REDUCTION OF SANTONIC ACID DERIVATIVES

Alfred G. Hortmann and Douglas S. Daniel

Department of Chemistry, Washington University, St. Louis, Missouri 63130 (Received in USA 21 April 1970; received in UK for publication 27 May 1970)

Transformations of santonic acid $(\underline{1})$ have been investigated in connection with attempts to utilize this substance as a starting material for the synthesis of structurally-related sesquiterpenes. This report summarizes some results of this study which have led to a clarification of earlier work¹ on the reduction of $\underline{1}$ with sodium amalgam, and describes several unusual reactions of santonic acid derivatives.

When santonic acid $(\underline{1})^2$ was heated under N₂ with 5% sodium amalgam in 2% aqueous NaOH solution for 6 hr at reflux temperature, "dihydrosantonic acid" (<u>2</u>, R=H) was obtained in 95% yield: mp 170-182.5°; ir (Nujol) 3390, 3330 and 1700 cm⁻¹; nmr (DMSO-<u>d</u>₆) & 0.92 (s,3), 1.09 (d, 3, <u>J</u>=7 Hz), 1.12 (d, 3, <u>J</u>=6.7 Hz), 2.61 (q, 1, <u>J</u>=7 Hz) and 4.25-4.92 (s[br], 3; -O<u>H</u>).³ Treatment of <u>2</u> (R=H) with diazomethane in ether afforded the methyl ester <u>2</u> (R=CH₃): mp 110.4-112° (11t.⁴ mp 111-114°); ir (CHCl₃) 3570, 3440 and 1725 cm⁻¹; nmr (CDCl₃) & 0.98 (s,3), 1.19 (d, 3, <u>J</u>=7 Hz) 1.23 (d, 3, <u>J</u>=7 Hz), 1.99 (d, 1, <u>J</u>=1.7 Hz), 2.13 (q, 1, <u>J</u>=6.5 Hz), 2.76 (q, 1, <u>J</u>=7 Hz), 3.67 (s,3), 2.92 (s[br], 1, -O<u>H</u>) and 3.28 (s[br], 1, -O<u>H</u>).³ Jones-Weedon oxidation⁵ of <u>2</u> (R=H) gave <u>1</u> in 77% yield.

Analogous products (previously unreported) were obtained starting with metasantonic acid (3).⁶ Reduction of 3 with 5% sodium amalgam in 10% aqueous sodium hydroxide for 2 hr gave a nearly quantitative yield of dihydrometasantonic acid (4, R=H); mp 163.5-177°; ir (Nujol) 3470, 3260 and 1687 cm⁻¹; nmr (DMSO-d₆) δ 0.94 (s,3), 0.97 (d, 3, J=7 Hz), 1.08 (d, 3, J=7 Hz), 1.96 (q, 1, J=7 Hz) and 2.60 (q, 1, J=7 Hz).³ Treatment of 4 with diazomethane gave the methyl ester (4, R=CH₃): bp 106-112°/0.1 mm (bath temp); ir (CHC1₃) 3560, 3360 and 1740 cm⁻¹; nmr (CDC1₃) δ 1.01 (s,3), 1.10 (d, 3, J=7 Hz), 1.17 (d, 3, J=7 Hz), 2.09 (q, 1, J=7 Hz), 2.78 (q, 1, J=7 Hz), 3.26 (s, 0.9; -0H), 3.69 (s,3) and 4.78 (s, 1; -0H). Jones-Weedon oxidation⁵ of 4 (R=H) gave 3 in high yield.

The structure $\underline{2}$ (R=H) drawn for "dihydrosantonic acid" is at variance with the structure $\underline{5}$ which was suggested² for this compound on the basis of previously reported^{4,7,8} data. However, further support for structures $\underline{2}$ (and $\underline{4}$) can be derived from the following observations: a) Shaking an nmr sample of $\underline{2}$ (R=CH₃) with D₂O resulted in a loss of area under the peaks at δ 2.92 (s,1) and 3.28 (s); b) addition of a few drops of acetic acid- $\underline{4}$, to the nmr sample of $\underline{4}$ (R=CH₃) gave rise to a new broad singlet (2H) at δ 6.3 and loss of the lH signals at δ 3.69 and 4.78; c) signals for CHOH do not appear in the spectra of either $\underline{2}$ (R=H or CH₃) or $\underline{4}$ (R=H or CH₃); and d) no hydrogen exchange occurred when $\underline{2}$ (R=H) was heated with NaOH/D₂O for four hours, followed by a normal workup procedure (similar treatment of $\underline{1}$ leads to incorporation of nearly three deuterium atoms per molecule).

