

STUDIES IN THE THIOPHENE SERIES. II.¹ PREPARATION
AND PHYTOCHEMICAL REDUCTION OF 2,2'-THENOIN
AND 2,2'-THENIL

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In continuation of investigations in the thiophene series (1), conducted in our laboratories, it was deemed suitable to study some typical aromatic aldehyde reactions as applied to the thiophene aldehydes. The benzoin condensation leading to the formation of hydroxy ketones had not been successfully attempted with thiophene-2-aldehyde.³ It has been previously reported that the application of potassium cyanide to thiophene-2-aldehyde causes complete resinification of the thiophene ring (2). While it is true that a water-alcohol solution of the aldehyde in the presence of cyanide ion does yield a somewhat tarry product, suitable recrystallization methods can be applied to obtain the hydroxy-ketone, 2,2'-thenoin (I).

This compound gives a color reaction similar to that shown by benzoin and other acyloin condensation products in the presence of alcoholic alkali. Benzoin gives a reddish purple color, furoin a deep blue-green color and, with thenoin a deep green coloration is produced, which disappears upon shaking and reappears when the solution is allowed to stand. The hydroxy ketone may be oxidized by iodine in the presence of sodium methoxide (3) to give the diketone, 2,2'-thenil (II), in excellent yields. The color reaction is not given by this compound. The quinoxaline derivative of 2,2'-thenil (IV) was prepared to verify the presence of an *alpha-diketo* grouping.

It has been shown previously (4) that carbonyl groups can be phytochemically reduced and this procedure has been applied to aromatic and heterocyclic hydroxyketo and diketo compounds, such as benzoin, benzil, furoin, and furil. Thiophene-2-aldehyde has also been reduced by the action of fermenting yeast to thiophene-2-carbinol (5). It was considered of interest, therefore, to attempt the phytochemical reduction of 2,2'-thenoin and 2,2'-thenil to determine the effect of the thiophene ring as compared to the benzene and furan rings. Since 2,2'-thenoin gives the above mentioned color reaction even in great dilutions and when added to a yeast suspension, its presence can be easily detected. The course of reactions taking place may be visualized in Chart I.

In the first attempt to reduce 2,2'-thenoin it was found that an *oxidation* had taken place to yield 2,2'-thenil instead of the expected 2,2'-dihydrothenoin (III). Although it is known that hydroxyketo compounds of this type are sus-

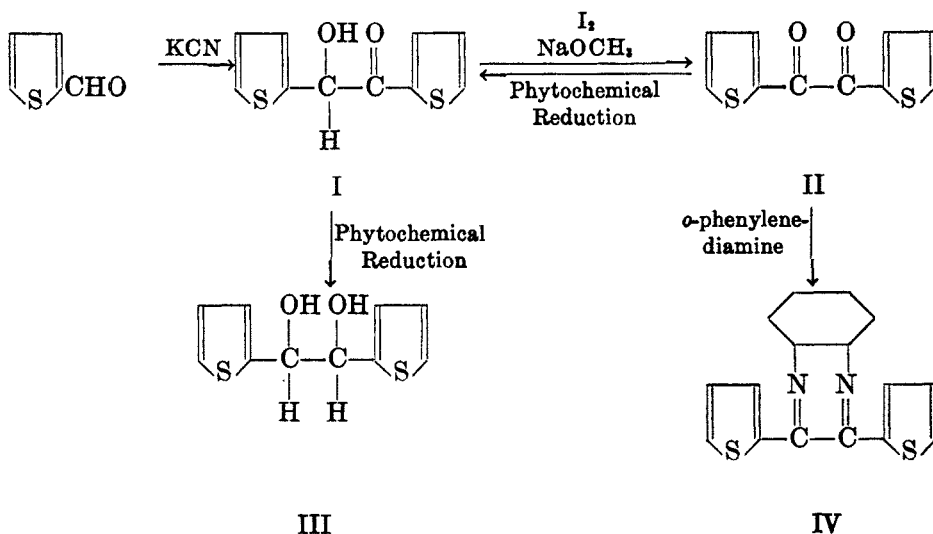
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³ For 3-substituted thiophenes see Ref. (6).

