An Alternative Synthesis of Tiopinac

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Tiopinac (1) [6, 11-dihydro-11-oxodibenzo[*b*,e]thiepin-3-acetic acid, (**1**)] has shown a high degree of antiinflammatory activity and a low incidence of side effects in animals (2). On the basis of these results, Tiopinac was chosen for human evaluation in 1978 (2a).

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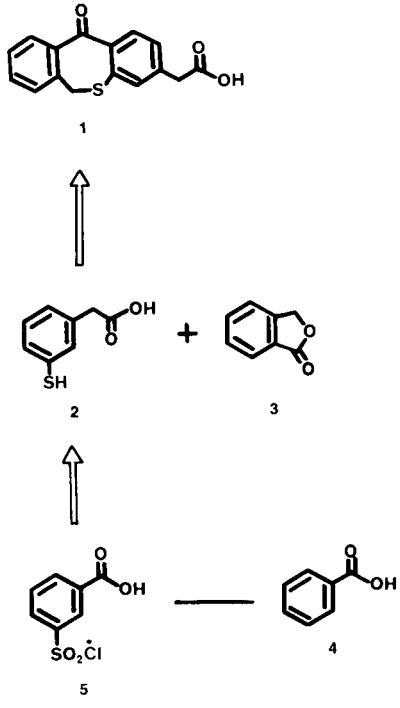
As a part of our development effort, we required a method for the preparation of **1** which was suitable for plant scale synthesis and which was inexpensive. The reported (**2a**) preparation of **1** employed the Arndt-Eistert extension reaction for elaboration of the acetic acid side chain. We found this extension reaction unsuitable for large scale preparations because the use of diazomethane was potentially hazardous. The reported (2a) preparation of **1**, and other preparations (3,4) also suffered from unacceptable cost profiles and the odor problems associated with the use of benzyl mercaptan on a large scale.



We reasoned that the development of a convenient preparation of 3-mercaptophenylacetic acid (**2**), followed by base catalyzed condensation with 1-(3*H*)-isobenzofuranone (phthalide, **3**) might obviate the above disadvantages. Our efforts to prepare **2** led to the preparation of a protected form of **2**. As a matter of convenience, we chose a protecting group for **2** which was suitable for direct cyclization to **1**.