If the reduction of $\frac{1}{2}$ was performed according to the procedure reported,⁷ which calls for

the use of 10% aqueous NaOH solution at the outset, <u>mixtures</u> of 2 (R=H) and <u>4</u> (R=H) were obtained which contained over 50% of <u>4</u> after 20 hr. In separate experiments it was established that prolonged treatment of <u>2</u> (R=H) with base in the absence of reducing agent also gave rise to mixtures of <u>2</u> (R=H) and <u>4</u> (R=H) in varying ratios which were found to be dependent upon the length of exposure; treatment of <u>1</u> under identical conditions led to negligible amounts of <u>3</u>. These data suggest that formation of <u>4</u> (R=H) from <u>1</u> occurs by epimerization of <u>2</u> (R=H), possibly <u>via</u> a lactonic intermediate. The likelihood that samples of "dihydrosantonic acid" used in work reported previously^{4,7,8} contained substantial amounts of <u>4</u> (R=H) is indicated by the heretofore puzzling observation reported by Cannizzaro⁸ that silver oxide oxidation of "dihydrosantonic acid" yields metasantonic acid. Repetition of this experiment using pure <u>2</u> (R=H) afforded only <u>1</u> and unoxidized <u>2</u>.

The formation of 2 (R=H) from 1 can be viewed as an example of an intramolecular pinacol reduction of a 1,4-diketone leading to a 1,2-cyclobutanediol. One example of this reaction-type has been reported⁹ and several unpublished examples effected by Wenkert and Yoder under Clemmensen reduction conditions have been cited in a recent review.¹⁰ Analogous processes for 1,3-diketones-cyclopropanediols have also been established recently.^{10,11}



Treatment of $\underline{2}$ (R=H) with acetic anhydride under conditions similar to those reported by Wedekind⁷ produced two acetates — an acetoxylactone and a diacetate acid.¹² The acetoxylactone ($\underline{6}$)³ had mp 140-141.8°; ir (CHC1₃) 1780 and 1735 cm⁻¹; nmr (CDC1₃) δ 1.10 (d, 3, \underline{J} =7 Hz), 1.13 (s,3), 1.32 (d, 3, \underline{J} =7.7 Hz), 2.04 (s,3), 2.59 (q, 1, \underline{J} =7 Hz) and 2.62 (q, 1, \underline{J} =7.7 Hz). The mp of $\underline{6}$ did not agree with that of Wedekind's acetoxylactone (mp 204°); however, an acetoxylactone ($\underline{7}$)³ obtained by treatment of dihydrometasantonic acid ($\underline{4}$, R=H) with acetic anhydride under identical conditions did correspond to that obtained from "dihydrosantonic acid" by Wedekind⁷: mp 204.5-206°; ir (CHC1₃) 1780 and 1735 cm⁻¹; nmr (CDC1₃) δ 1.08 (d, 3, \underline{J} =7 Hz), 1.17 (d, 3, \underline{J} =7 Hz), 1.19 (s,3), 2.02 (s,3), 2.57 (q, 2, \underline{J} =7 Hz). The diacetate acid $\underline{8}^3$ mp 235-237.5°, obtained from 2 (R=H) in low yield compares favorably with Wedekind's diacetate (mp 232°)⁷, and exhibits ir (CHC1₃) 1735 and 1705 cm⁻¹; nmr (CDC1₃) δ 0.98 (d, 3, \underline{J} =7 Hz), 1.05 (s,3), 1.18 (d, 3, \underline{J} =7 Hz), 2.08 (s,3), 2.12 (s,3) and 2.76 (q, 1, \underline{J} =7 Hz). Due to a lack of sufficient material, the diacetate obtained in low yield by treatment of $\underline{4}$ (R=H) with acetic anhydride was not completely purified and characterized, thus leaving the stereochemistry of $\underline{8}$ at the carboxyl-bearing carbon open to question.

