Ch 80 Research Report:

The Photochemistry of 6-epi-santonin

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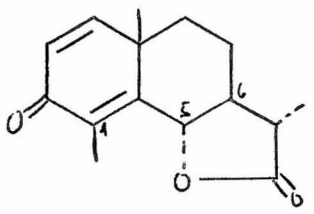
ABSTRACT: To test the hypothesis that 6-epi-santonin's different stereochemistry might allow a phenolic photoproduct, unlike santonin, several irradiations of 6-epi-santonin were run in an attempt to isolate a phenol. Although no phenol could be isolated, the results were ambiguous as to whether a phenol was actually present. An attempt to determine the product distribution was also made, but was not completed.

INTRODUCTION: The most typical photoproduct for a 2,4-cyclohexadienone is a phenol, by a process analogous to the acid-catalyzed dienone-phenol rearrangement. An interesting exception is santonin (I) which has no phenolic photoproducts in aprotic solvents* There are obviously two possible differences between santonin and an ordinary 2,4-cyclohexadienone which could explain this behavior: the methyl group on C-4 or the γ-lactone ring. If one considers the stereochemistry of santonin, he discovers that the trans lactone makes the molecule quite rigid and this rigidity might be responsible for the failure to produce a phenol. In order to test this theory, an epimer of santonin, 6-epi-santonin, with a



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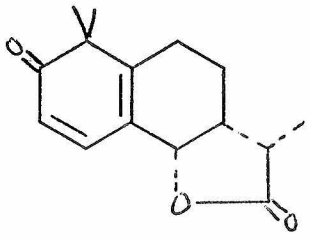
* M. Fisch, Ph.D. thesis, California Institute of Technology, 1964

cis lactone was made and its photochemistry studied to see if it did produce a phenol and also to see what other differences might be found in products and product distributions.

RESULTS: The first irradiation of 6-epi-santonin was done using a small sample dissolved in benzene, sealed in an evacuated NMR tube, and was run overnight. An NMR spectrum taken of the mixture after irradiation indicated moderate quantities of (II). An extraction of acidic compounds with 5% NaOH was attempted, but was hampered by the formation of an emulsion with the benzene. VPC, however, indicated the presence of only one neutral photoproduct, and there was evidence for an acidic product. An infrared spectrum of the acidic substance in chloroform showed a peak at 1776 cm^{-1} for the γ-lactone, and one at 1603 cm^{-1}, possibly a phenyl nucleus, but neither corresponding to a carboxylic acid, indicating that the acidic substance may be a phenol.



II

On the basis of these results, it was decided to run a much larger sample and do a quantitative extraction, using chloroform as a solvent instead of benzene in order to get around the emulsion difficulty mentioned above. 5% NaOH definitely extracted something and caused a separation into a neutral and an acidic fraction. The acidic fraction turned red-brown with $FeCl_3$, indicating the presence of a phenol. It was decided

to chromatograph this acidic fraction on silica gel to purify it, but a mistake was made in elution solvents. When this mistake was discovered, the column was flushed with ethyl acetate. This solution, however, gave no evidence of a santonin-like compound, and it was decided that the column had either caused the decomposition of the acidic product or held it all back.

After the next irradiation, several attempts were made to obtain a phenol in the crystalline state. After irradiation, the solution was stripped of benzene and the residue was redissolved in chloroform and extracted with 5% NaOH as before. The NaOH solution was acidified by bubbling carbon dioxide through it, so as to precipitate a phenol. The only precipitate formed, even after standing in the refrigerator, was proved to be inorganic by an infrared spectrum and a melting point determination. The solution was acidified with 5% HCl and extracted with chloroform. The chloroform was dried and stripped off and the residue weighed, giving a yield of 8.9% of possibly phenolic material. Infrared and ultraviolet spectra were inconclusive on this material, however. Two different methods of acetylation were attempted, but neither produced a crystalline product which could be identified as a santonin compound.

