COOH → $2C_3H_5S—S—CH_2—CH(NH_2)—COOH$ + H_2O and a secondary reaction may be $C_3H_5SO—S—C_3H_5$ + $HSCH_2—CH(NH_2)—COOH$ → C_3H_5SH + $C_3H_5SO—S—CH_2—CH(NH_2)—COOH$.

The presence of a chemical substance as unstable as allicin in garlic which has been stored for several months to a year raises the question as to the nature of its state in garlic. If this oxide exists in a bound form, it has been impossible to prevent its liberation by grinding the garlic under alcohol or acetone. If it is formed by oxidation of allyl disulfide, the reaction is not inhibited by grinding under the organic solvents which should prevent enzymatic catalysis of the oxidation. There is also posed the question as to whether the degradation of allicin in garlic leads to formation of the other sulfides present, or whether the antibacterial agent arises from oxidation of the sulfides. The other sulfides could well arise from allicin inasmuch as garlic contains from 0.3 to 0.5% of this compound as determined by antibacterial activity. We also believe that the characteristic odor of garlic should be ascribed to allicin rather than to the allyl sulfides.

The mechanism by which allicin acts as an antibacterial agent may be suggested by its reaction with cysteine. The sulfhydryl group is postulated to be a specific stimulator of cell multiplication.[8] Since allicin is considerably more bacteriostatic than bactericidal in action, it may operate by destroying —SH groups essential to bacterial proliferation, thus inhibiting growth. The heavy line of growth surrounding the zone of inhibition in cup-plate tests may be the result of the stimulating action of —SH groups in products formed in the degradation of the antibacterial agent. Hammett[8] points out that whereas SH is stimulating and sulfonates are inert, the intermediate stages of sulfide oxidation, such as the sulfoxides, are inhibitory to cellular proliferation in marine animals.

Summary

The antibacterial principle from *Allium sativum* has been assigned the structure allyl—S(=O)—S—allyl with the structure allyl—S—O—S—allyl not entirely eliminated. A discussion of its reactions is included.

(8) Hammett and co-workers, *Protoplasma*, **10**, 382 (1930); **13**, 261 (1931); **15**, 59 (1932); **16**, 253 (1932).

RENSSELAER, N. Y. RECEIVED OCTOBER 6, 1944

[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

Studies in the Santonin Series. II. The Bromination Products of Desmotropo-santonins and Desmotropo-santonous Acids[1]

BY HUANG MINLON,[2] C. P. LO AND LUCY J. Y. CHU

In a previous paper[3] it has been shown that santonin can be transformed into *l*-α-desmotropo-santonin acetate[4] through enol acetylation and that the four known optically active isomers of desmotropo-santonins can be converted into each other by treating with acid or alkali or by alternating the treatments. It is therefore desirable to study whether the halo-santonin and the halo-desmotropo-santonins can be similarly transformed and converted or not. It was found that when monobromosantonin (III), the constitution of which was well established by Wedekind,[5] was treated with acetic anhydride and sulfuric acid, it changed into the bromo-*l*-α-desmotropo-santonin acetate (IV). This gave the bromo-*l*-α-desmotropo-santonin (V) upon saponification. The same compound could also be obtained by the direct bromination of *l*-α-desmotropo-santonin (VI). It may be concluded from the first series of reactions that the bromine atom of the bromo-*l*-α-desmotropo-santonin must be in the aromatic ring. From the second series of reactions it is obvious that the bromine atom must occupy the position ortho to the phenolic hydroxyl group, since there is one and only one free position in the aromatic ring of *l*-α-desmotropo-santonin. The designation of this product as 2-bromo-*l*-α-desmotropo-santonin is therefore beyond any doubt.

The bromo-desmotropo-santonins are still unknown in the literature. These compounds can now be easily prepared by the direct bromination of the corresponding desmotropo-santonins. The yields are generally satisfactory.