ceptible to oxidation by air in alkaline solution, it did not seem likely that the oxidation resulted in this manner, since the fermentation mixture is acidic. Furthermore, in a separate experiment, in which air was vigorously bubbled through a slightly acidic alcoholic solution of 2,2'-thenoin, 2,2'-thenil was not obtained. It appears, therefore, more probable that the dehydrogenating enzyme system present in the yeast had effected the conversion. Since this attempt had been run with vigorous stirring to speed up the reaction, and air was not excluded from the flask, the conversion was carried on without stirring and in a carbon dioxide atmosphere. In this case it was found that thenoin could be reduced to dihydrothenoin and that thenil was first converted to thenoin and

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then to the dihydroxy compound. It is interesting to note that thenoin differs significantly from benzoin, since reduction products were not obtained from the latter by phytochemical means (4). Furthermore, unlike furil, in which reduction products are present almost immediately, it was not until the third day that the fermentation mixture containing 2,2'-thenil gave a color reaction for 2,2'-thenoin.

EXPERIMENTAL⁴

2,2'-Thenoin (I). In a 500-cc. flask fitted with a reflux condenser were placed 33.6 g. (0.3 mole) of thiophene-2-aldehyde (1), 100 cc. of ethyl alcohol, and 40 cc. of water. The solution was placed on a steam-bath and brought to reflux. A solution of 4 g. of potassium cyanide in 20 cc. of water was added, resulting almost immediately in a deep green coloration. After refluxing for two hours, the solution was cooled, acidified with acetic acid and allowed to stand for two days in an ice-box with occasional shaking. The somewhat tarry precipitate was filtered and washed successively with small portions of cold alcohol and

⁴ The analyses presented were carried out by M. Bier of this laboratory.

water. Recrystallization from methyl alcohol with charcoal yielded 10.2 g. (30%) of light cream colored crystals of 2,2'-thenoin. Upon microsublimation *in vacuo* we obtained white crystals, m.p. 108-109°.

Anal. Calc'd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59.

Found: C, 53.85; H, 3.53.

2,2'-Thenil (II). Thenoin (4.2 g., 0.02 mole) was dissolved in 90 cc. of pure methanol and to the boiling solution was added a freshly prepared hot solution of sodium methoxide, prepared by dissolving 1 g. of sodium in 20 cc. of pure methanol. To the boiling solution was added in small portions 5.6 g. of iodine. Upon cooling there was obtained 3.7 g. of bright yellow crystals. Recrystallization from alcohol with charcoal yielded 3.3 g. (79%) of 2,2'-thenil, m.p. 81-82°.

Anal. Calc'd for $C_{10}H_8O_2S_2$: C, 54.04; H, 2.72.

Found: C, 54.00; H, 2.71.

It is necessary to use pure methanol, since small amounts of contaminants, such as ethyl alcohol or acetone, may yield iodoform.

2,3-bis-(2-Thienyl)quinoxaline (IV). Formed by refluxing 1 g. of 2,2'-thenil with 0.8 g. of *o*-phenylenediamine dihydrochloride in 30 cc. of ethanol. Recrystallization gave white crystals m.p. 143-144°.

Anal. Calc'd for $C_{16}H_{10}N_2S_2$: C, 65.27; H, 3.43.

Found: C, 65.35; H, 3.56.

