

# The Synthesis of Some Derivatives of Benzo[*f*]naphtho[1,8-*bc*]thiepin-12-one

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The preparations of benzo[*f*]naphtho[1,8-*bc*]thiepin-12-one, its 6-methyl and 6-methoxy derivatives and their corresponding sulfoxides and sulfones are described. They involve the coupling of suitable halogen naphthyl derivatives with thiophenoxides with the help of copper and the cyclization of the resulting acids with phosphorus pentoxide in benzene. The oxidations to sulfoxides and sulfones were performed with iodo-benzene diacetate and hydrogen peroxide, respectively. The ir and pmr spectra are reported.

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In 1938, Knapp [1] reported the preparation of 6-methoxybenzo[*f*]naphtho[1,8-*bc*]thiepin-12-one (IV). His procedure involved the condensation of 1-bromo-2-methoxynaphthalene with thiosalicylic acid by means of copper and alkali in *n*-amyl alcohol to give 2-(2-methoxy-1-naphthylthio)benzoic acid which was then cyclized by means of phosphorus pentoxide in boiling toluene. The strategy of this type of synthesis requires the presence of a substituent at the 2-position of the naphthalene ring to prevent the highly favored cyclization to the 3,4-benzothioxanthene-9-one ring system. Knapp also attempted the preparation of the derivative with a methyl group at the 6-position (2- in the original naphthalene ring) but the coupling with thiosalicylic acid failed and, therefore, VII could not be prepared.

This seemingly important area of research remained dormant for many years until Protiva and collaborators [2] reported the preparation of benzo[*f*]naphtho[1,8-*bc*]thiepin-12-one (I) by the reaction of 8-iodo-1-naphthoic acid with thiophenol followed by cyclization with polyphosphoric acid. Derivatives obtained through the use of 4-chlorothiophenol and by reaction on the carbonyl group were also discussed.

Thus, a family of compounds has been defined that presents, on one hand, considerable theoretical interest concerning the conformation, particularly in connection with the different degrees of oxidation of the sulfur atom, stability and reactivity of the seven-membered ring and, on the other hand, potential pharmacological interest since the related ring system, thioxanthene-9-one, is the parent compound of several important drugs in the area of tranquilizers and schistosomicides [3].

This paper describes improved preparations of I and IV plus the 6-methyl derivative VII and their corresponding sulfoxides and sulfones. All substances are identified by

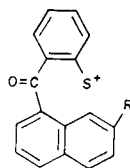
roman numerals in Table 1.

Compounds I, IV, and VII were obtained by the acid catalyzed cyclization of 8-(phenylthio)-1-naphthoic acid, 2-(2-methoxy-1-naphthylthio)benzoic acid, and 2-(2-methyl-1-naphthylthio)benzoic acid (X), respectively. The sulfoxide XI and the sulfone XII of 2-(1-naphthylthio)benzoic acid were also prepared.

The intermediate acids were prepared by two different modifications of Irma Goldberg's procedure [4] which in essence involves the copper catalyzed coupling of an aryl halide with a thiophenoxide. For 8-(phenylthio)-1-naphthoic acid, 8-iodonaphthoic acid was coupled with thiophenol according to Protiva *et al.* [2] which represents an improvement over the earlier procedure of Rule and Turner [5]. To obtain 2-(1-naphthylthio)benzoic acid, 2-(2-methoxy-1-naphthylthio)benzoic acid, and X, the corresponding 1-halonaphthalenes were coupled with thiophenol using dimethylformamide as the solvent, anhydrous potassium carbonate as the base and copper-zinc as the catalyst. This procedure not only improved Knapp's yield of 2-(2-methoxy-1-naphthylthio)benzoic acid but also afforded X which Knapp was not able to prepare.

The cyclization of the intermediate acids to the corresponding thiepinones was performed at moderate temperature with phosphorus pentoxide in benzene; *i.e.*, mild conditions and a non-protic acid were chosen. This was done in order to avoid possible rearrangements to benzothioxanthenes. In addition to the well known reversibility of the acylium ion attack which would lead to 3,4-benzothioxanthenes in the absence of a blocking group already observed by Protiva *et al.* [2], our preliminary experiments indicate that even if a blocking group is present at 6-, rearrangements may still occur. The most plausible path for an additional rearrangement is the opening of the seven-

membered ring to give a sulfenium ion which then cyclizes to a 1,2-benzothioxanthone. It must be kept in mind that it is generally believed that the Smiles synthesis of thioxanthone begins by a sulfenium ion attack as was first suggested by Archer and Suter [6]. Although such a rearrangement remains a subject for further study, from a preparative point of view, it is clear that milder cyclization conditions lead to purer products so that chromatographic separations or repeated recrystallizations can be avoided.



