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The Rearrangement of 10-Bromo-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one and Related Compounds in an Alkaline Solution

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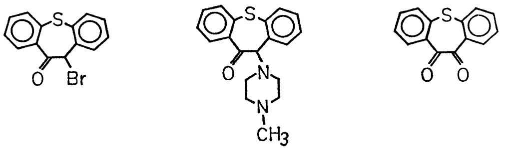
The reaction of 10-bromo-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one (**1**) with sodium methoxide in methanol has been shown to lead to thioxanthone (**4**) and 10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one (**5**). If the reaction of **1** in an aqueous sodium hydroxide solution is carried out, six products, **4**, **5**, 9-hydroxy-thioxanthene-9-carboxylic acid (**6**), thioxanthene-9-carboxylic acid (**7**), thioxanthene (**8**), and 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**9**), are formed. The structures of the products were established by elementary analysis, by an examination of the spectral data, by gas chromatography, and by an independent synthesis. The results were discussed in terms of the mechanism proposed.

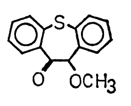
The synthesis of 10-(4′-methylpiperazino)10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one (**2**) for a biological evaluation has been described by Jílek *et al.*[1] The treatment of 10-bromo-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one (**1**) with 1-methylpiperazine has also been shown to lead to Compound **2** and to 10,11-dihydrodibenzo[*b*,*f*]thiepin-10,11-dione (**3**) and 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**9**).[1]



(**1**) (**2**) (**3**)

Chart 1.

As part of an investigation of the synthesis of the derivatives of dibenzo[*b*,*f*]thiepin with potential biological activity,[2] the present author has attempted to prepare 10-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one(I) from **1** and sodium methoxide. However, instead of the expected compound I, a neutral product, thioxanthone (**4**), was obtained in a 23% yield.



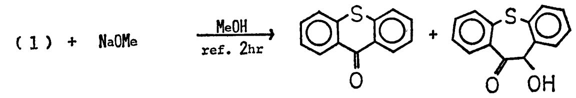
(I)

Chart 2.

The present paper will deal with detailed studies of the reaction of **1** and related compounds (**16**) and (**21**) with alkali.

Results and Discussion

In order to obtain information on the formation of **4**, the author first treated **1** with sodium methoxide in methanol under reflux. The reaction products separated by column chromatography on silica-gel from the reaction mixture were **4** and 10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-one (**5**) as is outlined in Scheme 1. Evidence for the **5** structure is based on the NMR and IR spectra; NMR (CDCl$_3$, ppm) δ 4.9 and 6.21 (1H, d, J=5.5 Hz, 11-proton) and 7.0—9.0 (8H, m, aromatic protons), IR (nujol, cm^{-1}) 3400(OH) and 1650(CO). The yields shown are for isolated recrystallized products.



(**4**) (**5**)
(23%) (<5%)

Scheme 1.

When Compound **1** was treated with a sodium hydroxide solution for 2 hr at 80 °C, six products were obtained, as is outlined in Scheme 2. The acidic product (**6**) separated from the aqueous phase in a 50% yield did not show a constant melting point. The IR spectrum of **6** in Nujol mull indicated absorption bands at 1675 cm^{-1} (CO) and 3450 cm^{-1} (OH), and the NMR spectrum exhibited a signal of aromatic protons at δ 7.2—7.8 in deuteriochloroform. The treatment of its potassium salt (**10**; R=OH) with methyl iodide in DMF at room temperature gave a yellow crystalline (mp 130—131 °C), which was identified as methyl 9-hydroxy thioxanthene-9-carboxylate(**11**) from the results of elementary analysis and its IR and NMR spectra. When **6** was treated with methanol containing a small amount of concentrated hydrochloric acid, methyl 9-methoxythioxanthene-9-carboxylate (**13**) was obtained in a 67% yield. From these experimental results, Compound **6** was identified as 9-hydroxythioxanthene-9-carboxylic acid. Thin-layer chromatography of the mother liquor of the recrystallization of **11** showed the presence of methyl thioxanthene-9-carboxylate (**12**)[3] upon comparison with a sample prepared by an independent route. Therefore, the tlc shows the formation of 9*H*-thioxanthene-9-carboxylic acid (**7**). It was proved therefore, that the acidic reaction products, **6**, contain a small amount of **7**.

