A New Laboratory Experiment Based on a Chemical Transformation of Santonin: Synthesis of Santonic Acid

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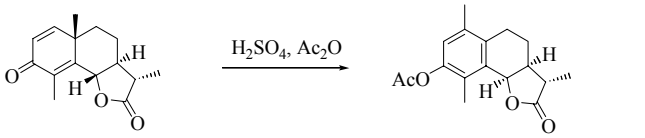
Abstract: In this paper we describe a new comprehensive laboratory experiment based on a chemical transformation of santonin. The experiment is designed as a puzzle-solving exercise for advanced undergraduate organic chemistry courses and consists of the structure elucidation of santonic acid, the product obtained by the action of strong alkalis on santonin. An enquiry-based approach helps the students achieve this goal by combining their knowledge of organic chemistry and spectroscopy together with mechanistic thinking.

Introduction

We have recently described an instructional exercise directed to the reintroduction of some topics of natural products chemistry in undergraduate courses of organic chemistry. The exercise was designed as a discovery-based laboratory experiment based on the dienone–phenol rearrangement of santonin (**1**) into α-desmotroposantonin acetate (**2**) (Scheme 1).



santonin (**1**) α-desmotroposantonin acetate (**2**)

Scheme 1

We selected this reaction because it played a crucial role on the structure elucidation of the anthelmintic sesquiterpene santonin and also on the clarification of the mechanism of the dienone–phenol rearrangement of some steroids [1].

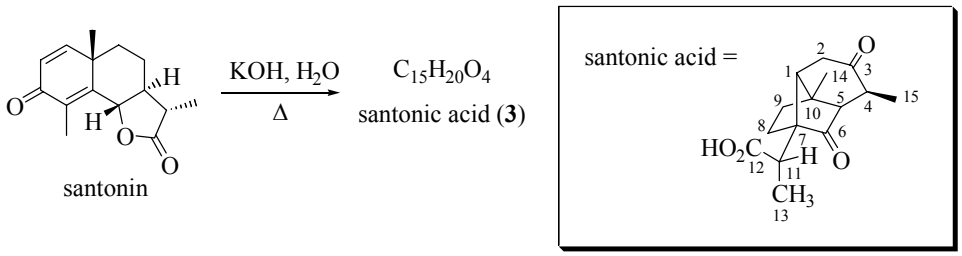
In order to preserve the discovery aspect of the laboratory exercises in our course we considered it convenient to introduce a new experiment every semester. For the first semester of 2001 we developed a new exercise based on another historically important transformation of santonin (**1**), namely its transformation into santonic acid (**3**) under base-catalyzed conditions (Scheme 2). As far as we know, the analysis of the transformation of santonin (**1**) into santonic acid (**3**) by Woodward et al. constituted one of the first examples of the application of mechanistic thinking to problems in natural products chemistry [2, 3]. Furthermore, the key intramolecular Michael addition sequence thus proposed for the formation of santonic acid was later used by Corey et al. for planning the total synthesis of longifolene [4], the strategy for which showed the rudiments of what today is known as retrosynthetic analysis.

The experiment described in this article was designed as a puzzle-solving laboratory exercise consisting in the transformation of santonin into santonic acid and in the structure elucidation of this product. In order to postulate a possible structure for santonic acid the students are guided to combine their knowledge of chemical reactivity and mechanism with the interpretation of spectral data.