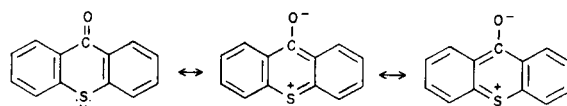
All sulfoxides were prepared with the help of isobenzene diacetate in glacial acetic acid [7]. The often advantageous addition of strong acid [8] was omitted because of the possibility of ring rearrangements.

The sulfones were prepared by the method of Ullmann and Lehner [9] with hydrogen peroxide in boiling glacial acetic acid. Sulfone III was also prepared by oxidation of the 2-(1-naphthylthio)benzoic acid followed by cyclization. It was speculated that the presence of the sulfone group

would deactivate one of the phenyl rings in naphthalene so strongly, that the cyclization would be directed to the other ring making the presence of a blocking group unnecessary. This was, indeed, observed. Thus, in addition to blocking groups, cyclization can be controlled by electron effects. Unfortunately, attempts to cyclize the corresponding sulfoxide were not successful.

The pmr spectra corroborated the assigned structures. Results are summarized in Table I. The ir spectra, on the other hand, provided some conformational hints. The more significant frequencies are listed in Table I together with those of the related compound, thioxanthone.

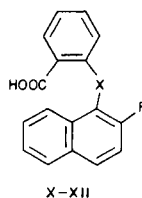
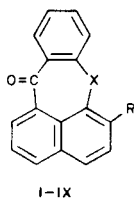
The properties of thioxanthone (for instance, its low carbonyl frequency) are generally explained on the basis of a significant contribution from polarized resonance forms:



This type of resonance should be less important in the case of the thiepinones and this is confirmed by the carbonyl frequencies of I, IV, and VII which are considerably higher than that of thioxanthone.

Table I

Structures, IR, PMR and Elemental Analyses of Reported Compounds



Substance	X	R	Significant ir frequencies (potassium bromide pellets)			NMR ( $\delta$ ) [a]	Elemental Analyses						
			CO band ( $\text{cm}^{-1}$ )	SO band ( $\text{cm}^{-1}$ )	SO <sub>2</sub> band ( $\text{cm}^{-1}$ )		C Calcd.	H Found	S Calcd.	S Found			
I	S	H	1660			7.2-8.3 (ArH)							
II	SO	H	1666, 1658	1039		7.2-8.6 (ArH)	73.36	73.10	3.62	3.80	11.52	11.28	
III	SO <sub>2</sub>	H	1672		1313, 1150	7.4-8.8 (ArH)	69.37	69.10	3.43	3.47	10.89	11.01	
IV	S	OCH <sub>3</sub>	1662			7.2-8.4 (9H, ArH), 1.07 (3H, OCH <sub>3</sub> )							
V	SO	OCH <sub>3</sub>	1666	1034, 1020		7.2-8.6 (9H, ArH), 4.09 (3H, OCH <sub>3</sub> )	70.14	69.96	3.89	3.95	10.40	10.60	
VI	SO <sub>2</sub>	OCH <sub>3</sub>	1660		1326, 1164	7.4-8.7 (9H, ArH), 4.14 (3H, OCH <sub>3</sub> )	66.68	66.44	3.70	3.79	9.89	9.85	
VII	S	CH <sub>3</sub>	1661			7.2-8.3 (9H, ArH), 2.85 (3H, CH <sub>3</sub> )	78.23	78.41	4.38	4.46	11.60	11.74	
VIII	SO	CH <sub>3</sub>	1667	1029		7.2-8.6 (9H, ArH), 3.08 (3H, CH <sub>3</sub> )	73.98	73.83	4.11	4.11	10.97	10.05	
IX	SO <sub>2</sub>	CH <sub>3</sub>	1671		1323, 1147	7.4-8.7 (9H, ArH), 3.08 (3H, CH <sub>3</sub> )	70.14	70.24	3.89	3.91	10.40	10.46	
X	S	CH <sub>3</sub>	1670			7.1-8.5 (10H, ArH), 2.62 (3H, CH <sub>3</sub> )	73.44	73.22	4.79	4.69	10.89	11.00	
XI	SO	H	1679	968, 947		7.2-8.6 (ArH)	68.90	68.76	4.08	4.11	10.82	10.87	
XII	SO <sub>2</sub>	H	1692		1302, 1148	7.5-8.8 (ArH)	65.37	65.26	3.87	4.02	10.27	10.40	
Thioxanthone			1642										
Thioxanthone 10-Oxide			1670	1022									
Thioxanthone 10,10-Dioxide			1680		1295, 1166								

[a] Compound I through IX in deuteriochloroform. Compound X through XII in DMSO-d<sub>6</sub>.