Compounds **4** and **9** as neutral products were isolated from the reaction mixture and were found to be identical in IR and NMR spectra with authentic samples. The gas chromatography of the neutral reaction mixture showed the presence of **5** and thioxanthene (**8**) by comparison with the retention time of authentic samples.[4] The yield of **6** is for an isolated product; the

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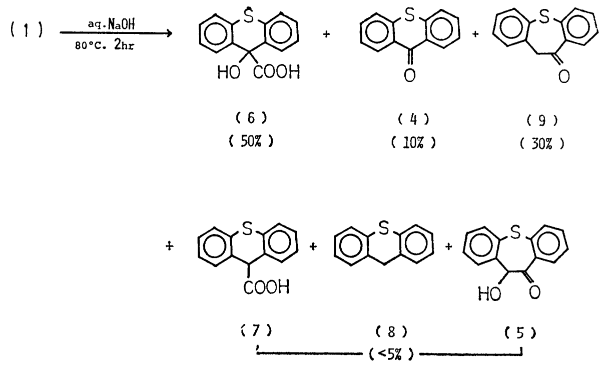
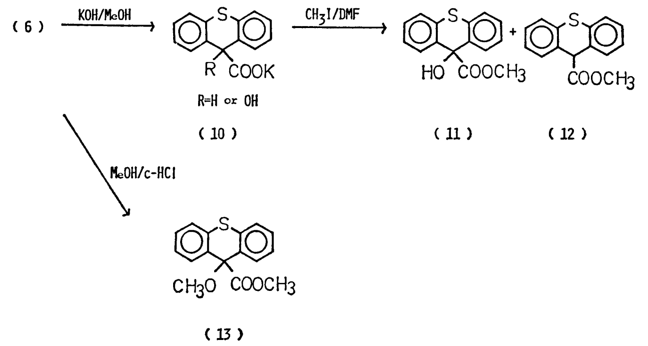
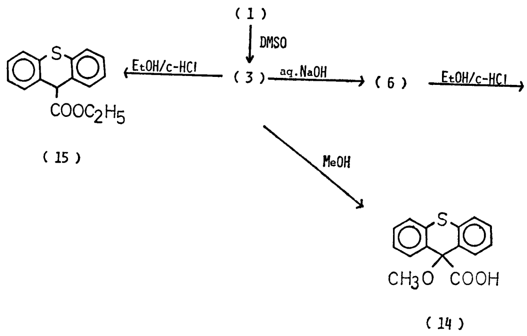


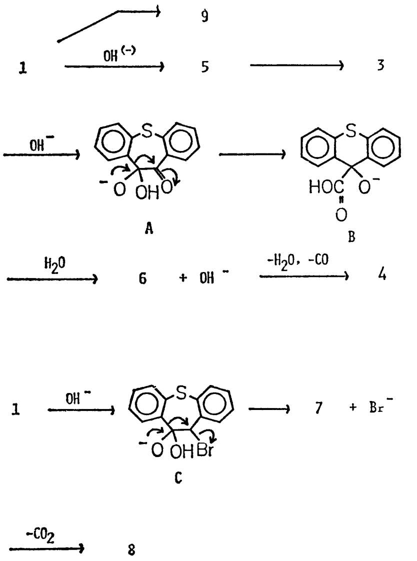
Scheme 2.



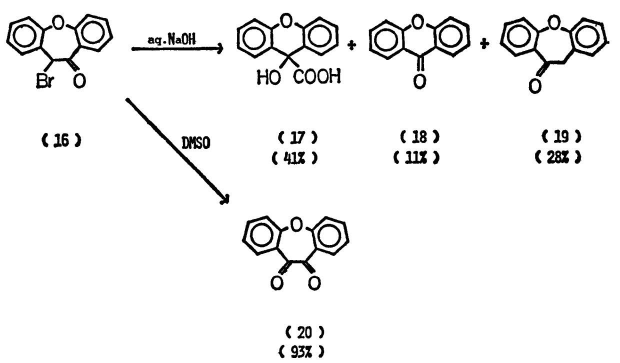
Scheme 3.