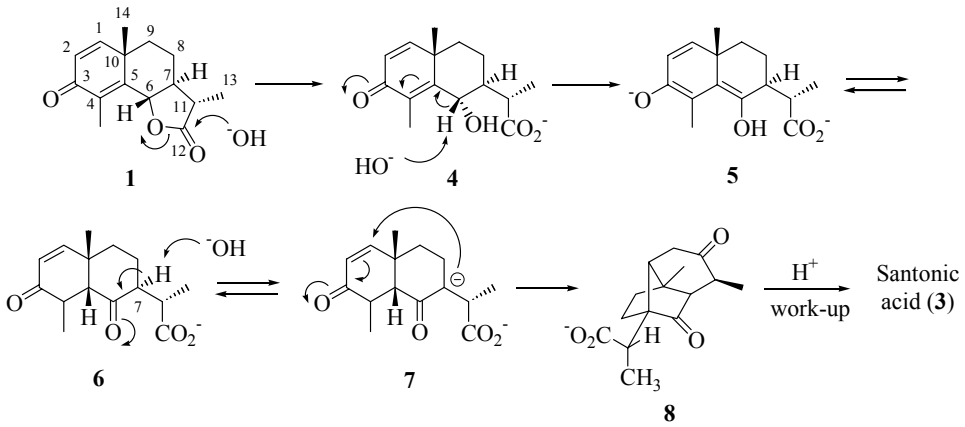
Results and Discussion

The puzzle consists in solving the structure of santonic acid, the product of the action of strong alkalis on santonin [5]. In the first part of the experiment each team, consisting of two students, carries out the synthesis of santonic acid. As soon as the reaction is in progress, the students analyze the IR and ^{1}H and ^{13}C NMR spectra of the starting material [6, 7]. Once the reaction is completed the students isolate the product and submit a sample for IR, ^{1}H, and ^{13}C NMR spectra [8, 9]. The second part of the experiment consists of the structure elucidation of santonic acid. To facilitate the process, several guidelines are provided to the students. They are given the molecular formula of the product ($C_{15}H_{20}O_4$), and they are asked to examine major similarities and differences in the IR and NMR spectra of santonin and santonic acid by following an enquiry-based procedure [10].

The appearance of a broad peak at 3168 cm^{-1} in the IR spectrum of santonic acid clearly indicates the presence of a hydroxy group. The carbonyl peaks in the spectrum of santonic acid are similar to the ones in the spectrum of santonin, which suggests that the carbonyls in the product are much like the carbonyls in santonin. The most striking feature of the ^{1}H NMR spectrum of santonic acid is that the signals corresponding to the vinylic protons of the enone system and the allyl proton at δ 4.81 ppm observed in the spectrum of santonin have disappeared. Furthermore, all the peaks appear in the range δ 1 to 3 ppm, showing that all the protons are aliphatic. Taking the molecular formula into account, the integration corresponds to 19 protons, revealing that one hydrogen is missing. This could be assigned to an OH hydrogen. In agreement with these observations, the ^{13}C NMR spectrum shows the disappearance of the signals corresponding to the dienone, corroborating that this system has been modified during the transformation, and the appearance of three downfield carbons (two aliphatic ketones and one acid or



Scheme 2



Scheme 3

Table 1. NMR Data Analysis for Santonic Acid

Carbon	^{13}C NMR	^{1}H NMR
C-1	51.1, CH	2.03–2.17 (m, 1H)
C-2	37.7, CH_2	2.45–2.74 (m, 2H)
C-3	209.6, C=O	-
C-4	43.7, CH	2.45–2.74 (m, 1H)
C-5	61.0, CH	2.03–2.17 (m, 1H)
C-6	216.1, C=O	-
C-7	62.6, C	-
C-8	26.6, CH_2	2.03–2.17 (m, 1H), 1.43–1.64 (m, 1H)
C-9	32.8, CH_2	1.43–1.64 (m, 2H)
C-10	44.5, C	-
C-11	37.2, CH	2.86 (q, 1H, J = 7.2 Hz)
C-12	179.6, C=O	-
C-13	12.8, CH_3	1.35 (d, 3H, J = 7.2 Hz)
C-14	16.3, CH_3	1.34 (s, 3H)
C-15	12.2, CH_3	1.14 (d, 3H, J = 6.7 Hz)

ester) plus twelve aliphatic carbons. The DEPT spectrum confirms that the downfield signals correspond to three carbonyl groups and further shows that santonic acid possesses two quaternary carbons, four methines, three methylenes, and three methyl groups.

The acidification of the reaction mixture for the isolation of santonic acid during the work-up of the reaction supports that the product contains some acidic moiety. A carboxylic acid group is in accordance with the spectral data, particularly with the presence of an absorption band corresponding to a hydroxy group in the IR spectrum.

These spectral data suggest that the dienone has been transformed into a saturated ketone and the lactone into a carboxylic acid. The lack of vinylic signals in the ^{1}H NMR and ^{13}C NMR spectra of santonic acid indicates that the six unsaturations deduced from the molecular formula result from three C=O double bonds plus three rings. Because the lactone ring is not present in the product, an additional ring must be formed during the course of the reaction. It is evident that this ring should result from an intramolecular reaction, which is likely to be a Michael addition to the enone system.

It can be concluded then that, under these reaction conditions, the following reactions can take place: hydrolysis of the lactone, deprotonation of the enone at the vinyligous hydrogen attached to C-6, and intramolecular Michael addition to the enone. As suggested by Woodward et al. [3], it is very likely that the base catalyzed opening of the lactone should take place first, giving rise to intermediate **4** (Scheme 3). This intermediate can then undergo an α,β to β,γ double bond shift to enol **5** and subsequent isomerization to tautomeric ketone **6**. Deprotonation of **6** at C-7 would yield enolate **7,** which can add effectively to the enone moiety in a conjugate fashion leading to tricyclic system **8**. Finally, protonation of the carboxylate group of **8** during work-up affords santonic acid (**3**).

