moles) was added to dry ether saturated with dry HCl gas at 0°C, followed by the addition of activated zinc powder (0.708 g, 0.01 moles) over 1 h. After stirring at 0°C for 1 h, it was cooled to room temperature and stirred for additional 1 h. The reaction mixture was quenched on crushed ice, basified with sodium carbonate and extracted with ether. The combined organic extracts were washed with water, dried over sodium sulphate and concentrated to furnish a yellow liquid, which was distilled under reduced pressure to yield a mixture of 4 and 5 in the ratio 3:2 (GC–MS) as a colourless oil, 0.37 g (69%). IR $\lambda_{\text{max}}$ (KBr) 2950, 1853, 1780, 1380, 1335, 1210, 930 cm$^{-1}$.

3.3.1. Compound 4
EI-MS ($m/z$) 248 (M$^+$), 192, 175, 147, 134, 121, 107, 105, 93 (100%), 91, 79 and 41. $^1$H NMR (CDCl$_3$) 1.04 (3H, t, $J = 7.0$ Hz), 1.20 (3H, s), 1.35 (3H, d, $J = 7.0$ Hz), 1.5–2.60 (8H, m), 2.78 (1H, br s), 3.09 (1H, q, $J = 7.0$ Hz), 4.92 (1H, br s). $^{13}$C NMR (CDCl$_3$, DEPT) 10.05 (q), 12.21 (q), 24.17 (t), 28.50 (q), 35.49 (t), 37.65 (t), 39.34 (t), 44.47 (d), 50.10 (s), 60.04 (s), 61.62 (d), 118.65 (d), 149.42 (s), 173.25 (s) and 174.00 (s) (Figures S1 and S2).

3.3.2. Compound 5
EI-MS ($m/z$) 248 (M$^+$), 192, 176, 147, 134, 121 (100%), 107, 105, 93, 91, 77 and 41. $^1$H NMR (CDCl$_3$) 1.04 (3H, t, $J = 7.0$ Hz), 1.18 (3H, s), 1.35 (3H, d, $J = 7.0$ Hz), 1.50–2.60 (9H, m), 3.09 (1H, q, $J = 7.0$ Hz), 5.09 (1H, br s). $^{13}$C NMR (CDCl$_3$, DEPT) 11.10 (q), 12.21 (q), 23.63 (t), 26.79 (q), 36.50 (t), 37.38 (t), 45.63 (d), 50.73 (t), 51.51 (d), 58.42 (s), 60.70 (s), 130.42 (d), 143.26 (s), 173.25 (s) and 173.66 (s) (Figures S1 and S2).

