

Synthesis of Heterocycles. 174 (1,2) Substituted Thiazines and Bisthiazinyls
from Dithiooxamide and Trichlorophenyl Malonates

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As part of our studies on the ring-closure reactions of malonic acid derivatives on the one hand (4) and of oxalic acid derivatives on the other (2), we have studied the thermal condensation of dithiooxamide (1) with a series of substituted trichlorophenyl malonates (2-4) (5). As representative malonic ester substituents we have used the benzyl, phenyl, and ethyl derivatives as well as the unsubstituted ester.

Two characterizable products, both in low yield, were obtained from reaction of each of the substituted esters 2-4 with dithiooxamide (1). The unsubstituted ester failed to provide any characterizable products. Spectral and elemental analyses revealed that the products were the expected monocyclic (8-10) and bicyclic products (5-7) resulting from reaction of 1 with one and two moles of the esters 2-4, respectively.

These compounds decompose in strong alkali so that direct pKa measurements were not attempted. However, both the bicyclic (5-7) and the monocyclic products (8-10) dissolve slowly in bicarbonate and are precipitated unchanged by acidification with acetic acid, or even potassium acid phthalate. The symmetric, bicyclic products invariably possessed the higher melting point and the lower solubility so that their insolubility in methanol provided a reasonable basis for separation from the more soluble monocyclic products which still possess an unreacted thioamide function.

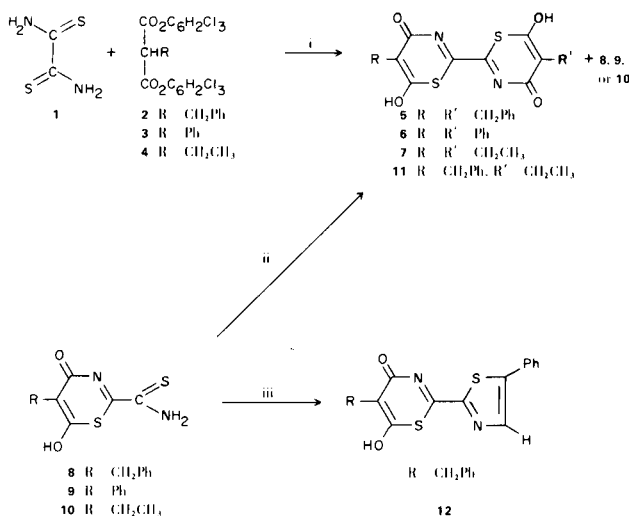
The monocyclic benzyl derivative 8 is converted into the bicyclic product 5 in high yield by reaction with more of the benzylmalonate 2. The relatively high yield obtained in this step indicates that the low overall yields probably result from side reactions or decomposition of dithiooxamide prior to reaction.

The failure of unsubstituted trichlorophenyl malonate to provide similar condensation products prompted other attempts to obtain 5-unsubstituted products. However, reactions of dithiooxamide with either Meldrum Acid (2,2-dimethyl-1,3-dioxolan-4,6-dione) (6) or carbon suboxide (7) failed to provide characterizable products.

Availability of the monocyclic substances (8-10) makes possible a much wider range of synthetic variation. First by reaction with a trichlorophenyl malonate (2-4) bearing

a different substituent we were able to demonstrate the practicability of preparing unsymmetrically substituted bis-thiazinyl systems. Thus, the 5-benzyl substituted monocyclic product 8 reacts with trichlorophenyl ethylmalonate (4) to give the unsymmetrical 5-benzyl-5'-ethyl compound 11.

Since the monocyclic products still bear an unreacted thioamide group, reactions with other common ring-forming reagents are still possible. Thus, reaction of the thioamide group of 8 with α -bromoacetophenone (8) provided the 2-(5-phenylthiazolyl)thiazine derivative 12.



i) 175-185°. ii) 8 + 2 → 5; 8 + 4 → 11. iii) 8 + PhCOCH₂Br (in refluxing ethanol).