At this point, it was decided that some of the earlier problems might be the result of air oxidation, either during the irradiation or after, so an irradiation under nitrogen was tried, and the product dis-

Table I

Results of Liquid-Liquid Chromatograph of Acidic Fraction

Cuts	Weight(mg)	IR Bands(cm^{-1})	Comments
2	8		Impure
1	41	1780,1730,1630,1567	NMR, UV
30	27	1780,1730,1605,1557	NMR, UV
24	2		Impure
23,19	27	1775,1670,1640,1605,1580	NMR, UV
17,18	8	1780,1675,1605	UV
13,14,15	14	1776,1736,1605	UV
62	4	1790,1695,1605	
61	4	1770,1600	
41,42	7	1774,1734,1600	UV
40	4		Impure

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tribution was to be found using liquid-liquid partition chromatography. The irradiation proceeded for twelve hours with dry nitrogen bubbling through, and the benzene solution was worked up in the usual manner and separated into an acidic and a neutral fraction. The acidic fraction accounted for 44% (222 mg) of the original 500 mg of sample. This material was chromatographed on a Celite 545 column using nitromethane as a stationary phase and 5:1 hexane:benzene (by volume) as a mobile phase, equilibrated beforehand. When the sample was dissolved in nitromethane to charge the column, a small amount would not dissolve. It was separated and an infrared spectrum was taken which indicated it was a santonin compound and probably had a hydroxyl group, but probably was not a phenol. Nothing more was done with it. Cuts of about 100 ml were taken, dried, weighed, and an infrared spectrum of the region from 1500 cm^{-1} to 1900 cm^{-1} x ~~and~~ taken,

along with NMR and ultraviolet spectra in some cases. A total of 159 mg of the original 222 mg was recovered, indicating either a very polar component that did not come off the column or a decomposition on the column. See Table I for data about the various fractions identified.

The neutral fraction was then chromatographed in the same manner. In this case, 174 mg of 278 mg was recovered. The same analysis as with the acidic fraction was started but not completed. The only useful information was that the major fraction had an infrared spectrum different from that of 6-epi-mazdasantonin, the expected major product. This fact may be due to decomposition of the fraction while sitting in the cupboard during the analysis of the acidic fraction, or to its staying on the column, although santonin experience would indicate that the latter possibility is unlikely.

DISCUSSION: On the basis of these results, it is hard to say anything about the existance or non-existance of a phenolic photoproduct of 6-epi-santonin. Certainly, the existance of an acidic component which is not a carboxylic acid would indicate a probable phenolic fraction. Unfortunately, the data obtained on the final irradiation with the liquid-liquid chromatograph are not sufficient to say much. The infrared spectra are extremely hard to interpret without the other wavelengths present, and in fact, they were

used mainly to check for the γ-lactone band indicating whether the product was a santonin compound or not. Also the fractions show many differences in the infrared, but the three for which an NMR spectrum was taken all have the same NMR spectrum. Presumably, some of the peaks are due to small amounts of impurities, with only a few of those listed corresponding to peaks in the major product. Further, the calibration is not very good, since the spectra were not taken to be used in identification. The NMR spectrum was also hard to interpret because the concentration of sample was not very high (in fact, the the ethanol peaks from the chloroform are as strong as the main peak present for the compound) and the noise drowns out all but one peak, at δ=1.8 which appears unsplit. This peak may be methyl groups or methylene groups, but it gives little information about the product. The ultraviolet spectra are probably the most informative of the three, but they are uniformly negative. See Table II.

Table II: Ultraviolet Data

Cuts	λ_{MAX} (mμ)
1,19,23,30	235 shoulder 309 352 shoulder
13-15	235 shoulder 307
41,42	232 shoulder 304 shoulder
17,18	307

These absorptions are all about the same intensity, but the actual value of the extinction coefficient is not known because the concentrations were not measured. The bands display none of the fine structure associated with aromatic absorptions, and they don not

seem to occur at the right wavelength for phenols, either. The 235 mμ shoulder apparent on all but the last one (cuts 17 and 18) is about right for a conjugated ketone which could be a product. The absorptions around 300 mμ may be n→π* carbonyl transitions, but these would be much weaker than the 235 mμ band, which they are not.

It seems apparent from the work that has been done that this investigation ought to be continued, and that with a continuation along the same lines as the investigations reported, good results could be obtained. The main problems encountered were apparent instability of some products and lack of time to develop suitable methods. The liquid-liquid partition chromatography appears to be about the best method of separation, and it was found to work quite well for santonin. It is, however, rather tedious and time consuming. The initial separation of an acidic and a neutral component presents problems because benzene forms emulsions very easily, while base extractions from chloroform may lead to degredations caused by carbenes. It might be better not to do this initial separation. Finally, the irradiation must be done in a neutral atmosphere to avoid possible air oxidations. I would like to say once more that I think the project is worthwhile and I would like to see it continued.