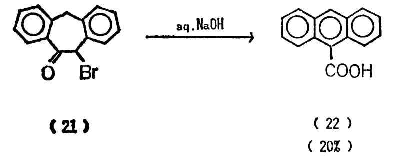
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

yields of **4**, **5**, **7**, **8** and **9** were determined by gas-chromatography of the crude reaction mixture, as is shown in Scheme 2.

The variation of the solvent in the reaction of **1** with alkali changed the products and the product ratios. For example, in water the acidic products were obtained in the highest yield. The formation of neutral products increased with an increase in the amount of methanol. Under anhydrous reaction conditions the acidic products were not isolated from the reaction mixture (see Experimental part).

The treatment of **1** in DMSO gave **3** in an 83.3% yield; it was converted to **6** in an aqueous sodium hydroxide solution.

Mechanisms. Compound **3** has been shown to lead to **6** in an aqueous sodium hydroxide solution and to 9-methoxythioxanthene-9-carboxylic acid (**14**) in methanol.[1] In acid hydrolysis, the formation of 9-Hydroxythioxanthene-9-carboxylate from both **3** and **6** has been reported.[5]

From the above-mentioned experimental results, the plausible mechanistic interpretations shown in Scheme 5 for the formation of **5**, **6**, **7**, and **9** from the reaction of **1** with a base can be advanced. The reaction of **1** with the hydroxy anion gives a secondary alcohol **5**, which is then dehydrogenated to afford diketone **3**.[6] The formation of **6** can be explained as resulting from the base-catalyzed benzilic acid rearrangement of the diketone **3**, as has been described in the literature.[1,9] Compound **9** may be formed by the reductive debromination of **1**. The formation of **7** from **1** and a base can also be explained as resulting from an intermediate, C, formed by the nucleophilic attack of the hydroxy anion on the carbonyl group of **1**. The two products, **4** and **8** appear to have been derived by the dehydration-decarbonylation of **6** and the decarboxylation of **7** respectively.

Table 1. Reaction of **1** with alkali

	Reaction condition[a)]		Products		Product ratio[c)]
	Base	Solvents (ml)	Acidic[b)] (%)	Neutral (g)	
1	Na	MeOH(15)	—	0.5	—
2	NaOH	H_2O(7.5)/MeOH(7.5)	0.5(35.7)	0.4—0.5	1.0—1.2
3	NaOH	H_2O(15)	0.7(50.0)	0.3	2.3

a) 1.5 g of **1** and two equivalent of sodium or sodium hydroxide, are used for all of experiments. Alkali concentration; 2 to 3%, Reaction temperature; 80 °C, time; 2 hr. b) Percentage of acidic substances was calculated on the basis of **3**. c) Weight ratio of acidic and neutral substances.

Similarly, the treatment of 10-bromo-10,11-dihydrodibenz[*b,f*]oxepin-11-one (**16**)[7)] in an aqueous sodium hydroxide solution gave 9-Hydroxyxanthene-9-carboxylic acid (**17**), xanthone (**18**), and 10,11-dihydrodibenz-[*b,f*]oxepin-11-one (**19**) in 41%, 11%, and 28% yields respectively. No xanthene-9-carboxylic acid or xanthene was isolated. The oxidation of **16** in DMSO gave **20** in a 93% yield (Scheme 6).

The treatment of 10-bromo-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-11-one (**21**)[8)] in an aqueous sodium hydroxide solution gave anthracene 9-carboxylic acid **21** in a 20% yield. No neutral products were obtained in this reaction.

Experimental

All the melting points are uncorrected. The IR spectra were taken with a Hitachi EPI-2 spectrometer. The NMR spectra were recorded by means of a Varian A-60 spectrometer in $CDCl_3$, using TMS as the internal standard.