EXPERIMENTAL

All compounds described below gave nmr (Varian A 60 A or HA 100), ir (Perkin-Elmer 421), and mass spectral (AEI-MS 20) data that were consistent with the proposed structures. Melting points are uncorrected.

5,5'-Dibenzyl-6,6'-dihydroxy[2,2'-bi-4H-1,3-thiazine]-4,4'-dione (5).

2,4,6-Trichlorophenyl benzylmalonate (2; 5.5 g., 10 mmoles) and finely divided dithiooxamide (0.6 g., 5 mmoles) were heated with an oil bath at 175° under slightly reduced pressure for 1 hour. Before cooling, the reaction mixture was diluted with 50 ml.

benzene. The brown solid was collected, washed with petroleum ether, and stirred with 100 ml. of 2% sodium bicarbonate for 3 hours. The insoluble material was removed by filtration and the product precipitated by addition of 2 ml. glacial acetic acid; yield 0.52 g., m.p. 220-228° dec. The crude product was digested with 20 ml. hot methanol and filtered (see below) to give 0.22 g. (10%) of product m.p. 253-261°, which was crystallized from dioxane to give 0.18 g. of small yellow prisms, m.p. 265-270° dec.

Anal. Calcd. for $C_{22}H_{16}N_2O_4S_2$: C, 60.55; H, 3.70; N, 6.42; S, 14.66. Found: C, 60.49; H, 3.73; N, 6.55; S, 14.37.

A twenty minute reflux in 3 ml. acetic anhydride converted 50 mg. of the product to a diacetyl derivative which was recrystallized from acetonitrile to give yellow needles, m.p. 220-225°.

Anal. Calcd. for $C_{26}H_{20}N_2O_6S_2$: N, 5.38; S, 12.30. Found: N, 5.76; S, 12.36.

5-Benzyl-2-thiocarboxamido-6-hydroxy-4H-1,3-thiazin-4-one (8).

The methanol solution from which **5** (above) was filtered was diluted with water to give 0.25 g. (18%) of orange-yellow prisms, m.p. 225-235° dec. Crystallization (methanol) gave a product m.p. 230-235° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_2S_2$: C, 51.81; H, 3.62; N, 10.07; S, 23.00. Found: C, 52.06; H, 3.64; N, 10.07; S, 22.93.

Conversion of 8 to 5.

Compound **8** (0.14 g., 0.5 mmole) was heated with **2** (0.77 g., 1.4 mmoles) for 2 hours at 180°. After dilution with benzene the yellow crystals were collected, to give 0.19 g. (86%) of product m.p. 265-270° dec. identical in all respects to **5** described above.

5,5'-Diphenyl-6,6'-dihydroxy[2,2'-bi-4H-1,3-thiazine]4,4'-dione (6).

2,4,6-Trichlorophenyl phenylmalonate (**3**; 5.25 g., 10 mmoles) and finely divided dithioamide (0.6 g., 5 mmoles) were heated with an oil bath at 175° for 45 minutes with a stream of carbon dioxide passing through the reaction mixture. Before cooling, 20 ml. of benzene was added and the solid was collected and washed with benzene to give 0.98 g. of brown powder. This was stirred with a mixture of 60 ml. of 2.5% sodium bicarbonate and 30 ml. of methanol for 3 hours. The dark insoluble material was removed by filtration and the product was precipitated with 2 ml. of acetic acid to give 0.9 g. of crude product. This material was stirred with 20 ml. of warm methanol for 1 hour and the solid collected by filtration (see below) and washed with benzene and then petroleum ether to give 0.21 g. (10%) m.p. 260-265° dec. Recrystallization from DMF-methanol (100°) afforded 0.19 g. of orange-red prisms, m.p. 280-285° dec.

Anal. Calcd. for $C_{20}H_{12}N_2O_4S_2$: C, 58.83; H, 2.96; N, 6.86; S, 15.68. Found: C, 58.86; H, 2.97; N, 6.90; S, 15.45.

