[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Structure of 1-Keto-7-hydroxysantenic Acid and its Relationship to ψ-Santonin[1]

BY WILLIAM G. DAUBEN AND PAUL D. HANCE[2]

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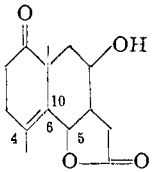
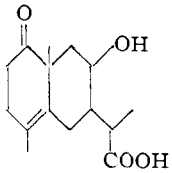
The structure of the hydrogenolysis product of ψ-santonin is shown to be 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid (IV). The bromolactone of this santenic acid upon dehydrobromination gives rise to ψ-santonin. This reaction, as well as nuclear magnetic resonance and ultraviolet absorption spectral studies, establishes the fact that the hydrogenolysis of the allylic lactone is accompanied by the migration of an olefinic linkage from a tetra- to a trisubstituted position.

The structure of ψ-santonin, a sesquiterpenic lactone isolated from various species of Artemisia,[3] has been the subject of a recent investigation in this laboratory and it has been postulated[1] that the compound can best be represented as structure I. The distinctive features of this new formulation are the placement of the double bond in a tetra-



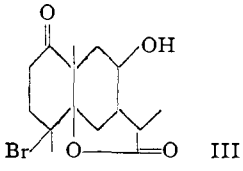
I



II

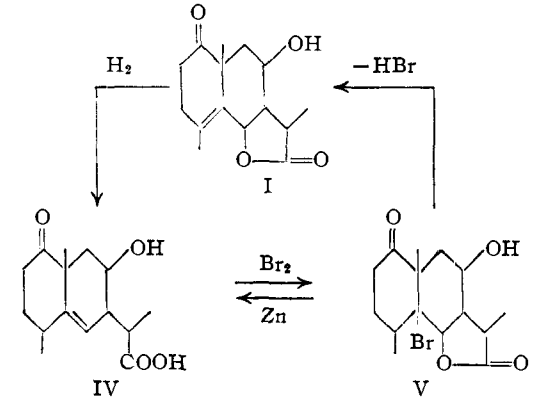
substituted position and the location of the free hydroxy group at C_7.[4] Some of the important evidence employed in substantiating such a structure was gained from a study of 1-keto-7-hydroxysantenic acid, the product formed by the dihydrogenation of ψ-santonin in acetic acid in the presence of palladium on charcoal. Since the material from such a hydrogenation was an acid which still retained a carbonyl group, an olefinic double bond and the original hydroxyl grouping, it was established that the reaction involved was the hydrogenolysis of the lactone ring of I. On the basis of such evidence and on the assumption that no double bond migration occurred during the reaction, it followed that 1-keto-7-hydroxysantenic acid could be represented as II. Since by a study of the lactonization of II, evidence was gained with regard to the position of the hydroxyl grouping, the only one feature of the compound requiring verification was the position of the double bond.

It is well-known that treatment of an unsaturated acid with bromine in the presence of base often gives rise to a bromolactone if the relationship of these two functional groups are proper and, indeed, Cocker and Hornsby[5] have reported that when II is allowed to react under such conditions, a crystalline bromolactone is obtained. This lactone upon treatment with zinc and ethanol regenerated the starting material. If structure II represented the correct formulation for 1-keto-7-hydroxysantenic acid, the bromolactone would be of the δ-type shown in III.



III

The presence of such a lactone could be demonstrated by the investigation of the lactonic carbonyl stretching frequency in the infrared since a δ-lactone is known[6] to absorb at 1740 cm.$^{-1}$ and since it has been shown that the presence of a halogen atom does not affect this characteristic frequency.[7] It was found, however, that the bromolactone absorbed at 1775 cm.$^{-1}$, a value expected of a γ-lactone rather than of a δ-lactone. Such a result would indicate either a β,γ- or γ,δ-unsaturated acid and the former possibility was tentatively rejected since the original santenic acid did not show the ease of decarboxylation characteristic of a β,γ-unsaturated acid. Direct evidence in this regard was obtained when it was found that the bromolactone upon dehydrohalogenation gave rise to ψ-santonin (I). The result of the dehydrobromination reaction clearly established the fact that the lactone ring formed in the preparation of the bromolactone was identical with the γ-lactone of ψ-santonin and that one end of the double bond in 1-keto-7-hydroxysantenic acid must be at C_5. Since the double bond in ψ-santonin has been shown to be between C_4 and C_{10}, the only available position for the double bond in the hydrogenolysis product is between C_5 and C_{10}, as shown in IV. Such a structure requires that the double bond undergoes a migration during the hydrogenolysis. This sequence of reactions can be summarized as shown below.



