The Synthesis of 3-Hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-Dioxide, a Prostaglandin Antagonist

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An economic synthesis of 3-hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-dioxide, a novel prostaglandin antagonist, is described. The key step in the synthesis is the formation of a carboxyphenylacetic acid by carboxylation of a toluic acid dianion, followed by cyclisation to the tricyclic ketone. Readily available starting materials are used in the synthesis and conditions have been found at each stage to give pure intermediates, requiring little purification, in high yield.

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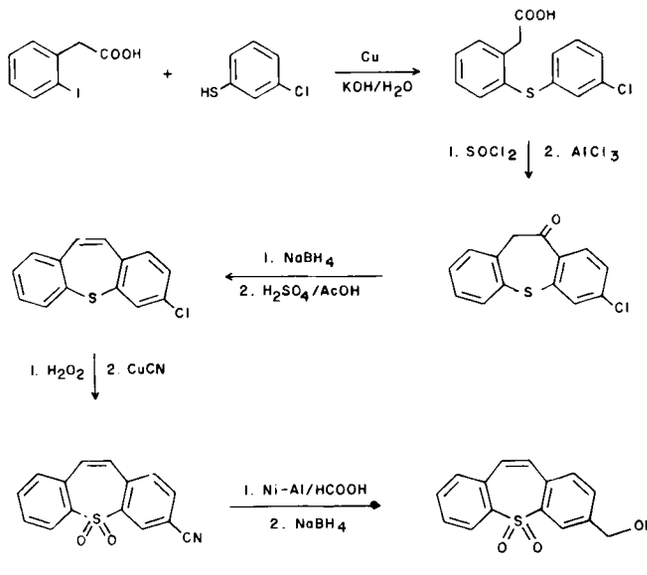
3-Hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-dioxide **13** is a novel antagonist of contractile prostanoids in the lung [1,2] which may be prepared as described by Hamel and Rokach [3,4] from 2-iodophenylacetic acid and 3-chlorothiophenol, Scheme 1.

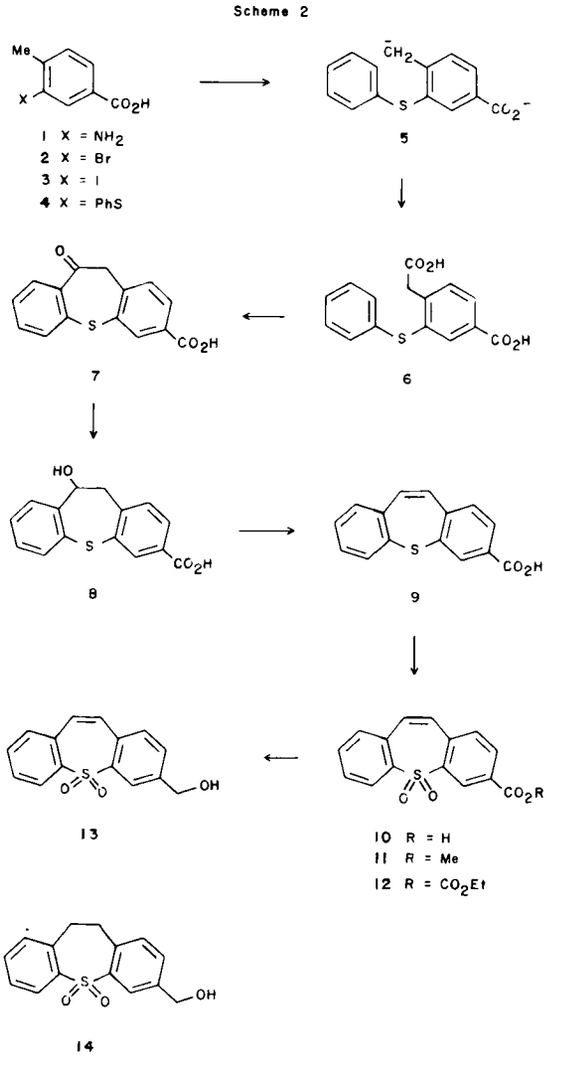
The need for larger quantities of this compound and the active metabolite dibenzo[*b*,*f*]thiepin-3-carboxylic acid 5,5-dioxide for safety assessment, clinical and other studies prompted a review of the process, with consideration given to availability and cost of starting materials and the suitability of the procedures to large scale plant. The main disadvantage of the route besides the high cost of the starting materials was the method used to elaborate the hydroxymethyl side chain *via* a nitrile from a chloro group.