The conversion of the bromo-α-desmotropo-santonins into the bromo-β-desmotropo-santonins by treating with acid was not possible. On the other hand the high melting bromo-desmotropo-santonins could be converted into the low melting ones by fusing with alkali. Thus we are able to

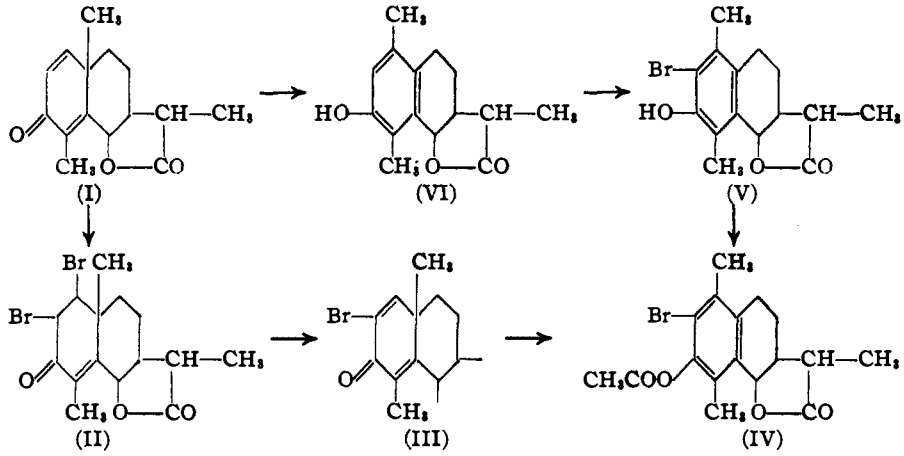
(1) Publication of this manuscript was at first postponed pending the submission of analytical data for the new compounds described. We have now learned from the authors that it has been impossible in China for a year or more to make the stipulated analyses and that there is little likelihood of the situation improving until after the conclusion of hostilities. In view of this situation and since the new substances had been tentatively identified by conversion into known derivatives, the manuscript was accepted for publication.—*The Editor.*

(2) Research Fellow, Associate Research Fellow, and Assistant Fellow, respectively.

(3) Huang Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943).

(4) For nomenclature of desmotropo-santonins and desmotropo-santonous acids, see previous paper, ref. 3.

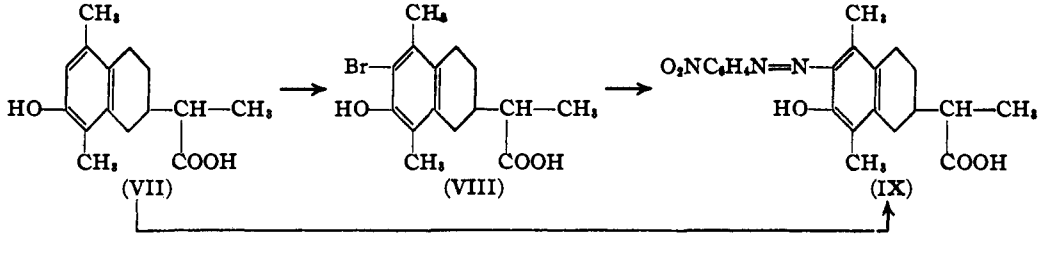
(5) Wedekind, *Ber.*, **41**, 364 (1908).



convert the bromo-*d*-β-desmotropo-santonin into the bromo-*d*-α-desmotropo-santonin which is identical with the product obtained by the direct bromination of *d*-α-desmotropo-santonin, and to convert the bromo-*l*-β-desmotropo-santonin into the bromo-*l*-α-desmotropo-santonin which is in no way different from that obtained by the bromination of *l*-α-desmotropo-santonin. However, the yields were rather low. The presence of the bromine atom, therefore, has no effect on the stereochemical course of the reaction.