Phytochemical reduction of 2,2'-thenoin. To 500 cc. of a 10% sucrose solution in a 3-liter flask, 50 g. of baker's yeast⁵ was added. After the onset of the fermentation, 3.1 g. of 2,2'-thenoin in 40 cc. of ethyl alcohol (95%) was added drop by drop at room temperature, a carbon dioxide source was connected to the flask and the mixture was saturated with carbon dioxide before and during the reaction. After 12 hours, samples were taken from the flask and it was found that only a slight Fehling test was given, but a strong color indicated the presence of unchanged thenoin. Accordingly, 250 cc. of the sugar solution and 25 g. of yeast were added to the flask. This procedure was continued each day for a total of five days. On the fourth day, the reaction for thenoin was negative. After the fifth day, the fermentation mixture was evaporated to one-third of its volume on a steam-bath and the syrupy liquid treated with sodium carbonate until alkaline, and then saturated with sodium sulfate. The material was extracted exhaustively with ether and the ethereal solution filtered through a sintered glass funnel and evaporated under reduced pressure. The residual oil was dissolved in alcohol and enough water added to cause cloudiness. After standing in the ice-box for two weeks, the oil crystallized. Filtration and recrystallization from benzene and petroleum ether with charcoal yielded 1.3 g. of dihydrothenoin, white crystals m.p. 90-91°. The compound showed slight optical activity, $[\alpha]_D^{25} = +0.95^\circ$ ($\alpha = +0.02$, $c = 2.09997$, $l = 1$; alcoholic solution).

Anal. Calc'd for $C_{10}H_{10}O_2S_2$: C, 53.08; H, 4.41.

Found: C, 53.05; H, 4.33.

Dibenzoate. Crude dihydrothenoin (1 g.) was dissolved in 6 cc. of anhydrous pyridine to which 2.0 g. of benzoyl chloride was added. The mixture was heated over a low flame for several minutes, and after cooling, 35 cc. of water was added, resulting in a yellow oil. The supernatant liquid was decanted and the oil washed with several portions of water. The substance was then dissolved in hot alcohol, cooled, and allowed to crystallize. The resulting substance was recrystallized from alcohol with charcoal to yield white crystals. m.p. 186-186.5°.

Anal. Calc'd for $C_{24}H_{18}S_2O_2$: C, 66.34; H, 4.17.

Found: C, 66.40; H, 4.25.

Phytochemical reduction of 2,2'-thenil. The same procedure as outlined above was followed, except that 6 g. of thenil was added to the fermentation mixture. The test for

⁵ The yeast used in these experiments was obtained through the courtesy of Mr. G. W. Kirby of the Fleischmann Laboratories, New York, N. Y.

thenoin was negative until the third day, indicating that the progress of the reaction was slow. At the end of the fifth day the fermentation mixture was concentrated, extracted with chloroform, and the chloroform extract filtered and evaporated *in vacuo*. The resulting yellow oil was dissolved in hot alcohol, and water added to cloudiness. After several days in the ice-box, the solid material was filtered. Since thenil is less soluble in alcohol than thenoin, the crude material was treated with alcohol, until the residue did not give a test for thenoin. This residue (1.5 g.) proved to be mainly unchanged thenil m.p. 79-81°. A mixed melting point showed no depression. The alcoholic solution was evaporated and the residue recrystallized from a water-alcohol mixture. There was obtained 0.4 g. of 2,2'-thenoin, which after sublimation *in vacuo* had m.p. 107-108°. A mixed melting point showed no depression. The fermentation mixture, which had been extracted with chloroform, was then extracted with ether, and the procedure indicated for the isolation of dihydrothenoin was followed. There was obtained 0.3 g. of dihydrothenoin, m.p. 90-91°. The color reaction for 2,2'-thenoin was carried out by mixing 1 cc. of the fermentation mixture with 3 cc. of alcohol and then adding a drop of concentrated alkali. If 2,2'-thenoin is present, a green color soon appears, which disappears upon shaking and reappears upon standing.

SUMMARY

1. A method is presented for the preparation of 2,2'-thenoin and 2,2'-thenil.
2. Phytochemical reduction was shown to be applicable to both compounds.
3. Differences in the phytochemical reducibility of these compounds in contrast to benzoin and furil were observed.

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