Methods for the preparation of dibenzo[*b*,*f*]thiepins fall into two categories, the cyclisation of substituted 2-phenylthiophenylacetic acids [5] or the acid catalysed ring expansion of 9-hydroxymethylthioxanthenes [6,7]. We adopted

Scheme 1



Scheme 2



the former more versatile route and our strategy took advantage of the ready availability of 3-amino-4-methylbenzoic acid **1** and the facile generation of a toluic acid dianion [8], which we have shown may be carboxylated to give a substituted phenylacetic acid. This provides a considerably shorter route than the conventional method of converting a methyl group into an acetic acid by bromination, cyanide displacement and hydrolysis.

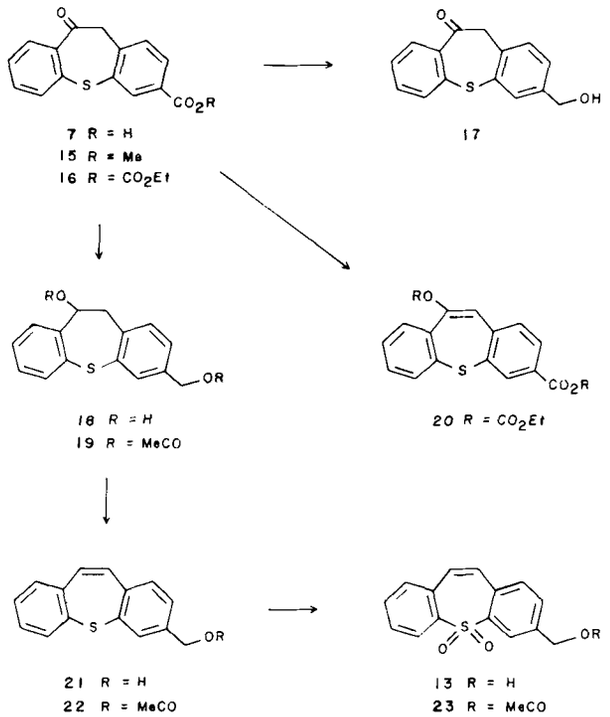
The first stage in the process, Scheme 2, involves conversion of the amino compound **1** into the sulphide **4**. The sulphide may be obtained directly from the diazotized amino acid **1** by a Ziegler reaction [9] with thiophenol, but this approach was not pursued due to literature reports of the explosive nature of the intermediate diazosulphides [10]. The safer but longer route *via* the halides **2** and **3** was investigated in some detail in order to optimise the Sandmeyer reactions and the coupling reactions between the halides and thiophenol.

The bromotoluic acid **2** was obtained in 88% yield from the amino acid **1** by a Sandmeyer reaction carried out at 35-40°. The bromo compound reacted with thiophenol and cuprous oxide (1 equivalent) in quinoline at 180-190° to give 4-methyl-3-phenylthiobenzoic acid **4** contaminated with diphenyl disulphide in 88% yield, *i.e.* 77% overall from the amino compound. The high temperature coupling reaction may be avoided by the use of the more reactive iodide **3**, which reacts with thiophenol in boiling aqueous sodium hydroxide solution, in the presence of a catalytic amount of cuprous iodide to give the pure sulphide **4** in quantitative yield. In the absence of a copper catalyst no reaction occurs. Cuprous iodide appears to be the best catalyst but copper powder or the copper oxides are also effective. Copper thiophenoxide is formed as an intermediate [11] and at the end of the reaction this may be removed by filtration for recycling.

The iodo acid **3** was obtained from the amino acid **1** by a Sandmeyer reaction carried out at reflux with a catalytic amount of cuprous iodide in 62% yield. Thus the overall yield of the 4-methyl-3-phenylthiobenzoic acid **4** from the amino compound *via* the iodide is 62%. Although the preparation of the sulphide by this route gave a lower yield, it was preferred to the bromide method which required a high reaction temperature and produced poorer quality product.

The blue toluic acid dianion **5**, easily prepared by addition of two equivalents of lithium diisopropylamide to a THF solution of the acid **4** and tetramethylurea at -15° [8], was quenched with carbon dioxide to give the diacid **6** in 96% yield. Dimethylimidazolidinone was an equally effective cosolvent as tetramethylurea in stabilisation of the dianion **5**, tetramethylethylenediamine was less so, whereas, in the absence of a cosolvent the diacid **6** was obtained in only 63% yield.