The bromo-desmotropo-santonous acids (bromo-santonous acids) were known a long time ago. They were generally prepared according to the procedure of Andreocci[6] indirectly from the desmotropo-santonous acids (santonous acids) by first changing them into the corresponding esters, brominating and then saponifying the bromo-esters thus obtained. As the previous worker could not ascertain the position of the bromine atom, the acids are generally designated as *x*-bromo-desmotropo-santonous acids (*x*-bromo-santonous acids). Since the desmotropo-santonins are easily brominated to obtain compounds possessing the bromine atom in the aromatic ring, we believe that the bromine atom of the bromo-desmotropo-santonous acids also occupies the analogous 2-position. In this work the desmotropo-santonous acids (VII) were subjected to direct bromination. The yields are as good as in the case of the bromination of the desmotropo-santonins. As this procedure involves a single step, it is obviously much simpler than the indirect method just mentioned.

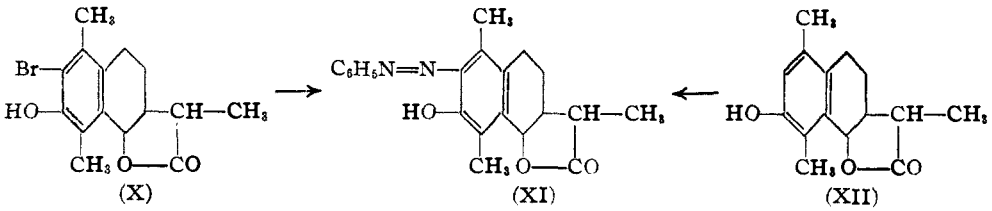
To determine the position of the bromine atom in the bromo-desmotropo-santonous acid (VIII), the latter was allowed to couple with *p*-nitrobenzene diazonium chloride. If the bromine atom occupied a position in the side chain containing the carboxyl group or in the alicyclic ring it is expected that the coupling would take place at the vacant position ortho to the phenolic hydroxyl group and the dyestuff obtained must contain bromine; if it occupied a position in the aromatic ring there should be either no coupling, owing to the fact that all the positions in the aromatic ring are fully occupied or an unusual coupling would take place in which the bromine atom is replaced by the aryl azo group, producing a bromine-free dyestuff. The latter reaction is by no means new. Hewitt and Mitchell[7] have reported that when 1-halo-β-naphthol was coupled with diazotized *p*-nitro-aniline, *p*-nitrobenzene-azo-β-naphthol was obtained as the coupling product. Another somewhat analogous reaction of a bromo-phenolic steroid was recently described by Inhoffen and Zühlsdorff.[8] In the present work it was found that when bromo-*d*-α-desmotropo-santonous acid was allowed to react with *p*-nitrobenzenediazonium chloride, the coupling was very rapid and a bromine-free dyestuff was actually obtained. This dyestuff when purified was found to be identical with that obtained from *d*-α-desmotropo-santonous acid and diazotized *p*-nitroaniline. It may be concluded here that the bromine atom of the bromo-desmotropo-santonous acids occupies a position in the ring



(6) Andreocci, *Gass. chim. ital.*, **25**, I, 501 (1895).

(7) Hewitt and Mitchell, *J. Chem. Soc.*, 1167 (1906).

(8) Inhoffen and Zühlsdorff, *Ber.*, **74**, 604 (1941).



and it is displaced by the *p*-nitrobenzene-azo group during the coupling process. This unusual coupling reaction is also exhibited by the bromo-desmotropo-santonin. Thus the product obtained by coupling the benzenediazonium chloride with bromo-*d*-β-desmotropo-santonin (X) has been found to be identical with benzene-azo-*d*-β-desmotropo-santonin (anilinazo-desmotropo-santonin) (XI) which Wedekind and Schmidt[9] have obtained from diazotized aniline and *d*-β-desmotropo-santonin (XII). This reaction also serves as a further proof of the position of the bromine atom in the bromo-desmotropo-santonins.