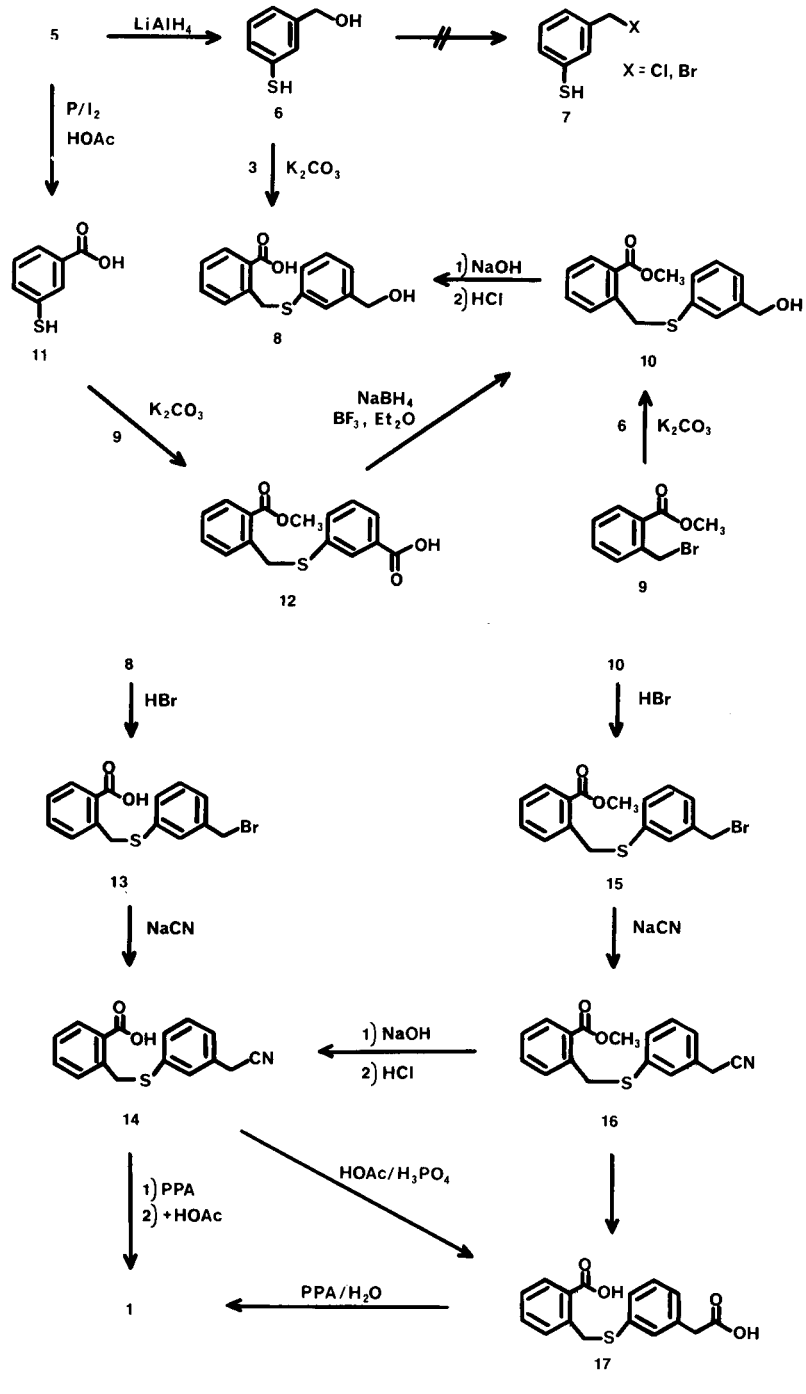
A perusal of the literature revealed that chlorosulfonation of benzoic acid (**4**) (5) was reported to give **5** in high yield and free from isomerides. Our investigation of this reaction supported the earlier report. The yields of **5** were routinely greater than 85%, and rigorous examinations of the nmr and cmr spectra failed to reveal the presence of isomerides.

Our initial attempts to convert **5** into **2** were based on a reported similar conversion of thiosalicylic acid (6). Reduction of **5** with lithium aluminium hydride gave *m*-mercaptobenzyl alcohol (**6**) (7) in high yield. However, attempts to chlorinate or brominate **6** led to low yields of products (**7**) which were extensively contaminated by impurities (8). This suggested that protection of the thiol group of **6** was required prior to elaboration of the acetic acid moiety.

Protection of the thiol group was initially attempted by condensation with phthalide (**3**). However, the best yield of **8** that we were able to achieve in this condensation was 27%. A higher overall yield (88%) of **8** was obtained by condensation with the more reactive methyl α-bromotoluate (**9**) (9) to give **10**, followed by ester group hydrolysis. Compound **8** did prove to be a viable intermediate in the preparation of **1** by subsequent elaboration of the acetic acid side chain and cyclization (*vide infra*). However, the use of **6** in a preparative scheme presented the problems associated with it's inherent foul odor and use of the pyrophoric reagent lithium aluminum hydride. We therefore initiated an investigation of what appeared to be a preferable synthesis of **8**.

Reduction of **5** by iodine catalyzed reaction with red phophorus in acetic acid (10) gave *m*-mercaptobenzoic acid (**11**) in high yield. In contrast with compound **6**, this material had no detectable odor under ordinary conditions. Condensation of **9** and **11** provided the ester acid **12** which was suitably protected for selective reduction to **10** by treatment with sodium borohydride and boron trifluoride etherate.