When dihydrosantonic acid (2, R=H) was treated with glacial acetic acid in a sealed tube at 140-150° for 10-20 hr, a crystalline olefin (mp 144.2-146.5°) was formed as the major product and assigned structure 9 on the basis of analytical³ and spectral data: ir (CHCl₃) 3400-2910, 1725, 1705, 1655 and 835 cm⁻¹; nmr (CDCl₃) δ 1.06 (s,3), 1.43 (d, 3, J=7 Hz), 1.75 (dt, 3, J_{ed}=7 Hz; J_{eb}=J_{eb}=2; H_e), 2.06 (q, 1, J_{ab}=J_{ab}=J_{ab}=2 Hz; H_a), 2.45 (apparent q [possibly a sextet], 2, J_{ba}=J_b, a=J_b= \sim 2 Hz; H_b, H_b,), 2.91 (q, 1, J=7 Hz), 3.16 (d, 1, J_{ca}=2 Hz; H_c) and 5.46 (apparent qdt, 1, J_{db}=7, J_{db}=J_{db}=2, J_{dx} \sim 1; H_d).¹³

The genesis of 9 might originate with a pinacol-type rearrangement of 2 (R=H):



The previously unreported epimeric alcohols having structure 5 and an isomeric hydroxyketoacid derived by reduction of the carbonyl group located on the 3-carbon bridge of 1 have also been prepared, and will be described in a full paper concerned with additional aspects of santonic acid chemistry.

<u>Acknowledgements</u>: We thank the National Institutes of Health for financial support (Grant No. GM-13441), and Professor Wesley Cocker (Trinity College, Dublin, Ireland) and Dr. F.R. Smith (Macfarlan Smith Ltd., Edinburgh, Scotland) for generous supplies of β-santonin.

FOOTNOTES AND REFERENCES

- For a summary, see J. Simonsen and D.H.R. Barton, "The Terpenes", Vol. III, Cambridge University Press (1952), p. 295 <u>ff</u>. The stereochemistry of C-11 in santonin has since been revised: J.D.M. Asher and G.A. Sim, <u>Proc. Chem. Soc.</u>, 335 (1962) and references cited.
- 2. R.B. Woodward, F.J. Brutschy and H. Baer, J. Amer. Chem. Soc., 70, 4216 (1948).
- 3. Satisfactory microanalyses in agreement $(\pm 0.3\%)$ with theory were obtained for all new compounds, as well as for previously reported compounds for which revised structures are indicated. Melting points are uncorrected. Nur spectra were run on a Varian A-60A instrument using tetramethylsilane at δ 0.00 as an internal standard; coupling constants are in hertz (Hz) with multiplicity indicated by s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, etc.
- 4. C. Harries and A. Stähler, Chem. Ber., 37, 258 (1904).
- 5. K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J. Chem. Soc., 39 (1946).
- 6. R.B. Woodward and P. Yates, Chem. Ind. (London), 1391 (1954).
- 7. E. Wedekind and O. Engel, J. Prakt. Chem., 139, 115 (1934).
- 8. S. Cannizzaro, Gazz. Chim. Ital., 6, 341 (1876).
- 9. G.W. Griffin and R.B. Hager, J. Org. Chem., 28, 599 (1963).
- 10. J.G. St. C. Buchanan and P.D. Woodgate, Quart. Rev. (London), 23, 522 (1969).
- T.J. Curphey, C.W. Amelotti, T.P. Layloff, R.L. McCartney and J.H. Williams, <u>J. Amer.</u> <u>Chem. Soc.</u>, <u>91</u>, 2817 (1969); W. Reusch and D.B. Priddy, <u>ibid.</u>, <u>91</u>, 3677 (1969).
- 12. See also ref 2.
- Peak assignments and coupling constants were verified by decoupling studies using a Varian HA-100 spectrometer. Protons b and b' apparently have identical δ values (2.45 ppm).