Experimental

Mono-bromo-santonin (III) was prepared from santonin (I) through dibromo-santonin (II) by the method of Wedekind.[5]

Bromo-*l*-α-desmotropo-santonin Acetate (IV).—One-half gram of monobromo-santonin was treated with 6 ml. of acetic anhydride and two drops of concentrated sulfuric acid. The solution was heated in a boiling water-bath until the color changed from green to slightly greenish-yellow (about two hours). It was then decomposed with hot water. The solid was filtered and crystallized from alcohol, yielding 0.23 g. of crystals melting at 158–160°. The dry product was dissolved in benzene and adsorbed by aluminum oxide. Elution with benzene yielded 0.09 g. of the pure substance, which on crystallization from alcohol gave colorless rectangular plates, m. p. 182–183°.

Bromo-*l*-α-desmotropo-santonin (V).—One-tenth gram of (IV) was refluxed with 10 ml. of 10% potassium hydroxide solution for one and half hours. The solution while warm was neutralized with dilute acid. The solid crystals were filtered and crystallized from alcohol, m. p. 119–121° (0.03 g.). The product on further recrystallization from alcohol yielded colorless prismatic needles of m. p. 121–123°.

Bromination of *l*-α-Desmotropo-santonin.—Two and one-half grams of *l*-α-desmotropo-santonin was dissolved in 200 ml. of dry chloroform and a solution of 0.7 ml. of bromine in 10 ml. of dry chloroform was added slowly. After the solution was allowed to stand for about half an hour, it was shaken three times with water and the chloroform removed. The residue was recrystallized two times from alcohol yielding 1.7 g. of bromo-*l*-α-desmotropo-santonin, as colorless long prismatic needles, m. p. 122°. It gave no depression of m. p. when mixed with (V).

Acetylation of Bromo-*l*-α-desmotropo-santonin.—Two-tenths gram of the above compound mixed with 0.4 g. of anhydrous sodium acetate and 2 ml. of acetic anhydride was refluxed for two hours and then decomposed with water. The bromo-*l*-α-desmotropo-santonin acetate was filtered and crystallized two times from alcohol as stout prisms, m. p. 185° (0.18 g.), not depressed by admixture with (IV).

Bromo-*d*-β-desmotropo-santonin (X).—Five grams of *d*-β-desmotropo-santonin was brominated as above; yield 5.5 g. of bromo-*d*-β-desmotropo-santonin, colorless prismatic needles, m. p. 210–211°.

(9) Wedekind and Schmidt, *Ber.*, **36**, 1391 (1903).

Bromo-*d*-α-desmotropo-santonin (XIII).—(a) From *d*-α-desmotropo-santonin: *d*-α-desmotropo-santonin was brominated as above. The bromo-*d*-α-desmotropo-santonin was obtained as colorless prisms, m. p. 121–122°. The mixed m. p. of this compound and (V) was 173–177° due to racemization of these two compounds (see below).

(b) From bromo-*d*-β-desmotropo-santonin: A half gram of bromo-*d*-β-desmotropo-santonin, 0.6 g. of potassium hydroxide and 1 ml. of water were heated in a test-tube with an air condenser in an oil-bath at 195–200 for three hours. The length of the condenser was so adjusted that there was only refluxing in the first two hours and slow evaporation during the third hour. The solid was dissolved in water and the boiling solution acidified. The precipitate was fractionally crystallized from alcohol. The first fraction gave 0.08 g. of short prisms, m. p. 200–206°; the second, 0.09 g. of triangular prisms, m. p. 155–160°; and the third, 0.13 g. of long thin plates, m. p. 115–120°. The last fraction was recrystallized two times from alcohol, yielding the bromo-*d*-β-desmotropo-santonin of the constant m. p. 121–122°. It gave no depression of m. p. when mixed with that obtained from (a).

Bromo-*l*-β-desmotropo-santonin (XIV).—*l*-β-Desmotropo-santonin was brominated as above. The bromo-*l*-β-desmotropo-santonin was obtained as colorless prismatic needles, m. p. 210–211°. The mixed m. p. of this compound and (X) was 196–198°.