(1) For the preceding papers in this series, see THIS JOURNAL, **75**, 3352 (1953); and *ibid.*, **76**, 606 (1954).

(2) Recipient of the Dow Fellowship in Chemistry for 1953–1954, University of California.

(3) Messrs. T. and H. Smith, Ltd., *Pharm. J.*, **80**, 3 (1935).

(4) For the definition of the nomenclature employed and the numbering system used in this series, see the second paper of reference 1.

(5) W. Cocker and S. Hornsby, *J. Chem. Soc.*, 1157 (1947).

(6) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

(7) D. H. R. Barton and P. deMayo, *J. Chem. Soc.*, 887 (1954); E. E. van Tamelen and M. Shamma, THIS JOURNAL, **76**, 2315 (1954).

The assignment of a $\Delta^{5(10)}$-santenic acid structure to the hydrogenolysis product requires the presence of a trisubstituted olefinic bond whereas ψ-santonin itself possesses a tetrasubstituted unsaturated linkage. If such be the case, confirmatory evidence should be gained by examination of the infrared spectra of these compounds in the region characteristic for olefinic hydrogen stretching motions (2950–3100 cm.$^{-1}$) and the hydrogen bending motions of a trisubstituted double bond (800–840 cm.$^{-1}$). Although it was originally believed that the spectrum in the 3000 cm.$^{-1}$ region was of value for this type of diagnosis,[1] subsequent work[1] showed this to be untrue. Likewise, the 800–840 cm.$^{-1}$ region possessed many absorption bands and did not lend itself to analysis.

In view of the failure of infrared spectroscopy to yield definite results, the nuclear magnetic resonance spectra of I and IV were examined. Recently, Meyer, Saika and Gutowsky[8] found that the proton spectrum of a molecule was distinctive enough to be of value in a structure analysis and they compiled a comprehensive chart of the chemical shifts of δ-values, with respect to the proton resonance in water, for a number of organic compounds. It was reported that the δ-values for protons on saturated and unsaturated carbon atoms were quite distinctive and could be employed in a diagnostic manner. It was found in this present investigation that the small resonance shift for an olefinic proton as compared to the standard hydroxylic proton made the analysis difficult so the compounds studied were the acetate of ψ-santonin[1] and the methyl ester of 1-keto-7-acetoxy-$\Delta^{5(10)}$-santenic acid. The spectrum (Fig. 1, curve A) of the former clearly displayed the resonance absorption due to the various types of protons attached to saturated carbon atoms but was clear in the region (+0.2) where an olefinic hydrogen would be expected to absorb. However, the spectrum of the santenic acid derivative (Fig. 1, curve B) did display distinct absorption in the olefinic hydrogen region (+0.2), as would be expected for a compound of structure IV. Furthermore, by analysis of the areas under the curve obtained with the santenic ester in these distinctive regions, it was possible to estimate that for every proton attached to an olefinic linkage, there were 24 protons attached to saturated carbon atoms; the expected value based upon the acetate methyl ester of IV would be 1:25. Thus, these data not only add qualitative and quantitative support to the proposed structure of 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid for the hydrogenolysis product of ψ-santonin but also supply further evidence in support of the presence of a tetra-substituted double bond in the original sesquiterpenic lactone.

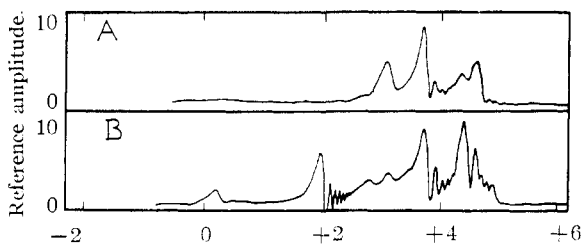


Fig. 1.—Nuclear magnetic resonance spectra: curve A, ψ-santonin acetate; curve B, methyl 1-keto-7-acetoxy-$\Delta^{5(10)}$-santenate. The following operating conditions were employed: frequency, 30 mc.; sweep width, 56 milligauss; sweep rate, 5.6 mg./sec.; H_1 amplitude, 3.5-low; reference, H_2O.

(8) L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, **75**, 4567 (1953).