The sequence for elaboration of the acetic acid side chain of **1** was examined using both the acid **8** and the ester **10**. Bromination of either **8** or **10**, by treatment with dry hydrogen bromide in sulfolane (12) gave impure benzylic bromides **13** and **15**. The impurities present in the



products appeared to be the result of partial disproportionation (13) at the carbon-sulfur bond by revealing a pattern of peaks in the nmr spectrum which corresponded in part to **11** and either **9** or α-bromotoluic acid. The extent of this disproportionation was small and the impure materials were used without further purification. Treatment of **13** and **15** with sodium cyanide in either aqueous acetone or aqueous dioxane gave the corresponding acetonitrile derivatives **14** and **16**, both of which could be hydrolyzed to the diacid **17** in high yield.

Attempted cyclization of **17** to give **1** by the known procedure (3) gave yields which approached only 50%. Similar direct cyclization/hydrolysis of **14** gave no impovement in yield. The use of other reported methods (14,15) for this type of cyclization also gave yields lower than

50%. It was subsequently found that predigestion of polyphosphoric acid with 5-6 weight percent of water, followed by the addition of **17** increased the yield of **1** to 75%. We made no attempt to determine what effect this predigestion with water had on the structure of polyphosphoric acid (16). However the increase in yield was confirmed on a moderate scale.

EXPERIMENTAL

Melting points are corrected. The nmr spectra were recorded on a Varian A60 or HA100 spectrometer. The cmr spectra were recorded on a Bruker WH90 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the δ scale from internal tetramethylsilane.

3-Chlorosulfonylbenzoic Acid (**5**).

Benzoic acid (**4**, 100 g) was placed in a 1 liter round bottom flask. Clorosulfonic acid (400 ml) was added to the flask. The mixture was heated at 120-125° for 2 hours and then allowed to cool to 40-50°. The reaction mixture was added dropwise to an excess of crushed ice. The precipitated product was collected by filtration and dissolved in 750 ml of ethyl acetate. The aqueous layer which formed was separated and the organic layer was washed with 100 ml of water. The organic layer was dried with sodium sulfate and evaporated to near dryness. Hexane (300 ml) was added. The product was collected by filtration, washed with 200 ml of hexane and dried in air to give 154.6 g (85.6%) of **5**, mp 134-135°, lit (5) mp 131°; nmr (deuteriochloroform): δ 7.70 (t, J = 8 Hz, H3), δ 7.95-8.15 (m, H4 and H6), δ 8.28 (t, J = 1.5 Hz, H2); cmr (deuteriochloroform): 196.21 (CO), 145.09, (C-3), 131.53, (C-1).

3-Mercaptobenzyl Alcohol (**2**) (7).

3-Chorosulfonylbenzoic acid (**5**, 28.7 g) was suspended in 200 ml of teterahydrofuran. Lithium aluminum hydride (15 g) was added in portions over a 1 hour period. Approximately half-way through the additon the mixture became too thick for adequate agitation and another 200 ml of tetrahydrofuran was added. The mixture was stirred for 2 hours at ambient temperature and then treated dropwise with 30 ml of water followed by 10% sulfuric acid (500 ml). The lower layer which formed on settling was separated and extracted with 3 × 100 ml diethyl ether. The organic layers were combined, washed with 3 × 50 ml of water, dried with magnesium sulfate and evaporated to constant weight to give 27.8 g (> quantitative) of **5** as light yellow liquid. For analysis a small sample was bulb-to-bulb distilled at 70° (bath)/10^{-3} Torr. The nmr spectrum (deuteriochloroform) of **5** showed deuterium exchangeable singlets at δ 2.83 and δ 3.50 as well as a complex multiplet centered at δ 7.18.

Anal. Calcd. for C_7H_8OS: C, 59.97; H, 5.75; S, 22.87. Found: C, 59.80; H, 5.62; S, 22.71.

2-(1-Hydroxymethyl-3-thiophenylmethyl)benzoic Acid (**8**).

Method A.