Bromo-*l*-α-desmotropo-santonin from Bromo-*l*-β-desmotropo-santonin.—The above product was fused with potassium hydroxide and water as above and gave long, thin plates of bromo-*l*-α-desmotropo-santonin after two crystallizations from alcohol, m. p. 121–122°, not depressed by admixture with (V). The mixed m. p. of this compound and (XIII) was 170–175° due to racemization of these two compounds (see below).

Bromo-*dl*-α-desmotropo-santonin (XV).—(a) Bromination of *dl*-α-desmotropo-santonin: Racemic desmotropo-santonin was brominated as above. The bromo-*dl*-α-desmotropo-santonin was obtained as rectangular plates, m. p. 188–189°.

(b) From *d*- and *l*-bromo-α-desmotropo-santonin: Racemic bromo-α-desmotropo-santonin was obtained by crystallizing equal quantities of (V) and (XIII) from alcohol as rectangular thin plates, m. p. 187–189°, not depressed by admixture with that obtained in (a).

Bromo-*dl*-β-desmotropo-santonin (XVI).—(a) Bromination of *dl*-β-desmotropo-santonin: Racemic β-desmotropo-santonin was brominated as above. The bromo-*dl*-β-desmotropo-santonin was obtained as short prisms, m. p. 203–204 (bath preheated to 190°) depressed to 197–199° by admixture with either bromo-*d*-β- or bromo-*l*-β-desmotropo-santonin.

(b) From *d*- and *l*-bromo-β-desmotropo-santonins: Racemic bromo-β-desmotropo-santonin was obtained by crystallizing equal quantities of (X) and (XIV) from alcohol as short prisms, m. p. 203–204° (bath preheated to 190°), not depressed by admixture with that obtained in (a).

Bromination of *d*-α-Desmotropo-santonous Acid.—One gram of *d*-α-desmotropo-santonous acid was dissolved in 200 ml. of dry chloroform. A solution of 0.22 ml. of bromine in 10 ml. of dry chloroform was added. After standing for a half hour, the solution was washed three times with water. The chloroform was then removed and the residual oil was crystallized from a mixture of ether and gasoline, 1.2 g. of small plates being obtained. The bromo-*d*-α-desmotropo-santonous acid gave the constant

m. p. of 116–118°. Andreocci reported 116° after one recrystallization from ether and gasoline.

Bromination of *l*-β-Desmotropo-santonous Acid.—*l*-β-desmotropo-santonous acid was brominated as above. The bromo-*l*-β-desmotropo-santonous acid was obtained as rectangular plates, m. p. 122–123°. Since Andreocci reported the m. p. of this acid as 92°, his procedure was repeated. The methyl ester of *l*-β-desmotropo-santonous acid was brominated as usual. The crude bromo-ester was saponified by 10% aqueous potassium hydroxide solution without further purification. The alkaline solution was then filtered and acidified. The solid separated was collected and dissolved in ether. The ethereal solution was extracted with sodium bicarbonate solution. The bicarbonate extract was then acidified and the collected precipitate crystallized from a mixture of ether and gasoline. After four recrystallizations from ether and gasoline, the bromo-*l*-β-desmotropo-santonous acid gave the m. p. of 120–122°; mixed m. p. with the above product 120–121°.

Coupling of Bromo-*d*-α-desmotropo-santonous Acid with *p*-Nitrobenzenediazonium Chloride.—Twenty-five hundredths gram of bromo-*d*-α-desmotropo-santonous acid was dissolved in 5 ml. of 10% potassium hydroxide solution. The solution was cooled to 0° and a cold solution of *p*-nitrobenzenediazonium chloride (one-tenth of the solution obtained by diazotizing 1 g. of *p*-nitroaniline in 2.5 ml. of concentrated hydrochloric acid with 0.55 g. of sodium nitrite in a few ml. of water) was added. The coupling took place immediately and the solution showed a deep red color. The solution was then acidified and the precipitate collected. The dried product was recrystallized two times from alcohol as red needles, m. p. 214–215°. A qualitative test for halogen gave a negative result.