EXPERIMENTAL:

I. Purification of 6-epi-santonin: A large quantity of

6-epi-santonin was obtained from M. Fisch and purified by chromatography on 130 gms grade II alumina. The solvent was 3:1 benzene:hexane. The purified product was a white crystalline solid, melting point 104.1-105.0°C.

II. Irradiations: All the irradiations were done in water-jacketed immersion reactors with a 100 ml solution volume. The light source was a 200 w Hanovia ultraviolet lamp with a uranyl glass filter. A solution of about 500 mg (accurately weighed) 6-epi-santonin in 100 ml benzene and placed in the reactor. Irradiations were run for about twelve hours, since this period had been shown earlier to lead to complete reaction. The irradiation under nitrogen used an immersion reactor with a fritted glass disk at the bottom fitted with a stopcock to admit the nitrogen. Nitrogen used was CIT high purity dry nitrogen. After the irradiation was over, the benzene solution was poured out and the reactor was washed with several portions of benzene, then the benzene was stripped off, leaving a powdery brownish residue.

III. Separation into neutral and acidic fractions: The residue from the irradiation was dissolved in chloroform and extracted with 5% NaOH several times (usually about eight), each extraction resulting in a colored aqueous layer. The residual chloroform layer was dried over $MgSO_4$ and stripped of solvent. The NaOH solution was acidified with HCl and reextracted again requiring several extractions to get the color

out. This chloroform solution was dried over $MgSO_4$ and stripped of solvent.

IV. Chromatograph of acidic fraction on silica gel: The acidic fraction from one of the irradiations was dissolved in benzene and put on a column of 15 gms Davidson silica gel deactivated with 5% distilled water by weight (corresponds to grade III alumina). The column was to be run with benzene-ethyl acetate in varying amounts until the substance came off, but it was discovered that nitromethane had been used instead of ethyl acetate, so the column was thoroughly flushed with ethyl acetate. The resulting solution showed no γ-lactone peak in the infrared.

V. Attempted crystallizations and derivatives:

A. Slow neutralization with carbon dioxide: After extraction of the irradiation mixture with NaOH, the aqueous solution was slowly neutralized by bubbling carbon dioxide through it. After the pH had reached 7, no crystallization had occurred, so the solution was cooled in an ice bath. After this failed to cause a precipitate, it was cooled overnight in a refrigerator. This caused precipitation of a very high melting (>300°C) white crystalline product, which had no γ-lactone peak in the infrared. The solution was acidified and extracted as before.

B. Acetylation: The product obtained after reextraction of the basic solution was reacted with acetic anhydride to form an acetate by two procedures:

1. Dissolve the phenol in 3N NaOH and add

ice. This is followed by acetic anhydride. The mixture is shaken for one minute.

2. Reflux the phenol and acetic anhydride for 10-15 minutes, then pour into cold water. This solution is boiled to destroy the excess acetic anhydride and then cooled.

Both these procedures gave a fine, yellow-orange solid product in small yield after cooling, but the infrared spectrum showed no γ-lactone peak for a santonin-like compound.

VI. Liquid-liquid partition chromatograph: The supporting material was Celite 545 prepared in the following manner: it is washed overnight in hot 6N HCl and then rinsed with water. This procedure is repeated except that three water rinses are used. Next the Celite is washed overnight in 1:1 methanol:ethyl acetate and then rinsed six times with water. It is then oven dried for twelve hours, after which it is ready to use.

The solvents used were nitromethane as a stationary phase and 5:1 hexane:benzene (by volume) as a mobile phase. All the solvents were redistilled and dried, and the phases were equilibrated on a shaker for two hours before use.

The column was prepared by charging 320 gms Celite with 160 ml stationary phase and packing it in a 20 cmx 200 cm water jacketed column. The substance to be chromatographed was dissolved in 10 ml stationary phase and adsorbed on 20 gms Celite, then packed on top of the other Celite. The column and the solvent

supply were thermostated to 30.0°C and the column was allowed to equilbrate for 30 min before the mobile phase was started through it. The solvent was also equilibrated in a thermostated container before use.

The cuts were about 100 ml each, and were collected on an automatic cut collector. They were transferred to weighed beakers and the solvent was boiled off. The residue, if any, was weighed and dissolved in chloroform, transferred to a test tube, and an infrared spectrum of the region 1500 cm^{-1} -1900 cm^{-1} was run.

Acknowledgement: I wish to thank Dr. J. H. Richards for offering me the project, and I especially wish to thank Mike Fisch for doing most of the thinking and being generally invaluable assisstance, as well as good company.