# Synthesis of 5,6-Dimethoxythiophen-3*H*(2)one and 6,7-Dimethoxythiochroman-2-one. Derivatives of Tetramethoxy-10,11-dihydrodibenzo[*β*,*f*]thiepin-10-one

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Reduction of 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonyl chloride and 4,5-dimethoxy-2-carboethoxyethylbenzenesulfonyl chloride with zinc, hydrochloric acid, produced the corresponding *o*-mercapto-acids which then cyclized to thiaindanone and thiochromanone, respectively. Thiaindanone and thiochromanone reacted readily with aniline to give 4,5-dimethoxy-2-mercaptophenyl-*N*-phenylacetamide and 4,5-dimethoxy-2-mercaptophenyl-*N*-phenylpropylamide. Mercaptophenyl-*N*-phenylacetamide yielded in two steps the 4,5-dimethoxy-2-*N*-phenylacetamido(3′,4′-dimethoxyphenylthio)benzene, which was cyclized to the 2,3,7,8-tetramethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one. Reduction of thiepinone with sodium borohydride leads to the corresponding alcohol.

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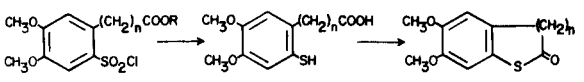
In continuation of our studies on the chemistry of thiazo heterocyclic compounds (1), we examined methods for effecting synthesis of *o*-mercaptophenyl-*N*-phenylacetamides which could be our initial material for the preparation of compounds with pharmacological interest (2).

Van Zyl and co-workers (3) in order to synthesize this type of compounds, have prepared 2-hydroxythianaphthene by oxidation of 2-thianaphthenyllithium in the presence of an alkyl Grignard reagent, which with aromatic amine produces the corresponding mercapto-amides. On the other hand Lumma and Berchtold (4) have prepared thiophen-3*H*(2)one in low yield from methyl 2-chlorosulfonyl-5-methoxyphenylacetate.

In view of the poor availability of thiophen-3*H*(2)one and 2-thiochromanone we used in the initial phase of the present work, 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonyl chloride (5) and 4,5-dimethoxy-2-carboethoxyethylbenzenesulfonyl chloride (6).

With zinc and hydrochloric acid, compounds I and II



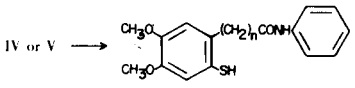
I, R = $CH_3$, n = 1
II, R = $C_2H_5$, n = 2

III

IV, n = 1
V, n = 2

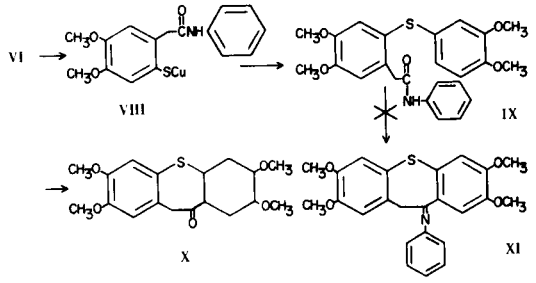
were reduced in dimethoxy-*o*-mercaptophenylacetic acid and the dimethoxy-*o*-mercaptopropionic acid. The 5,6-dimethoxythiophen-3*H*(2)one was obtained directly from the reduction of compound I. Treatment of 4,5-dimethoxy-1-mercaptopropionic acid with concentrated hydrochloric acid gave the 6,7-dimethoxythiochroman-2-one.

Thiaindanone and thiachromanone reacted readily with aniline to give anilides VI and VII, respectively, in good yields.



VI, n = 1
VII, n = 2

By condensation of 3,4-dimethoxybromobenzene with the cuprous salt of 4,5-dimethoxy-1-mercaptopropionic acid (VI) in quinoline at 210° according to a similar procedure (7), we obtained 2-(3′,4′-dimethoxyphenylthio)-4,5-dimethoxyphenyl-*N*-phenylacetamide (IX).



VIII

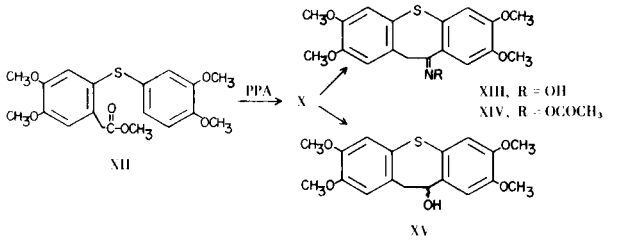
IX

X

XI

The Pictet-Spengler cyclization of anilide IX with polyphosphoric acid did not produce compound XI but 2,3,7,8-tetramethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (apparently due to the hydrolysis of anilide to the corresponding acid).