5-Phenyl-2-thiocarboxamido-6-hydroxy-4H-1,3-thiazin-4-one (9).

The methanol solution obtained above was diluted with water to precipitate the monocyclic product, 0.40 g. (30%) m.p. 222-230° dec. Repeated crystallizations from methanol were necessary to remove the bicyclic product (**6**) and provided orange rods, m.p. 225-230° dec.

Anal. Calcd. for $C_{11}H_8N_2O_2S_2$: C, 50.01; H, 3.05; N, 10.60; S, 24.23. Found: C, 50.23; H, 3.11; N, 10.98; S, 24.53.

5,5'-Diethyl-6,6'-dihydroxy[2,2'-bi-6H-1,3-thiazine]-4,4'-dione (7).

Finely divided dithioamide (**1**; 0.48 g., 4 mmoles) and the ethyl derivative (**4**; 6.24 g., 20 mmoles) were heated for 40 minutes at 185° under a slight vacuum. The reaction mixture

was diluted with benzene, the solid was collected and washed with benzene. Unreacted ester (3.6 g.) was recovered from the benzene by washing with sodium bicarbonate, drying and concentration to a residue which was crystallized from ethanol. The solid was stirred for 2 hours with 50 ml. 2% sodium bicarbonate and filtered. The filtrate was acidified with 2 ml. acetic acid to give 0.40 g. of yellow product. This was stirred with 30 ml. of warm methanol (see below) and the solid collected, 0.16 g. (13%), m.p. 260-270° dec. Recrystallization from DMF-water (100°) gave yellow blocks, m.p. 260-270° dec.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S_2$: C, 46.16; H, 3.87; N, 8.97; S, 20.50. Found: C, 46.30; H, 3.88; N, 9.06; S, 20.45.

5-Ethyl-6-hydroxy-2-thiocarboxamido-6H-1,3-thiazin-4-one (10).

To the methanol solution above was added an equal volume of water and the precipitate collected, 0.18 g. (20%), m.p. 213-220° dec. Recrystallization (methanol-water) gave orange prisms, m.p. 217-220° dec.

Anal. Calcd. for $C_7H_8N_2O_2S_2$: C, 38.90; H, 3.73; N, 12.96; S, 29.61. Found: C, 39.48; H, 3.76; N, 12.68; S, 29.52.

5-Benzyl-5'-ethyl-6,6'-dihydroxy[2,2'-bi-6H-1,3-thiazine]4,4'-dione (11).

The monocyclic benzyl compound (**8**, 30 mg.) was heated at 190° with the ethyl substituted ester (**4**, 200 mg.) for 90 minutes. The reaction mixture was diluted with benzene and the solid collected, 50 mg. m.p. 255-260° dec. Recrystallization from dioxane gave fine yellow prisms having the same m.p.; nmr (pyridine- d_5): δ ; 1.23 (CH₃); 2.82 (CH₂); 4.16 (CH₂Ph); 7.51 (C₆H₅).

Anal. Calcd. for $C_{17}H_{14}N_2O_4S_2$: N, 7.48; S, 17.08. Found: N, 7.53; S, 17.12.

5-Benzyl-6-hydroxy-2[5-phenylthiazolyl]6H-1,3-thiazin-4-one (12).

The monocyclic benzyl compound (**8**, 40 mg.) was heated with 40 mg. α -bromoacetophenone in 5 ml. absolute ethanol for 1 hour. On cooling 40 mg. of crystalline product separated, m.p. 255-260°. Recrystallization from methanol gave yellow needle aggregates, m.p. 258-260°; nmr (DMSO- d_6): δ ; 3.78 (CH₂); 7.24 (C₆H₅-CH₂); 7.4, 8.0 (C₆H₅-C); and 8.51 (CH).

Anal. Calcd. for $C_{20}H_{14}N_2O_2S_2$: N, 7.40; S, 16.91. Found: N, 7.68; S, 16.92.

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