Compound **6** (109 mg) was dissloved in 1.56 ml of *N,N*-dimethylformamide. Potassium carbonate (216 mg) was added to the solution. The resulting mixture was stirred at room temperature for 5 minutes and phthalide (**3**, 104 mg) was then added. The mixture was heated at 80° for 2 hours and allowed to cool. This was acidified by the addition of 3.8 ml of 1*N* hydrochloric acid and extracted with 3 × 2 ml of diethyl ether. The ether extracts were washed with 3 × 2 ml of water, dried with magnesium sulfate and evaporated to a yellow oil. This oil was partitioned in 4 ml of saturated sodium bicarbonate solution and 2 ml of diethyl ether. The aqueous layer was extracted with 2 ml of diethyl ether and then acidified to *p*H 2-3 (paper) by the addition of concentrated hydrochloric acid. The resulting mixture was extracted with 2 × 2 ml of diethyl ether and the ether layers were backwashed with 2 ml of water. The ether layers were evaporated to dryness and the residue crystallized from 1 ml of hot toluene to give **8** (58 mg, 27%), mp 103-106°; nmr (deuteriochloroform plus perdeuteriomethanol): δ 7.1-8.0 (m, 9H, ring protons).

Anal. Calcd. for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.86; H, 5.11; S, 11.62.

Method B.

Compound **10** (51 g) was dissolved in 175 ml methanol. A solution of sodium hydroxide (8.4 g) in 175 ml of water was added. This was heated at reflux temperature for 1 hour and then allowed to cool to room temperature. The methanol was evaporated *in vacuo*. The remaining solution was diluted with 300 ml of water and extracted with 178 ml of ethyl acetate. The aqueous layer was acidified to *p*H 2-3 (paper) by the addition of concentrated hydrochloric acid and extracted with 350 ml of ethyl acetate. The ethyl acetate layer was evaporated to an oil and the oil was dissolved in 120 ml of toluene. The solid which separated on cooling was collected by filtration and dried in air to give 39.0 g (78.4%) of **8**, identical with the material prepared by method A.

3-Mercaptobenzoic Acid (**11**).

Compound **5** (156 g) was placed in a 2 liter three-neck flask. Acetic acid (240 ml) and red phosphorus (78.5 g, 20 g of which had been recovered from a previous run) were added to the flask. The mixture was heated to 110°. A solution of iodine (2.82 g) in 66 ml of acetic acid was added dropwise over about 30 minutes while maintaining the color of iodine vapors. The mixture was cooled to 100° and treated dropwise with 41 ml water over a 10 minute period. The resulting mixture was heated at reflux temperature for 1.5 hours and then cooled to 90°. Saturated sodium chloride solution (250 ml), then water (500 ml) were added. The mixture was cooled at 0-5° for 1 hour and the solids were collected by filtration. The damp cake was slurried with 450 ml of acetone and the excess red phosphorus was removed by filtration. The acetone was evaported from the filtrate, while adding 500 ml of water. The solid which formed was filtered and dried *in vacuo* to give 100.1 g (91.7%) of **11**, mp 138-141° (lit (5) mp 146-147°); cmr (deuteriochloroform plus perdeuteriomethanol): 168.98 (CO), 133.78 (C4), 131.99 (C1), 131.37 (C3), 130.66 (C2) 129.26 (C5), 127.27 (C6).

Anal. Calcd. for $C_7H_6O_2S$: C, 54.53; H, 3.92. Found: C, 54.53; H, 3.84.

3-(2-Carboxymethylbenzylthio)benzoic Acid (**12**).

Methyl *o*-toluate (*9*, 98 g) (9) was dissolved in 327 ml of dichloromethane and bromine (36.4 ml) was added to the solution. This was irradiated with a 120 watt tungsten lamp for 2.75 hours, at which time the color of bromine had disappeared. The solution was transferred to a pressure equalized addition funnel and added dropwise over 30 minutes at 5-12° to a stirred solution of **11** (62.7 g) and potassium carbonate (221 g) in 327 ml of water. After the end of the addition the mixture was stirred at 12° for 40 minutes and acidified by the dropwise addition of 265 ml of concentrated hydrochloric acid over a 1 hour period. Ethyl acetate (250 ml) and water (100 ml) were added to the mixture. This was allowed to settle, and formed two layers. The upper organic layer was washed with 400 ml of water. The organic phase separated as the bottom layer upon being allowed to settle. The organic layers were dried with sodium sulfate and evaporated until the onset of crystallization. Hexane (500 ml) was added. The solid which had formed was filtered and dried in air to give **12** (135.1 g, 84.3%), mp 105-107°; nmr (deuteriochloroform): δ 3.90 (s, 3H, CH_3), δ 4.57 (s, 2H, CH_2S), δ 7.1-8.2 (m, 8H, ring protons), δ 11.4 (bs, 1H, COOH).