The structure of thiepinone X was proved by independent synthesis from the XII with polyphosphoric acid.




Reduction of X with sodium borohydride led to alcohol XV.

Ketone X was converted to the 10-ketoxime by heating with excess of hydroxylamine hydrochloride in a mixture of pyridine-ethanol. The ketoxime was acetylated with excess of acetic anhydride and pyridine to give the corresponding oxime acetate (XIV).

## EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. Nmr spectra were determined with a Varian Associates A-60 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Division, Demokritos and the National Research Institute.

4,5-Dimethoxy-2-carbomethoxymethylbenzenesulfonyl Chloride (I).

This compound was prepared in 50% yield from methyl 3,4-dimethoxyphenylacetate with chlorosulfonic acid (5). Recrystallization was from ethyl acetate-*n*-hexane, m.p. 109-110°.

*Anal.* Calcd. for $C_{11}H_{13}ClO_6S$: C, 42.78; H, 4.21. Found: C, 42.55; H, 4.40.

5,6-Dimethoxythiophen-3*H*(2)one (IV).

In a three-necked flask fitted with a mechanical stirrer, condenser and addition funnel, was placed 5.47 g. of 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonyl chloride, 5.15 g. of zinc powder and 55 ml. of ether. Hydrochloric acid was added dropwise over a period of 2 hours, while the mixture was stirred.

The reaction was completed at reflux in one hour. After cooling, water was added to the reaction mixture, and it was extracted with chloroform. The chloroform solution was washed with water, dried over magnesium sulfate and the solvent evaporated under reduced pressure.

The residue crystallized from methanol to produce compound III in 97% yield, m.p. 126-127°; ir: $\nu$ max 1700 $cm^{-1}$ (C=O) and absent of SH at 2550 $cm^{-1}$. The nmr spectrum of III showed at $\tau$ 3.05 (two aromatic protons), 6.05 and 6.1 (two $OCH_3$) and at $\tau$ 5.67 and 6.5 the two protons of $-CH_2-$.

*Anal.* Calcd. for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.76. Found: C, 57.23; H, 4.96.

6,7-Dimethoxythiochroman-2-one (V).

Following the above procedures for the reduction of 4,5-dimethoxy-2-carboethoxyethylbenzenesulfonyl chloride (6) and work up of the product in a usual way gave an oil; ir: $\nu$ max 1730 (COOH) and 2550 $cm^{-1}$ (SH). This oil was heated on a steam bath with 20 ml. of hydrochloric acid for one hour and then at room temperature for 24 hours. The crystalline precipitate was collected by filtration to give compound V in 67% yield, m.p. 130-132° (methanol); ir: $\nu$ max 1725 $cm^{-1}$ (C=O) and absence of SH at 2550 $cm^{-1}$. The nmr spectrum showed at $\tau$ 3.1 and 3.2 (two aromatic protons), 6.15 and 6.25 (two $OCH_3$) and four protons centered at 7.3 ($-CH_2CH_2-$).

*Anal.* Calcd. for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.35. Found: C, 58.61; H, 6.00.

Procedures for the Preparation of Amides VI and VII.

Upon heating of compounds IV and V with 1 ml. of aniline on a steam bath for one hour, amides VI and VII were obtained in crystalline form by addition of ether. The following compounds were obtained.

2-Mercapto-4,5-dimethoxyphenyl-*N*-phenylacetamide (VI).

This compound, m.p. 177-180°, was crystallized from methanol, yield 80%; ir: $\nu$ max 3280 (NH), 2540 (SH) and 1650 $cm^{-1}$ (CO).

*Anal.* Calcd. for $C_{16}H_{17}NO_3S$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.14; H, 5.28; N, 4.40.

2-Mercapto-4,5-dimethoxyphenyl-*N*-phenylpropylamide (VII).

This compound, m.p. 195°, was crystallized from a mixture of chloroform-methanol, yield, 71%; ir: $\nu$ max 3280 (NH) and 1660 $cm^{-1}$ (CO).

*Anal.* Calcd. for $C_{17}H_{19}NO_3S$: C, 64.35; H, 5.99; N, 4.41. Found: C, 64.80; H, 5.97; N, 4.41.

Cupric Salt of 2-Mercapto-4,5-dimethoxyphenyl-*N*-phenylacetamide (VIII).