3.4. Reaction of santonic acid (2) with CAN
A solution of santonic acid (2, 0.5 g, 0.002 moles) in acetonitrile (20 mL) was added to a solution of CAN (5.5 g, 0.01 moles) in water (50 mL). After stirring for 90 min, it was extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic extracts were washed with saturated aqueous NaHCO$_3$ and dried over anhydrous sodium sulphate. The neutral fraction on concentration yielded a viscous mass (0.223 g) which was chromatographed on silica gel. Elution with petroleum ether–benzene (1:1) afforded a white crystalline solid, recrystallised from ethanol to yield nitrate 6 (35 mg, 7%), mp. 179°C. MS ($m/z$) 281 (M$^+$), 207, 178, 122 (100%), 94 and 79. $^1$H NMR (CDCl$_3$): 1.08 (3H, d, $J = 6.7$ Hz, C$_4$–CH$_3$), 1.45 (3H, d, $J = 6.4$ Hz, C$_{11}$–CH$_3$), 1.46 (3H, s, C$_{10}$–CH$_3$), 1.85–1.93 (2H, m, C$_9$–H), 1.98 (1H, ddd, $J = 14.1$, 11.2 and 7.3 Hz, C$_8$–H), 2.07 (1H, ddd, $J = 14.1$, 8.7 and 5.4 Hz, C$_9$–H), 2.25 (1H, td, $J = 3.9$ and 2.0 Hz, C$_1$–H), 2.57 (2H, d, $J = 3.9$ Hz, C$_2$–H), 2.61 (1H, dd, $J = 4.5$, 2.0 Hz, C$_5$–H), 2.87 (1H, qd, $J = 6.7$ and 4.5 Hz, C$_4$–H), 5.29 (1H, q, $J = 6.4$ Hz, C$_{11}$–H) (Figure S3). Further elution with benzene yielded another white solid, recrystallised from benzene–petroleum ether to afford a (6:4) mixture of diketone 8 and triketone 9 (42 mg), mp. 104°C. $^1$H NMR (CDCl$_3$) 1.11 (3H, d, $J = 6.7$ Hz, C$_4$–CH$_3$), 1.8–2.0 (4H, m, C$_8$–H, C$_9$–H), 2.06 (1H, td, $J = 6.8$ and 1.8 Hz, C$_1$–H), 2.33 (3H, s, C$_{11}$–CH$_3$), 2.45 (1H, dd, $J = 17.3$ and 6.8 Hz, C$_2$–H$_2$), 2.83 (1H, qd, $J = 6.8$ and 4.4 Hz, C$_4$–H), 5.31 (1H, d, $J = 11.0$ Hz, C$_{13}$–H), 5.42 (1H, d, $J = 17.3$ Hz, C$_{13}$–H), 5.70 (1H,
dd, \( J = 17.3 \text{ and } 11.0 \text{ Hz, } C_{11}–H \) (Figure S4). Continuing elution with CHCl\(_3\)–benzene (1:9) afforded a third solid, recrystallised from benzene–petroleum ether to yield nitrate 7 (38 mg, 7%), mp. 192°C. MS (\( m/z \)) 281 (M\(^+\)), 207, 178 (100%), 122, 94 and 79. \(^1\)H NMR (CDCl\(_3\)) 1.09 (3H, d, \( J = 6.8 \text{ Hz, } C_4–CH_3 \)), 1.35 (3H, d, \( J = 6.6 \text{ Hz, } C_{11}–CH_3 \)), 1.46 (3H, s, C\(_{10}–CH_3 \)), 1.85–1.95 (2H, m, C\(_9–H \)), 2.00 (1H, ddd, \( J = 14.4, 12.3 \text{ and } 6.6 \text{ Hz, } C_8–H \)), 2.60 (2H, d, \( J = 4.0 \text{ Hz, } C_2–H \)), 2.60 (1H, d, \( J = 4.2 \text{ Hz, } C_5–H \)), 2.86 (1H, qd, \( J = 6.8 \text{ and } 4.2 \text{ Hz, } C_4–H \)), 5.35 (1H, q, \( J = 6.6 \text{ Hz, } C_{11}–H \) (Figure S5). \(^13\)C NMR (\( \delta \text{ ppm, CDCl}_3, APT \)) 11.8 (q, C\(_4–CH_3 \)), 14.2 (q, C\(_{11}–CH_3 \)), 22.2 (q, C\(_{10}–CH_3 \)), 31.5 (t, C\(_2 \)), 34.5 (t, C\(_8 \)), 36.1 (t, C\(_9 \)), 41.7 (s, C\(_{10} \)), 48.0 (d, C\(_5 \)), 58.0 (d, C\(_1 \)), 80.0 (d, C\(_{11} \)) (Figure S6). Further elution with ethyl acetate yielded another white solid, recrystallised from benzene to afford 10 (27 mg, 6%), mp. 182°C. \(^1\)H NMR (CDCl\(_3\)) 1.08 (3H, d, \( J = 6.8 \text{ Hz, } C_4–CH_3 \)), 1.27 (3H, d, \( J = 6.3 \text{ Hz, } C_{11}–CH_3 \)), 1.45 (3H, s, C\(_{10}–CH_3 \)), 1.8–2.0 (4H, m, C\(_8–H, C_9–H \)), 2.33 (1H, td, \( J = 6.3 \text{ and } 1.8 \text{ Hz, } C_1–H \)), 2.52 (1H, ddd, \( J = 16.6 \text{ and } 6.3 \text{ Hz, } C_2–Hb \)), 2.58 (1H, dd, \( J = 4.2 \text{ and } 2.1 \text{ Hz, } C_5–H \)), 2.84 (1H, dd, \( J = 16.6 \text{ and } 1.5 \text{ Hz, } C_2–Ha \)), 2.86 (1H, qd, \( J = 6.8 \text{ and } 4.2 \text{ Hz, } C_4–H \)), 4.01 (1H, q, \( J = 6.3 \text{ Hz, } C_{11}–H \) (Figure S7).

4. Conclusions
Santonic acid (2) on Zn–HCl–ether reduction resulted in the cleavage of the C5–C6 bond to afford succinic anhydrides 4 and 5, whereas 2 with CAN underwent oxidative decarboxylation to yield products 6–10.

Supplementary material
Supplementary material relating to this article is available online, alongside Figures S1–S7.

Acknowledgements
We thank Dr Bruno Maurer for recording the NMR spectra of 4 and 5 and his critical comments, Prof. RB Bates for NMR measurements and help in the characterisation of 6–10 and Dr VP Joshi for the MS of 6 and 9. The authors thank the CSIR, New Delhi for the award of a senior research fellowship to KPF. We thank the reviewer(s) for critical evaluation and improving the manuscript.