This migration of a tetrasubstituted double bond to a trisubstituted position permits an explanation of the low wave length ultraviolet absorption of ψ-santonin and its di- and tetrahydro derivatives (VI). It has been previously demonstrated by Bladon, Henbest and Wood[9] that the rising absorption below 220 mμ, due to the tail of the maximum below 200 mμ of an isolated olefinic linkage, can be correlated with the degree of substitution of the double bond, a tetrasubstituted olefin absorbing with approximately twice the intensity of a trisubstituted moiety. Accordingly, the observed intensities[1] at 210 mμ for I, IV and VI of 8300, 4480 and 3630, respectively, are in agreement with the concept of a migration of the double bond from a tetra to a trisubstituted position.

The formation of a compound possessing the structure IV is not only unique in that migration of the double bond occurs but also that the migration is away from what would be expected to be the thermodynamically stable position. A mobility of an unsaturated system in this type of reaction may be masked in many hydrogenolyses due to the fact that saturation of the double bond generally occurs.[10] The non-reactivity toward hydrogen over palladium–charcoal catalyst of the new double bond in this santenic acid would seem to indicate that its further hydrogenation is retarded by the presence of substituents at C_4, C_6 and C_9 in such a steric orientation to give rise to a large catalyst hindrance. A similar arrangement of groups is present in various triterpenes which also possess an unreactive double bond. This unusual hydrogenolysis of ψ-santonin is under further investigation.

Acknowledgment.—The authors are indebted to Messrs. T. and H. Smith, Edinburgh, for kindly supplying the ψ-santonin used in this study and to Dr. James N. Shoolery of Varian Associates, Palo Alto, California, for the nuclear magnetic resonance data.

Experimental[11]

1-Keto-7-hydroxy-10-bromosanten-12,5-olide (V).—To a solution of 0.3 g. of 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid

(9) P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(10) With the Senecio alkaloid *Riddelliine*, Adams and Van Duuren (THIS JOURNAL, **75**, 4638 (1953)) reported that hydrogenolysis of the allylic ester occurred without saturation or migration of the double bond. In this compound, however, the double bond is allylic to an amino group as well as to an ester and the steric and electronic environment of the linkage in such a system is very different.

(11) All analyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley. All melting points are corrected. The infrared spectra were obtained with a Model 21 Perkin–Elmer spectrophotometer using sodium chloride optics and the cells were approximately 0.1 mm. thick.

and 0.3 g. of sodium carbonate in 20 ml. of water, bromine (0.18 ml.) was added dropwise with vigorous stirring. The precipitate was filtered, washed with water and recrystallized from ethyl acetate to give 0.33 g. (84%) of the bromolactone, m.p. 165–170° dec. (lit.[5] m.p. 180° dec.).

Anal. Calcd. for $C_{15}H_{21}O_4Br$: C, 52.18; H, 6.13; Br, 23.15. Found: C, 52.37; H, 6.24; Br, 23.40.

Preparation of ψ-Santonin (I) from Bromolactone (V).—The bromolactone (0.4 g.), prepared as above, was heated with 4 ml. of 2,4,6-collidine and 2 ml. of toluene at 140° for 3 hours. The cooled solution was poured into water, extracted with chloroform and the organic layer washed with dilute acid, bicarbonate solution and dried. Decolorization of the solution with Norit and evaporation of the solvent yielded a solid which upon recrystallization from benzene–chloroform gave 0.18 g. (59%) of ψ-santonin, m.p. and mixed m.p. with authentic material, 189.8–190.8°, $[\alpha]^{25}D$ −161.0° (*c* 0.41, EtOH). The ultraviolet and infrared spectra of the product were identical with those of ψ-santonin.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.38; H, 7.77.

1-Keto-7-hydroxy-$\Delta^{5(10)}$-santenic Acid (IV).—Hydrogenation of ψ-santonin according to the method of Clemo and Cocker[12] and recrystallization from methanol gave 82% of the product, m.p. 191.0–193.4°, $[\alpha]^{25}D$ −3.3° (*c* 1.01, EtOH), $[\alpha]^{25}D$ −6.6° (*c* 0.635, HOAc). Clemo and Cocker[12] report a m.p. 188–189° but a $[\alpha]^{20}D$ −239 (*c* 0.96 HOAc) which we have never obtained.

The methyl ester was prepared with diazomethane and recrystallized from ether–hexane, m.p. 76.8–78.7°, $[\alpha]^{25}D$ +5.6° (*c* 1.6, EtOH) (lit.[12] m.p. 77°). The ester upon reaction with acetic anhydride and a drop of pyridine in the warm for 2 hours followed by evaporation of the reagents and washing of the residue with acid, base and water yielded the crystalline acetate ester. The material was recrystallized from ether–hexane and then sublimed, m.p. 105.8–106.3°.