The thioxanthone ring has been shown to be planar [10] while in the sulfoxide, with little or no contribution of the polarized forms, it becomes folded [11]. It seems likely that the thiepinones and, *a fortiori*, their sulfoxides and sulfones are folded. The sulfinyl frequencies seem to indicate a pseudoequatorial preference [12] as in the case of thioxanthone [11].

## EXPERIMENTAL

The homogeneity of the compounds and the course of the reactions was monitored by thin-layer chromatography on alumina or silica gel plates developed in either benzene or chloroform. Visualization was performed with ultraviolet light followed by exposure to iodine vapors. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Elemental microanalyses for all the compounds were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. All the results were in good agreement with calculated values. Infrared spectra were recorded in a Beckman Acculab 1 spectrophotometer. The proton nuclear magnetic resonance spectra were taken at 35° with a Hitachi Perkin-Elmer R-24 B instrument.

### Preparation of the Intermediate Acids.

Thiosalicylic acid (20.0 mmoles) and the 1-halo-2-substituted naphthalene (20.0 mmoles) were refluxed for 15 hours in 60 ml of dimethylformamide together with 6.0 g of anhydrous potassium carbonate, 0.120 g of copper powder and 0.020 g of zinc powder. After cooling, 100 ml of water was added and the mixture filtered. On acidification to pH 2.0 with 5% hydrochloric acid, the product precipitated out. Recrystallization from acetic acid included an activated charcoal treatment. 8-(Phenylthio)-1-naphthoic acid was prepared according to Protiva *et al.* [2]. 1-Bromo-2-methoxynaphthalene gave 2-(2-methoxy-1-naphthylthio)benzoic acid with a yield of 79% and a mp of 223-228° (lit 226-228° [1]) while the 1-iodo derivative afforded the same compound with a yield of 81% and a mp of 224-228°. 1-Bromo-2-methylnaphthalene gave X, 92%, mp 220-224° and 1-bromonaphthalene, 2-(1-naphthylthio)benzoic acid, 69%, 217-223° (lit 213-215° [1]).

### Cyclizations.

The intermediate acid (3.00 mmoles) was stirred for 4 hours (9 for I) at room temperature (60° in the case of I) with 2.0 g of phosphorus pentoxide in 40 ml of benzene with exclusion of moisture. The mixture was treated with 30 g of ice, the pH adjusted to 10 with 5% sodium hydroxide and distilled to eliminate the benzene. The insoluble product was collected by filtration, washed with water, dried, and, finally, recrystallized from a suitable solvent with charcoal treatment. Compound I was obtained from *n*-heptane in a yield of 33%, mp 145-148° (lit 146-149° [2]). Compound IV was obtained from glacial acetic acid in a yield of 45%, mp 198-202° (lit 184-185° [1]). Compound VII was obtained from *n*-heptane

in a yield of 67%, mp 151-153° and III, prepared from XII, recrystallized from glacial acetic acid in a yield of 57%, mp 290-291°.

### Oxidations to the Sulfoxides.

The sulfide (2.50 mmoles) together with iodobenzene diacetate (2.50 mmoles) was refluxed for 1 hour in 10 ml of glacial acetic acid. After cooling to room temperature, the sulfoxide was collected by filtration, washed with very little acetic acid and dried. Recrystallization including a treatment with activated charcoal was from the same solvent for V and XI and from toluene for II and VIII. In view of the fact that the fluorescence of the tlc spots of V rapidly changed from blue to green under exposure to ultraviolet light, the preparation of V and subsequent manipulations were performed under light exclusion. Compound II was obtained in a yield of 27%, mp 205-207°. Compound V was obtained in a yield of 68%, mp 258-259°. Compound VIII was obtained in a yield of 38%, mp 264-265°. Compound XI was obtained in a yield of 65%, mp 247-250°.

### Preparation of the Sulfones.

The sulfide (2.00 mmoles) was refluxed with 1.0 ml of 30% hydrogen peroxide in 10 ml of glacial acetic acid for 1 hour. An additional 1.0 ml of 30% hydrogen peroxide was added and refluxed for another hour. The product was collected by filtration at room temperature, washed with dilute acetic acid (1:1) and dried. It was recrystallized from glacial acetic acid with charcoal treatment except IX which was recrystallized from toluene. Compound III was obtained in a yield of 74%, mp 290-291°. Compound VI was obtained in a yield of 48%, mp 296-297°. Compound IX was obtained in a yield of 44%, mp 264-265°. The isolation of XII required the addition of 30 ml of water to the oxidation solution, yield 59%, mp 184-187°.

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