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.60. Found: C, 63.42; H, 4.55; S, 10.71.

3-(2-Carboxymethylbenzylthio)benzyl Alcohol (**10**).

Method A.

Into a 2 liter Morton flask was placed 183 ml of tetrahydrofuran and 17 g of sodium borohydride. A solution of 132.4 g of **12** in 370 ml of tetrahydrofuran was added dropwise over a 0.5 hour period while maintaining the temperature at 10-15°. A solution of boron trifluoride etherate (69 ml) in 94 ml of tetrahydrofuran was added dropwise over a

0.5 hour period while maintaining the temperature at 10-15°. The reaction mixture was aged for 3 hours and then acidified by the dropwise addition of 100 ml of 3*N* hydrochloric acid over a 0.5 hour period. The temperature was allowed to rise to 23° during this acidification. Water (170 ml) was then added. The solution was evaporated free of tetrahydrofuran. The remaining material was partitioned in 300 ml of ethyl acetate and 150 ml of water. The ethyl acetate layer was washed (1 × 200 ml water plus 50 ml of saturated sodium chloride solution), dried with sodium sulfate and evaporated to near dryness. Toluene (100 ml) was added and the evaporation was continued to constant weight to give **10** (130.0 g, >quantitative) as a light yellow oil. For analysis a 135 mg sample in 2 ml of dichloromethane was applied to a plate (1 mm × 20 cm × 20 cm) of silica gel GF. The plate was eluted with cyclohexane/diethyl ether (2:1). The uv positive band at R_f 0.6 was eluated with 25 ml of diethyl ether and evaporated to an oil weighing 105 mg. nmr (deuteriochlorofrom): δ 3.82 (s, 3H, CH_3), δ 4.47 (s, 2H, CH_2S), δ 4.58 (m, 2H, CH_2O).

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.48; H, 5.59; S, 11.31.

Method B.

Compound **6** (0.70 g) was dissolved in 12.5 ml of *N,N*-dimethylformamide. A solution of potassium carbonate (1.38 g) in 12.5 ml water was added, followed by a solution of **9** (1.15 g) in 3.7 ml of *N,N*-dimethylformamide. The mixture was agitated at ambient temperature for 20 minutes and then diluted with 20 ml of water. This was extracted with 2 × 15 ml of ethyl acetate. The organic layers were washed with 2 × 15 ml of water, dried with sodium sulfate and evaporated to an oil weighing 1.60 g (>quantitative). Treatment of this material with sodium hydroxide, followed by acidification gave **14**, mp 105.5-107.5°, in a yield which corresponded to 88% of the theoretical from compound **6**.

3-(2-Carboxymethylbenzylthio)benzyl Bromide (**15**).

Compound **10** (127.7 g) was dissolved in 235 ml sulfolane by warming to *ca.* 35°. The solution was then cooled to 15°. Dry hydrogen bromide was bubbled into the solution until the saturation point was reached (2 hours and 45 minutes). Progress of the reaction was monitored by tlc in hexane/ethyl acetate (3:1), which showed complete bromination approximately 1 hour after the end of the hydrogen bromide addition. Water (630 ml) was added. The resulting mixture was extracted with 2 × 300 ml of ethyl acetate. The ethyl acetate extracts were combined and washed with 2 × 300 ml of 30% saturated sodium chloride solution. The organic layer was dried with sodium sulfate and evaporated to constant weight to give crude **15** (145 g, 93.2%) which contained a trace of sulfolane, and traces of disproportionation products (see text). This material was used directly in the next step of the reaction sequence; nmr (deuteriochloroform): δ 3.87 (s, 3H, CH_3), δ 4.38 (s, 2H, CH_2S) δ 4.95 (s, 2H, CH_2Br), δ 7.0-8.0 (m, 8H, ring protons).