Although the rationalization of the outcome of the reaction is not a simple task, most advanced undergraduates can solve the structure of santonic acid provided the instructor guides

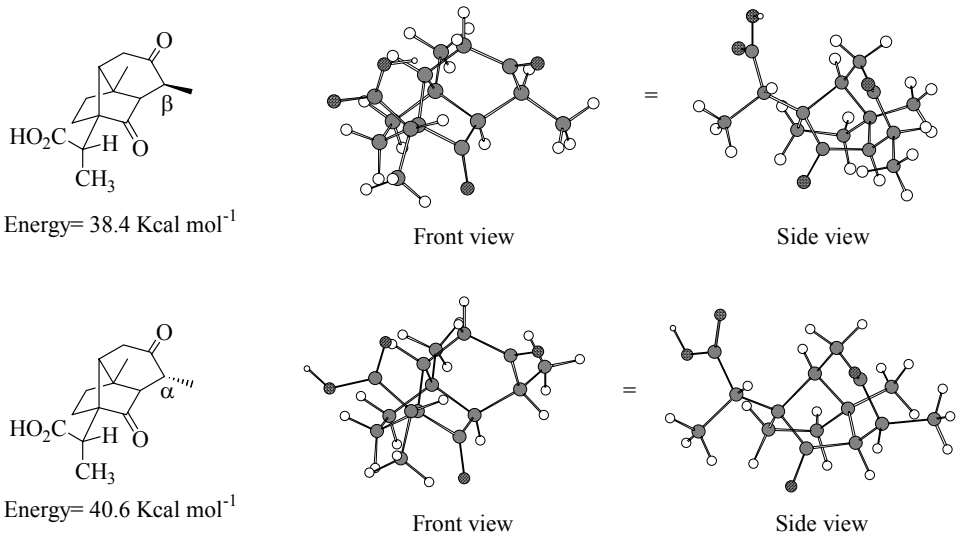


Figure 1. Geometries of the most stable conformation of each stereoisomer.

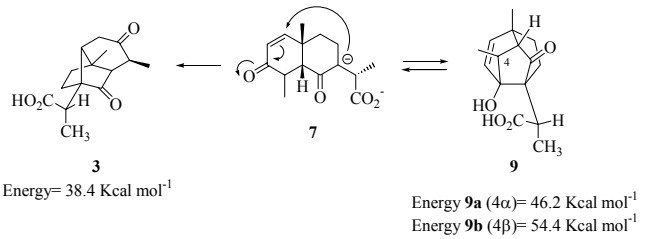
them during the final discussion by giving them a few hints. At this stage it is important to remark that the cis fusion of the decaline system of ketone **7** is a stereochemical prerequisite for a successful cyclization to tricyclic system **8**.

The structure proposed for santonic acid (**3**) matchs the spectroscopic data very well (Scheme 2). Students should check if the structural features deduced from the spectra agree with structure **3**. For example, they should verify the count of quaternary carbons, methines, methylenes, and methyls derived from the DEPT spectrum. Unfortunately, the ^{1}H NMR spectrum of the product shows significant overlap, making interpretation extremely complicated; however, students should be able to assign some peaks. For instance, the doublet–quartet pattern corresponding to the CH3–CH fragment of the side chain can be easily identified. The use of two-dimensional NMR ([H,H and H,C COSY [COrrelation SpectroscopY) and H,C COLOC (COrrelation spectroscopy via LOng range Coupling]) can also be added to the experiment so as to fully assign the peaks as shown in Table 1. Nonetheless, this is an unduly complex task for advanced undergraduates and therefore it is not crucial to include it in the experiment.

To complete the experiment, the stereochemistry of santonic acid can be given as a final topic for discussion. Based on the facts that the configuration of C-11 was not modified during the reaction and that santonic acid is the most stable epimer at C-4, the students should be able to deduce the configuration of this center by molecular modeling calculations. At this point, the teaching assistants show the students how to use the MM+ force field of the package HyperChem for minimizing the energy of both products [11]. To find the most stable conformation of each stereoisomer, conformational searches were carried out. Figure 1 shows the geometries and the calculated total energies of the global minima thus located. These results demonstrate the β epimer at C-4 is 2.2 kcal mol^{-1} more stable than the α epimer. Because the stereochemistry at C-11 of santonin does not suffer any change under these conditions, the relative configurations of all stereogenic centers of santonic acid are therefore established.

This experiment can be conveniently modified so as to cover the needs of different organic chemistry courses. For instance, the analysis of the competition between the conjugate addition and the direct addition of enolate **7** that leads to santonic acid (**3**) and aldol **9** respectively can be an additional topic for discussion (Scheme 4).