To a solution of VI (6.6 g., 0.0217 mole) in 50 ml. of ethanol under nitrogen, cuprous oxide (1.76 g., 0.0123 mole) was added and the mixture was heated and stirred for 3 hours. After cooling the precipitate was collected by filtration and it was dried in a dessicator under calcium chloride (8.43 g.).

2-(3′,4′-Dimethoxyphenylthio)-4,5-dimethoxyphenyl-*N*-phenylacetamide (IX).

The cuprous salt of VIII (8.43 g.) was added to a solution prepared by dissolving 4.8 g. of bromoveratrole in 25 ml. of quinoline and 1 ml. of pyridine. The solution was refluxed for 3 hours. The reaction mixture was then poured into ice-water containing 35 ml. of concentrated hydrochloric acid. The precipitate was collected by filtration and extracted with hot chloroform. The organic layer was washed with dilute hydrochloric acid, then with water and dried over magnesium sulfate. Removal of the solvent produced a semisolid that was purified by filtration over a column of 50 g. of aluminium oxide (eluent, chloroform). After removal of the solvent the residue was crystallized from ethyl acetate-*n*-hexane to give compound IX in 68% yield, m.p. 140-141°; ir: $\nu$ max 3340 (NH) and 1690 $cm^{-1}$ (CO).

*Anal.* Calcd. for $C_{24}H_{25}NO_5S$: C, 65.60; H, 5.69; N, 3.18. Found: C, 65.85; H, 5.87; N, 3.19.

2,3,7,8-Tetramethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (X).

In a two-necked flask fitted with a stirrer and a reflux condenser was placed 0.5 g. of IX and 5 g. of polyphosphoric acid. The mixture was stirred and heated at 100° for one hour. The hot mixture was poured into ice-water and made basic with concentrated ammonium hydroxide. The precipitate was collected by filtration, washed with water and dried. After recrystallization from ethanol produced compound X in 47% yield, m.p. 172-173°; ir: $\nu$ max 1650 $cm^{-1}$ (CO).

*Anal.* Calcd. for $C_{18}H_{18}O_5S$: C, 62.42; H, 5.20. Found: C, 62.20; H, 5.48.

Hydrolysis of Amide IX.

To a solution of IX (2.5 g.) in 20 ml. of ethanol was added 20 ml. of concentrated hydrochloric acid. The mixture was heated on a steam bath for 5 hours. The solution was poured into cold water and the precipitate collected by filtration. Recrystallization from methanol gave compound XII in 80% yield, m.p. 91-92°; ir: $\nu$ max 1735 $cm^{-1}$ (CO).

*Anal.* Calcd. for $C_{19}H_{21}O_6S$: C, 60.48; H, 5.56. Found: C, 60.61; H, 5.38.

Following the procedures for the synthesis of X we cyclized ester XII to 2,3,7,8-tetramethoxy-10,11-dihydrodibenzo[*b*,*f*]-thiepin-10-one in 83% yield.

2,3,7,8-Tetramethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one Oxime (XIII).

Thiepinone (5.2 g.) was dissolved in 30 ml. of pyridine and 50 ml. of ethanol. Hydroxylamine hydrochloride (5 g.) was added to this solution and the mixture was heated under reflux for 2 hours. The solution was poured into ice-water, and the resulting precipitate was collected by filtration, washed with water and dried, to give 5.04 g. (93% yield) of compound XIII. Twice recrystallization from methanol gave a m.p. 184-186°.

*Anal.* Calcd. for $C_{18}H_{19}NO_5S$: C, 59.83; H, 5.26; N, 3.88. Found: C, 60.50; H, 5.37; N, 3.56.

Acetylation of XIII.

Reacting compound XIII (1 g.) in an excess of acetic anhydride and pyridine at room temperature over night gave thiepinone oxime acetate (XIV) in 86% yield after recrystallization from methanol, m.p. 175-177°; ir: $\nu$ max 1765 (CO).

*Anal.* Calcd. for $C_{20}H_{21}NO_6S$: C, 59.55; H, 5.21; N, 3.47. Found: C, 59.73; H, 5.60; N, 3.24.

Reduction of X with Sodium Borohydride.

To a solution of 1.050 g. of X in 50 ml. of methanol was added an excess of sodium borohydride (2 g.). The mixture was allowed to stand at room temperature for two hours. After this time the solution was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent and crystallization from ethanol-ether gave 0.5 g. (47%) of XV, m.p. 155-157°.

*Anal.* Calcd. for $C_{18}H_{20}O_5S$: C, 62.00; H, 5.74. Found: C, 61.20; H, 5.55.

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