3-(2-Carboxymethylbenzylthio)phenylacetonitrile (**16**).

The above crude bromide (**15**, 145 g) was dissolved in 600 ml of acetone. Water (90 ml) and sodium cyanide (39 g) were then added. The solution was heated at gentle reflux for 1 hour and then allowed to cool at room temperature. The solution was evaporated free of acetone and the residue was partitioned in 300 ml each of water and ethyl acetate. The aqueous layer was separated and extracted with 100 ml of ethyl acetate. The ethyl acetate layers were combined and washed with 200 ml of 10% potassium carbonate solution, then with 2 × 200 ml of 20% saturated sodium chloride solution. This was dried with sodium sulfate and clarified with 5 g Norit A, then evaporated to an oil to give crude **16** (133.5 g, >quantitative) which was used directly in the next step; ir (film): 2300 cm^{-1} (CN); nmr (deuteriochloroform): δ 3.88 (s, 3H, CH_3), δ 3.67 (s, 2H, CH_2CN), δ 4.53 (s, 2H, CH_2S) δ 7.0-8.0 (M, 8H, ring protons).

3-(2-Carboxybenzylthio)phenylacetonitrile (**14**).

Method A.

The above crude oil (133.5 g) was dissolved in 0.5 liters of methanol and added to a stirred solution of methanol (0.5 liter), water (0.1 liter) and sodium hydroxide (20 g). The solution was heated at gentle reflux for 1 hour and then allowed to cool to room temperature. The solution was evaporated free of methanol. The remaining material was diluted with 250 ml of water and extracted with 1 × 150 ml then 1 × 75 ml of ethyl acetate. The aqueous layer was acidified by the addition of 43 ml of concentrated hydrochloric acid and extracted with 2 × 200 ml of ethyl acetate. The organic extracts were washed with 2 × 250 ml of 20% saturated sodium chloride and dried with sodium sulfate. This was evaporated to *ca.* 150 ml volume and diluted with 600 ml of hexane. The light brown solid which formed was collected by filtration dried in air to give **14** (8.7 g, 69.3% from **10**). For analysis a small sample was recrystallized from acetone/toluene, mp 108-110°; nmr (deuteriochloroform): δ 2.40 (s, 0.5H, H_2O), δ 3.68 (2, 2H, CH_2CN), δ 4.60 (s, 2H, CH_2S), δ 7.0-8.1 (m, 8H, ring protons), δ 9.43 (bs, 1H, XD_2O, COOH).

Anal. Calcd. for $C_{16}H_{13}NO_2S \cdot \frac{1}{4} H_2O$: C, 66.76; H, 4.73; N, 4.87; S, 11.14. Found: C, 67.04; H, 4.67; N, 4.79; S, 10.99.

Method B.

A solution of bromo acid 13 (25 g) in 150 ml of dioxane was added over a 1 hour period to a solution of sodium cyanide (14 g) in a mixture of water (150 ml) and dioxane (100 ml) while maintaining the temperature near 70°. Water (100 ml total) was added to the mixture in 25 ml aliquots over a 1 hour period. The solution was cooled and acidified to *p*H 2-3 (paper) by the addition of 3*N* hydrochloric aicd. The mixture was partitioned in 400 ml each of water and ethyl acetate. The ethyl acetate layer was washed with 2 × 200 ml of water and 2 × 200 ml of saturated sodium chloride solution, then evaporated to dryness to give **14** (20.0 g, 95.2%), identical with material prepared by Method A.

3-(2-Carboxybenzylthio)phenyl acetic acid (**17**).

Method A.