The students can be induced to determine the relative stabilities of compounds **3** and **9** using molecular modeling tools. The comparison of the computed total energies allows the students to confirm that the compound formed in the reaction (**3**) is in fact the thermodynamically favored product (Scheme 4). It is likely that the highly strained nature of compounds **9** will tend to accelerate the retro-aldol process, which favors equilibration to **3**.



Scheme 4

The frontier orbital effect that assists conjugate addition over the aldol reaction can also be invoked to explain this result. Because the enolate is a soft nucleophile, it will preferentially attack the soft β carbon (C-1) instead of the relatively hard carbonyl carbon (C-3) of enone **7** [12].

Finally, we would like to mention that we are currently developing a comprehensive experiment based on a chemical transformation of santonic acid (**3**). Therefore, we suggest that the samples of santonic acid obtained during this laboratory are stored so that they can be used in the future.

Conclusion

The central theme of the puzzle-solving experiment described in this paper is the synthesis of santonic acid and the structure elucidation of this product. It challenges students to simultaneously use spectroscopic data analysis and mechanistic reasoning. The experiment offers the opportunity

to integrate and apply prior concepts of carbonyl chemistry (lactone hydrolysis, enolization and direct and conjugate addition of enolates) to a new situation where the context makes them look complicated.

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Suporting Materials. One supporting file is available containing instructor notes at (http://dx.doi.org/10.1007/s00897000561b).

References and Notes

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4. Corey, E. J.; Ohno, M.; Mitra, R. B; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964,** *86,* 478–485.
5. Santonin is commercially available from Aldrich (10 g, $24.20) and Sigma (10 g, $24.20; 50 g $107.20). At current prices each two-student setup uses $0.49, or less, worth of santonin.
6. The IR spectra were recorded on a Bruker IFS 25 as solids in KBr disks, and the NMR spectra were acquired on a Bruker AC-200-E in $CDCl_3$ solution (referenced to TMS) at 200.13 MHz for hydrogen and 50.33 MHz for carbon.
7. Santonin (**1**) mp 175.1–176.2 °C; $[\alpha]_D$ -171.0 (c = 2.0, EtOH). IR ν_{max} (cm^{-1}) = 2936, 1786, 1654, 1624. ^{1}H NMR = 1.28 (d, 3H, $J_{11,13}$ = 6.9 Hz, H-13); 1.34 (s, 3H, H-14); 1.44-2.07 (m, 5H, H-7, H-8, H-9); 2.14 (d, 3H, $J_{6,15}$ = 1.36 Hz, H-15); 2.43 (dq, 1H, $J_{7,11}$ = 11.7, $J_{11,13}$ = 6.9 Hz, H-11); 4.81 (dd, 1H, $J_{6,7}$ = 10.9 Hz, $J_{6,15}$ = 1.32 Hz, H-6); 6.25 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-2); 6.7 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1). ^{13}C NMR = 10.69 (C-15); 12.28 (C-13); 22.75 (C-8); 24.89 (C-14), 37.59 (C-9); 40.69 (C-11); 41.22 (C-10); 53.31 (C-7); 81.16 (C-6); 125.50 (C-2); 128.20 (C-4); 151.13 (C-5); 154.96 (C-1); 177.53 (C-12); 186.11 (C-3).
8. Alternatively, the students can record their own spectra.
9. Santonic acid (**3**); mp 166.4–168.4 ºC (H_2O, Lit.[3] mp 170-172 ºC); $[\alpha]_D$ -71.0 (c = 2.0, $CHCl_3$). IR ν_{max} (cm^{-1}) = 3168, 1734, 1684, 1178. ^{1}H NMR = 1.14 (d, 3H, $J_{4,15}$= 6.7 Hz, H-15); 1.34 (s, 3H, H-14); 1.35 (d, 3H, $J_{11,13}$ = 7.2 Hz, H-13); 1.43-1.64 (m, 3H, H-8α, H-9); 2.03-2.17 (m, 3H, H-1, H-5, H-8β); 2.45-2.74 (m, 3H, H-2, H-4); 2.86 (q, 1H, $J_{11,13}$ = 7.2 Hz, H-11). ^{13}C NMR = 12.20 (C-15); 2.79 (C-13); 16.30 (C-14); 26.63 (C-8); 32.84 (C-9); 37.20 (C-11); 37.70 (C-2); 43.67 (C-4); 44.52 (C-10); 51.10 (C-1); 61.02 (C-5), 62.56 (C-7); 179.60 (C-12), 209.60 (C-3); 216.08 (C-6).
10. To make this a more realistic example of an actual laboratory problem, instead of the molecular formula, elemental analysis and mass spectral data can be supplied.
11. HyperChem, Hypercube, Inc.
12. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry;* Oxford University Press: New York, 2001; Chapter 10, pp 227–242 and Chapter 29, pp 749–769.