Reaction of 10-Bromo-10, 11-dihydrodibenzo[b,f]*thiepin-11-one **1** with Alkali. The Reaction of* **1** *with Sodium Methoxide in Absolute Methanol*: A solution of 3.0 g of **1** in methanol containing sodium methoxide (prepared from 400 mg of sodium metal and 30 ml of methanol) was refluxed for 3 hr. After the removal of the methanol *in vacuo*, the residue was treated with a mixture of water and ethyl acetate. The ethyl acetate layer was washed with water, dried, and evaporated. A benzene solution of the oily residue (1.5 g) was adsorbed on 75 g of a silica gel (Mallinchrodt®, 100 mesh) and eluted with benzene. The subsequent evaporation of the eluent gave yellow crystals, which were recrystallized three times from cyclohexane to give 0.5 g (23%) of thioxanthone **4** as yellow needles; mp 210—212 °C; Found: C, 73.58; H, 3.65; S, 15.30%. Calcd for $C_{13}H_8OS$: C, 73.58; H, 3.80; S, 15.08%.

Rod-like crystals were obtained from the mother liquors of recrystallization and were crystallized from cyclohexane to give pale yellow, rod-like crystals; mp 121—124 °C. NMR($CDCl_3$, ppm) δ 4.90 and 6.21 (1 H, d, J=5.5 Hz, 11-proton), and 7.0—9.0(8H, m, aromatic protons). IR; ν_{max} (Nujol) 3400(OH), 1650(CO) and 1580 (aromatic)cm^{-1}. The structure of this compound was assumed to be 10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-11-one **5** on the basis of the IR and NMR spectra.

*Reaction of **1** with Aqueous Sodium Hydroxide.* A suspension of 3.0 g of **1** in an aqueous sodium hydroxide solution (sodium hydroxide, 0.8 g; water, 30 ml) was stirred for 2 hr at an inner temperature of 80 °C. After cooling, the oil was extracted with ethyl acetate, and the ethyl acetate layer was washed with water, dried, and evaporated. The residue thus obtained was recrystallized from cyclohexane to give 0.8 g (34.8%) of crystals **9**; mp 63—65 °C.

The aqueous layer was acidified with dil. hydrochloric acid and then allowed to stand to cool. The precipitate was filtered and air-dried at room temperature to give 1.3 g (50%) of crystals **6**.

*Methyl 9-Hydroxy-thioxanthene-9-carboxylate **11**.* A 0.4-g portion of **6** was dissolved in 10 ml of methanol containing 0.19 g of potassium hydroxide, and then the methanol was removed *in vacuo* below 30 °C. The colorless solid thus obtained was suspended in 15 ml of DMF. To the mixture we added 1 ml of methyl iodide, and the mixture was stirred for 48 hr at room temperature. To this solution we then added 1 ml of methyl iodide, after which stirring was continued for 48 hr. The reaction mixture was poured into 50 ml of water, made alkaline to pH 10 to 11 with a 10% sodium hydroxide solution, and extracted with ethyl acetate; the solution was then chromatographed on a silica-gel column using ethyl acetate as the eluent. The evaporation of the effluent offered pale yellow crystals, which were recrystallized from cyclohexane to give 0.3 g(67%) of pale yellow crystals **11**; mp 131—131.5 °C. Found: C, 66.15; H, 4.43; S, 11.80%. Calcd for $C_{15}H_{12}O_3S$: C, 66.17; H, 4.44; S, 11.76%.