Compound **16** (0.50 g) was dissolved in 3.5 ml of methanol. Water (1.0 ml) and concentrated sulfuric acid (0.3 ml) was then added. This was heated at reflux temperature for 23 hours and allowed to cool to room temperature. The reaction mixture was poured into 100 ml of water and extracted with 2 × 5 ml of ethyl acetate. The ethyl acetate layer was extracted with 2 × 5 ml of saturated sodium bicarbonate solution. The aqueous layer was extracted with 2 × 5 ml of ethyl acetate. The ethyl acetate layers were combined and clarified with Norit A. The filtrate was evaporated to 2 ml and diluted with 10 ml of hexane to give **15** (0.46 g, 90%), identical with a sample obtained by the following method.

Method B.

Compound **14** (8.80 g) was suspended in 39 ml of acetic acid. Phosphoric acid (39 ml, 85%) was then added. This was heated at gentle reflux temperature (140° bath) for 7 hours and allowed to cool to room temperature. Water (50 ml) was then added. The solid which had formed was collected by filtration, slurried twice in 50 ml of water, and dried in air to give **15** (8.35 g, 90%), mp 127-129°, lit (3) mp 126-127°; nmr (perdeuteriodimethylsulfoxide): δ 3.51 (s, 2H, CH_2CO); δ 4.68 (s, 2H, CH_2S); δ 7.0-8.0 (m, 10H, ring protons and COOH).

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.50. Found: C, 63.61; H, 4.67; S, 10.77.

3-(2-Carboxybenzylthio)benyl Bromide (**13**).

Compound **8** (40 g) was dissolved in 120 ml of sulfolane by heating to approximately 40°. The solution was cooled to 15° and dry hydrogen bromide gas was bubbled into the solution for 3 hours while maintaining the temperature near 15°. At this time the mixture had become saturated with hydrogen bromide and a white solid had separated. This was agitated for 2 hours and then diluted with 240 ml water. The solid which had formed was collected by filtration and washed free of acid with water to give crude **12** (47 g, 92%). This product contained traces of disproprotionation products (see text) and was used without further purification;

nmr (deuteriochloroform): δ 4.37 (s, 2H, CH_2Br); δ 4.55 (s, 2H, CH_2S), δ 7.0-8.0 (m, 8H, ring protons).

6,11-Dihydro-11-oxodibenzo[*b,e*]thiopin-2-acetic Acid (Tiopinac, **1**).

Polyphosphoric acid (553 g) was placed in a 1 liter three neck flask. This was heated to 80° and water (32 ml) was added over a 50 minute period while maintaining the temperature at 80-90°. The resulting soltuion was aged at 90° for 0.5 hour. Compound **17** (58 g) was then added. The mixture was agitated and maintained at 90° for 1 hour and 20 minutes. Water (400 ml) was then added, while maintaining the temperature below 85°. The resulting mixture was poured into 500 ml of water. The solid which formed was filtered and washed with 100 ml of water. The solid was dissolved in 40 ml of ethyl acetate and washed with a mixture of 200 ml of water and 100 ml of saturated sodium chloride solution. The ethyl acetate layer was clarified with 5 g of Norit A and evaporated to the point of crystallization. Toluene (200 ml) was added and the mixture was evaporated free of ethyl acetate. The solid which had formed was collected by filtration and recrystallized from acetone (60 ml)/toluene (200 ml) by boiling off the acetone to give **1** (40.9 g, 75.1%), mp 159-161°, lit (2) mp 155-156°. This material showed a high performance liquid chromatography purity of 102.2% versus a reference standard [10 μm LiChrosorb RP-18, 1% acetic acid in water/methanol (34:66)], and gave a nmr spectrum which was identical with an authentic (2a) sample.

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(8) The major impurities from these reactions appeared to be the disulfides of **5** and of **6**.

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(10) Reduction of **5** by this method has been reported (11) to give **9** in 75% yield, and free from disulfide impurities. Using the reported (11) procedure we consistently found *ca.* 10% of the disulfide present in the product. A procedure was developed which gave pure **11** in >90% yield (see experimental).

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