Note
1. Present address: Prof. S.C. Bhattacharyya Organic Synthesis Laboratory, VerGo Pharma Research, Verna, Goa 403722, India.

References
Arantes F, Barbosa L, Alvarenga E, Demuner A, Bezerra D, Ferreira J, Costa-Lotufo L, Pessoa C, Moraes M. 2009. Synthesis and cytotoxic activity of \( \alpha \)-santonin derivatives. Eur J Med Chem. 44:3739–3745.
Birładeanu L. 2003. The stories of santonin and santonic acid. Angew Chem Int Ed. 42:1202–1208.
Blay G, Cardona L, Collado A, García B, Morcillo V, Pedro J. 2004. Synthesis of spirovetivane sesquiterpenes from santonin. Synthesis of (+)-anhydro-\( \beta \)-rotunol and all diastereomers of 6,11-spirovetivadiene. J Org Chem. 69:7294–7302.
Furtado I, Mavinkurve S, Paknikar S. 1998. Microbial transformation of \( \alpha \)-santonin to 11-demethyl-eudesm-4,3,6-dione. Lett Appl Microbiol. 6:27–30.
Goswami P, Hazarika S, Das A, Chowdhury P. 2004. Ceric ammonium nitrate (CAN) catalyzed Baeyer–Villiger oxidation of carbonyl compounds, specially 20-oxosteroids. Indian J Chem. 43B:1275–1281.
Ho T. 1973. Ceric ion oxidation in organic chemistry. Synthesis:347–354.
Hortmann A, Daniel D. 1972. Chemistry of santonic acid. Oxidative and reductive modifications. J Org Chem. 37:4446–4460.
Hortmann A, Daniel D, Schaefer J. 1968. Determination of the configuration and conformation of γ-metasantonin. J Org Chem. 33:3988–3990.

Hwu J, King K. 2001. Versatile reagent ceric ammonium nitrate in modern chemical synthesis. Current Sci. 81:1043–1053.

Lamm A, Chen A, Reynolds W, Reese P. 2009. Fungal hydroxylation of (−)-santonin and its analogues. J Mol Catal B Enzym. 59:292–296.

Li C, Yu X, Lei X. 2010. A biomimetic total synthesis of (+)-ainsliadimer A. Org Lett. 12:4284–4287.

Mehta G, Pandey P, Ho T. 1976. Regiospecific Baeyer–Villiger oxidation of polycyclic ketones with ceric ion. J Org Chem. 41:953–956.

Moyano E, Ceballos N, Yranzo G, Zinczuk J, Rúveda E. 2005. Formation of santonide and parasantonide in the pyrolysis of santonic acid a new insight into an old reaction. ARKIVOC. xii:352–362.

Naik U. 1987. Studies in natural products [Ph.D. thesis]. University of Bombay.

Naik U, Paknikar S, Bates R, Camou F. 1987. The bromination product of santonic acid in wet chloroform. Tetrahedron Lett. 28:5641–5642.

Natarajan A, Tsai C, Khan S, McCarren P, Houk K, Garcia-Garibay M. 2007. The photoarrangement of α-santonin is a single-crystal-to-single-crystal reaction: a long kept secret in solid-state organic chemistry revealed. J Am Chem Soc. 129:9846–9847.

Paknikar S, Malik B, Bates R, Caldera S, Wijayaratne T. 1994. Stereochemistry of 4,5-dihydroxy-α-santonin and structure of a new santonin oxidation product. Tetrahedron Lett. 44:8117–8118.

Paquette L, Fischer J, Brown A. 1985. Synthesis of (4)peristylane and functionalized derivatives of this hemispherical ring system. J Am Chem Soc. 107:686–691.

Toda M, Hayashi M, Hirata Y, Yamamura S. 1972. Modified Clemenson reductions of keto groups to methylene groups. Bull Chem Soc Jpn. 45:264–266.

Trahanovsky W, Cramer J, Brixius D. 1974. Oxidation of organic compounds with cerium (IV). XVIII. Oxidative decarboxylation of substituted phenylacetic acids. J Am Chem Soc. 96:1077–1081.

Williams P, Zinczuk J, Barrioc D, Pirol O, Nascimento E, Etcheverry S. 2008. Potential antitumoral properties of a new copper complex with santonic acid. Bioorg Med Chem. 16:4313–4322.

Woodward R, Brutschy F, Baer H. 1948. The structure of santonic acid. J Am Chem Soc. 70:4216–4221.