*Methyl 9-Methoxy-thioxanthene-9-carboxylate **13**.* A 1.5-g portion of **6** was dissolved in a mixed solvent of 15 ml of methanol and 5 ml of conc. hydrochloric acid. The solution was then refluxed for 2 hr. After the removal of the methanol, the residue was extracted with ethyl acetate, and the ethyl acetate layer was dried over magnesium sulfate and evaporated. The solid thus obtained was recrystallized from cyclohexane to give **13**; mp 136.5—138 °C. Found: C, 67.17; H, 4.87; S, 11.06%. Calcd for $C_{16}H_{14}O_3S$: C, 67,12: H, 4.93; S, 11.18%. NMR($CDCl_3$, ppm) δ 2.98(3H, s, CH_3O-), 3.56(3H, s, $COOCH_3$), and 7.1—7.9(8H, m, aromatic protons). IR ν_{max} (Nujol) 1740(CO) and 1250(-O-)cm^{-1}.

10,11-Dihydrodibenzo[b,f]*thiepin-10,11-dione **3**. Oxidation of **9** by Selenium Oxide*: To a solution of 6.8 g of **9** in 15 ml of dioxane, we added a solution of 3.33 g of selenium oxide in a mixed solvent of 40 ml of dioxane and 2.5 ml of water. This solution was refluxed for 2 hr. The inorganic substance was then filtered off, and the filtrate was evaporated *in vacuo*. The residue thus obtained was recrystallized from cyclohexane to give 3.5 g (66.3%) of **3**; mp 135—136 °C (lit,[1)] 135—136 °C).

*Oxidation of **1** by DMSO*: A solution of 1.5 g of **1** in 15 ml of DMSO was stirred for 1 hr on a boiling-water bath. After the subsequent removal of the DMSO *in vacuo*, the residue was recrystallized from cyclohexane to give 1.0 g(83.3%) of **3** as yellow needles; mp 135—136 °C.

10,11-Dihydrodibenz[b,f]*oxepin-10,11-dione **20**.* A solution of 2.5 g of **16** in 25 ml of DMSO was stirred for 2 hr on a boiling-water bath. After the subsequent removal of the DMSO *in vacuo*, the residue was recrystallized from benzene to give 1.8 g (93%) of **20**; mp 118—119 °C (lit,[9)] 119 °C).

*The Reaction of **16** with Alkali.* A suspension of 5.0 g of **16** in an aqueous sodium hydroxide solution (sodium hydroxide, 1.36 g; water, 50 ml) was stirred for 2 hr at 80 °C. After cooling, the oil was extracted with ethyl acetate. The aqueous layer was acidified with 10% hydrochloric acid, allowed to stand to cool, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate, and evaporated. The residue thus obtained was recrystallized from a mixed solvent of benzene and hexane to give 1.75 g (14%) of **17**, IR; ν_{max} (Nujol) 2400(HO), 1740 and 1720(COO)cm^{-1}. NMR ($CDCl_3$, ppm) δ 7.2—7.8 and 8.2—8.3(8H, m, aromatic protons). The neutral reaction products were chromatographed on a silica-gel column using a mixture of benzene and cyclohexane (1 : 5) as the eluent. Compounds **18** and **19** were isolated in 11% and 28% yields respectively. These compounds were identical with samples of **18**[10] and **19**[11] obtained by an independent route as regards IR and NMR spectra.

*The Reaction of **21** with Alkali.* A solution of 2.1 g of **21**[8] in aqueous sodium hydroxide(sodium hydroxide, 0.5 g; water, 21 ml) was heated at 80 °C for 2 hr with stirring. The reaction mixture was then extracted with ethyl acetate, and the aqueous layer was acidified with dil. hydrochloric acid. The precipitate was filtered and recrystallized from a mixed solvent of acetone and *n*-hexane to give 0.3 g(20%) of crystals; mp 217 °C. NMR($CDCl_3$, ppm) δ 7.3—8.0 (aromatic protons). IR; ν_{max} (Nujol) 2700, 2500 (OH) and 1675(CO)cm^{-1}. The IR and NMR spectra of the compound were identical with those of anthracene 9-carboxylic acid, and the melting point of this compound was not depressed by admixture with the authentic sample.

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3) The ester **12** was obtained by esterification of 9*H*-thioxanthene-9-carboxylic acid.

4) The gas chromatograpy showed the presence of the diketone **3** at 30 min after the reaction bigan, but at the end of the reaction, **3** was not determined.

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