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.04; H, 8.06.

(12) G. R. Clemo and W. Cocker, *J. Chem. Soc.*, 30 (1946).

BERKELEY 4, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, NAVAL ORDNANCE TEST STATION]

The Synthesis of Secondary Nitramines by the Nitrolysis of N,N-Disubstituted Amides

BY JOHN H. ROBSON AND JOAN REINHART

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The nitrolysis of N,N-disubstituted amides in trifluoroacetic anhydride has been further investigated. When the substituents are *n*-alkyl groups, the nitrolysis of acetamides, methanesulfonamides and benzenesulfonamides gives almost quantitative yields of the corresponding secondary nitramines. The nitrolysis, however, is retarded easily both by steric hindrance from the N-alkyl groups and by electronegative substituents.

The nitrolysis of N,N-disubstituted amides has long been known as a possible route for the synthesis of secondary nitramines.[1] In fact, Franchimont[2] obtained the first known nitramine by the nitrolysis of *unsym*-dimethylurea. Such nitrolyses usually were carried out in what was described as "absolute" or "fuming" nitric acid and gave the nitramines in very poor yield if at all. Thus acetamides, oxamides, sulfonamides, carbamates and ureas generally failed to give the nitramines if substituted with other than N,N-dimethyl, piperazino or morpholino groups. Prior to the very recent and elegant Emmons nitrosamine oxidation method[3] the only useful laboratory method for the preparation of secondary nitramines was Wright's[4] chloride-catalyzed nitration of secondary amines. The latter method, although of quite general applicability, frequently involves undesirable side reactions and may be very slow in certain cases.

It was shown previously[5] that a series of N,N-disubstituted formamides were nitrolyzed readily to the secondary nitramines in trifluoroacetic anhydride. These reactions were very rapid even at 0° and the nitramines were obtained essentially in quantitative yield. Neither starting amide nor nitrosamine by-product was detected. Because of the utility of a method for the synthesis of secondary nitramines which involves only the preparation of easily obtainable amide intermediates, this nitrolysis has been studied further with a number of amides in which both the N-alkyl substituents and the acyl moieties have been varied (Table I).

TABLE I

THE NITROLYSIS OF VARIOUS TYPES OF N,N-DISUBSTITUTED AMIDES IN TRIFLUOROACETIC ANHYDRIDE

Amide	Yields, % Nitramine	Nitrosamine[a]	Recovd. amide
N,N-Diethylacetamide	81	0	..
N,N-Di-*n*-propylacetamide	93	..	0
N,N-Di-*n*-butylacetamide	82	0	0
N,N-Di-*n*-hexylacetamide	95	..	..
N,N-Di-*n*-heptylacetamide	98	..	..
N,N-Diethylmethanesulfonamide	94	0	0
N,N-Di-*n*-butylmethanesulfonamide	87	0	0
N,N-Di-*n*-butylbenzenesulfonamide	78	0	..
N,N′-Diformylpiperazine	45	..	..
N,N′-Diformylpiperazine[b]	0	..	0
2,6-Diformyl-2,6-diaza-4-oxaheptane	0	..	..
N,N-Diisopropylformamide[c]	0	..	68
N,N-Dicyclohexylformamide[c]	0	..	51
N,N-Diisobutylacetamide	4	..	81
N,N-Diisobutylacetamide[d]	15	..	..
N,N-Di-*n*-butyltrichloroacetamide	0	0	91
N,N-Di-β-cyanoethylacetamide	0	..	79
Ethyl N,N-diethylcarbamate	0	..	0
Ethyl N,N-di-*n*-butylcarbamate	0	0	0
N,N-Diethylurea	18	..	0

[a] The yields are indicated only in cases where the nitrosamine could be isolated either by distillation or by extraction with concentrated hydrochloric acid. [b] Reaction carried out in acetic anhydride. [c] Reaction time two hours at 0°. [d] Reaction time four hours at 20°.

(1) Review article by H. J. Backer, *Sammlung Chem. und Chem. Tech. Vortrage*, **18**, 359 (1912); see also A. H. Lamberton, *Quart. Revs.*, Vol. V, No. 1 (1951).

(2) A. P. N. Franchimont, *Rec. trav. chim.*, **2**, 121 (1883).

(3) W. D. Emmons, THIS JOURNAL, **76**, 3468 (1954).

(4) W. J. Chute, K. G. Herring, L. E. Toombs and G. F. Wright, *Can. J. Research*, **26B**, 89 (1948).

(5) J. H. Robson, THIS JOURNAL, **77**, 107 (1955).