Scheme 3



Cyclisation of the diacid to the ketoacid **7** was initially achieved using trifluoroacetic acid/anhydride and a catalytic amount of boron trifluoride. This gave the acid **7** in good yield, but contaminated with its anhydride which was hydrolysed during the work up with base. Methanesulphonic acid/phosphorus pentoxide has been reported [12] as a more convenient substitute for polyphosphoric acid, but an attempt to use this reagent for the cyclisation of diacid **6** was unsuccessful. Cyclisation in polyphosphoric acid diluted with water gave the ketoacid **7** in 96% yield. Handling viscous polyphosphoric acid is a little difficult on the large scale, but dilution with a small amount of water increased the mobility of the mixture and also prevented anhydride formation.

Two alternative approaches to the final compound **13** from the ketoacid **7** are possible, by simultaneous or sequential reduction of the 10-oxo and 3-carboxy groups. Both routes have been explored, and Scheme 3 outlines the method involving simultaneous reduction of the groups.

The ketoacid **7** was converted into the methyl ester **15** but reduction with sodium borohydride in methanol and *t*-butyl alcohol [13] gave a mixture containing the diol **18** (46%) and the partially reduced hydroxy acid **8** (14%) and keto-alcohol **17** (37%). The reduction was incomplete even after a longer reaction time or additional reducing agent had been added. Reaction of the ketoacid with ethyl chloroformate/triethylamine gave the mixed anhydride **16** with some enol ester **20** which was reduced with sodium borohydride to give the diol **18** in 89% yield.

Careful addition of concentrated sulphuric acid to the diol **18** in acetic acid at 10-15° gave a solution of the diacetate **19**, which on heating to 40° eliminated acetic acid to give the acetate **22**. The crude ester, an oil, was hydrolysed to give the pure alcohol **21** in 62% yield. Oxidation of the sulphide **21** with sodium perborate [14] in acetic acid gave poor quality sulphone **13** in 91% yield. The acetate **22** may also be oxidised *in situ*. Dehydration of the diol in acetic acid containing sulphuric acid gave a solution of the acetate **22** which was oxidised by addition of sodium perborate. Work up of the mixture including saponification gave the crude alcohol **13** in 89% yield, but again purification of the product was difficult.

Thus due to the difficulties of purification in high yield of the diol or alcohol derivatives obtained by reduction of both the ketone and acid groups, sequential reduction of these groups was investigated, Scheme 2.

The ketoacid **7** was reduced with sodium borohydride and the alcohol **8** dehydrated to give 3-carboxydibenzo-[*b,f*]thiepin **9** in 81% yield. Oxidation of the sodium salt of the sulphide **9** in water to the sulphone **10** using sodium perborate was not very successful, although in acetic acid the sulphone **10** was obtained on addition of sodium perborate in 95% yield. Similarly, oxidation of the sulphide **9** in acetic acid with hydrogen peroxide gave the sulphone **10** in 95% yield.

Reduction of the acid **10** to the alcohol **13** was initially carried out *via* the ester **11** with "activated" sodium borohydride. Sodium borohydride/*t*-butyl alcohol/methanol [13] was the most successful, but as in all cases using "activated" reducing agents, small amounts (2-5%) of the dihydro derivative **14** were also formed which were extremely difficult to remove from the desired product. Activation of the carboxyl group by conversion of the acid **10** into the mixed anhydride **12** followed by treatment with sodium borohydride gave the alcohol **13** in 92% yield. This represents a 42% overall yield from 3-amino-4-methylbenzoic acid by the nine stage process.

EXPERIMENTAL

Melting points were determined with a Buchi apparatus and are uncorrected. Infra red (ir) spectra were recorded on a Perkin Elmer 781 spectrophotometer as nujol mulls. A Bruker FT (250 MHz) spectrometer was used to determine nuclear magnetic resonance (nmr) spectra, with tetramethylsilane (TMS) as internal reference and deuterioacetone:deuteriodimethylsulphoxide (5:1) as solvent (unless otherwise stated) [17]. High pressure liquid chromatography (hplc) using a Waters chromatograph with a uv detector (λ = 239 nm) and Hypersil 5 micron ODS, 25 cm x 4.5 mm column was used to measure the purity of compounds with the following solvent systems: 1) 55% methanol:45% 0.0025*M* phosphoric acid for 10 minutes, gradient to 90% methanol during 10 minutes, flow 1.5 ml min^{-1}; 2) 65% methanol:35% 0.0025*M* phosphoric acid for 10 minutes, gradient to 90% methanol during 10 minutes, flow 1.5 ml min^{-1}.