Coupling of *d*-α-Desmotropo-santonous Acid with *p*-Nitrobenzenediazonium Chloride.—Thirty-seven hundredths gram of *d*-α-desmotropo-santonous acid was coupled with one-fifth of the above diazotized solution as above. The dyestuff was recrystallized two times from alcohol and obtained as red soft needles, m. p. 214–215°, not depressed with the dyestuff obtained above.

Coupling of Bromo-*d*-β-desmotropo-santonin (X) with Benzenediazonium Chloride.—The procedure of Wedekind and Schmidt[9] was followed using bromo-*d*-β-desmotropo-santonin instead of *d*-β-desmotropo-santonin. An immediate coupling occurred and the solution showed a deep red color. The solution was then acidified and the precipitate collected. It was treated with boiling alcohol and the alcohol insoluble substance was crystallized from benzene as yellow fine needles, m. p. 259–260° with decomposition. It gave no depression of m. p. by admixture with an authentic sample of benzeneazo-*d*-β-desmotropo-santonin (XI) (m. p. 261–262°) obtained by coupling *d*-β-desmotropo-santonin (XII) with diazotized aniline (Wedekind and Schmidt[9]).

Summary

1. Bromo-*l*-α-desmotropo-santonin acetate was obtained by the enol acetylation of monobromo-santonin.

2. The desmotropo-santonins could be directly brominated to the corresponding bromodesmotropo-santonins. The racemic bromo-desmotropo-santonins could be obtained by either brominating the racemic desmotropo-santonins or racemizing the bromo-*d*- and bromo-*l*-desmotropo-santonins.

3. The bromo-*d*-β- and bromo-*l*-β-desmotropo-santonins could be converted into the bromo-*d*-α- and bromo-*l*-α-desmotropo-santonins, respectively, by fusing with alkali.

4. The bromo-*d*-β and bromo-*l*-α-desmotropo-santonous acids were prepared by the direct bromination of the corresponding desmotropo-santonous acids.

5. The position of the bromine atom in the bromo-desmotropo-santonins and the bromo-desmotropo-santonous acids has been established.

KUNMING, CHINA RECEIVED FEBRUARY 21, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Sulfaquinoxaline and Some Related Compounds

BY JOHN WEIJLARD, MAX TISHLER AND A. E. ERICKSON

Of the large number of the known N[1] heterocyclic derivatives of sulfanilamide, only a few have proved acceptable as chemotherapeutic agents. These drugs, including sulfapyridine, sulfathiazole, sulfadiazine and sulfapyrazine have the common structural unit N=C—NH of which the N=C group is part of an aromatic, heterocyclic system. With the exception of certain of the methyl derivatives such as sulfamethyldiazine, nearly all other ring substituted derivatives of this class have been found to be less effective than the parent compounds. This generalization also extends to the benzoheterocyclic sulfa drugs, such as 2-sulfanilamidoquinoline, 2-sulfanilamidobenzothiazole, and 2-sulfanilamidoimidazole.[1]

In connection with the synthesis of new sulfonamides, we prepared 2-sulfanilamidoquinoxaline (III) which, in contrast to the known benzoheterocyclic sulfa compounds, is of interest as a chemotherapeutic agent. The pharmacology and the chemotherapeutic activity of sulfaquinoxaline and of some of its derivatives mentioned in this report are being extensively studied by the Merck Institute for Therapeutic Research, and detailed reports of these investigations will be published elsewhere. Bacterial efficacy experiments with sulfaquinoxaline indicate that this drug is as effective as sulfadiazine or sulfapyrazine in experimental pneumococcal infections in mice when fed every six hours over a five day period, and much more effective when fed once daily over a five day period. Sulfaquinoxaline was found to be remarkable in that following a single dose, the drug remains in the blood for a long time and, consequently, chemotherapeutically effective blood concentrations can be maintained by ad-

(1) For general literature reviews, see E. H. Northey, *Ind. Eng. Chem.*, **35** 829 (1943).