3-Bromo-4-methylbenzoic Acid (**2**).

A solution of sodium nitrite (240 g, 3.5 moles) in water (330 ml) was added slowly to a suspension of 3-amino-4-methylbenzoic acid (500 g, 3.3 moles) in hydrochloric acid (8%, 1.9 litres, 4.8 moles) at <0°. The diazonium salt solution was added over 1.5 hours to hydrobromic acid (47%, 4.5 litres) and cuprous bromide (840 g, 5.86 moles) at 35-40°. The mixture was stirred overnight at room temperature. The precipitate was collected, washed with water and dried to give 671 g (94%) of the bromo compound **2** mp 201-203° (lit [18] mp 204°); hplc solvent 1, Rt 7.2 minutes 94%.

3-Iodo-4-methylbenzoic Acid (**3**).

A solution of sodium nitrite (105 g, 1.5 moles) in water (150 ml) was added slowly to a suspension of 3-amino-4-methylbenzoic acid (232.5 g, 1.5 moles) in hydrochloric acid (8%, 1.1 litres, 2.9 moles) at <0°. The diazonium salt solution was added over 30 minutes to a boiling solution of potassium iodide (400 g, 2.4 moles) and cuprous iodide (50 g, 0.3 mole) in water (350 ml). The mixture was stirred and heated under reflux for 2 hours. Heating was discontinued and sodium metabisulphite (10 g) in water (50 ml) was added cautiously. The precipitate was collected, washed with water and dried. The solid was dissolved in hot ethanol (2 litres), filtered to remove cuprous iodide and the filtrate crystallised by addition of water (1.5 litres) to give 255 g (61%) of the iodo compound **3** mp 204-206° (lit [18] mp 205-206°); hplc solvent 1, Rt 12.1 minutes, 96%; Rt 9.9 minutes 3% chloro compound.

4-Methyl-3-phenylthiobenzoic Acid (**4**) from Iodo Compound **3**.

The iodo compound **3** (1.24 kg, 4.73 moles) was dissolved in a solution of sodium hydroxide (792 g, 20 moles) in water (8.2 litres), thiophenol (540 ml, 5.26 moles) and cuprous iodide (59 g, 0.3 mole) were added and the mixture heated under reflux (nitrogen atmosphere) for 8 hours. The cooled solution was filtered to remove copper salts and the filtrate acidified. The precipitate was collected, washed with water and dried to give 1153 g (100%) of the 4-methyl-3-phenylthiobenzoic acid (**4**) mp 167-169°; hplc solvent 2, Rt 12.3 minutes 99.3%. Recrystallisation from ethyl acetate gave an analytical sample mp 169-171°; ir: 2660 and 2550 cm^{-1} (OH, carboxylic acid), 1685 cm^{-1} (C=O, carboxylic acid); nmr: δ 2.41 (s, Me, 3H), 7.23-7.42 (m, Ph, 5H), 7.42 (d, 5-H, 1H, J = 6 Hz), 7.84 (q, 6-H, 1H, J = 1 and 6 Hz), 7.86 (d, 2-H, 1H, J = 1 Hz).

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.12. Found: C, 68.80; H, 5.00; S, 13.06.

4-Methyl-3-phenylthiobenzoic Acid (**4**) from Bromo Compound **2**.

A mixture of the bromo compound **2** (1 kg, 4.65 moles), thiophenol (499 ml, 4.86 moles) and cuprous oxide (352 g, 2.46 moles) in quinoline (2.2 litres) was heated (nitrogen atmosphere) to 180°. Water distilled from the mixture to give a black solution, which was heated at 185-190° for 45 minutes. The solution was cooled to 110° and poured into stirred hydrochloric acid (6*N*, 14 litres). The precipitate was collected, washed with hydrochloric acid (6*N*), water and dried to give 1088 g (96%) of the sulphide (**4**) mp 165-168°; hplc solvent 2, Rt 12.3 minutes, 92%; Rt 24 minutes, 5% (PhSSPh).

4-Carboxy-2-phenylthiophenylacetic Acid (**6**).

A solution of the benzoic acid (**4**) (2.44 kg, 10 moles) and tetramethylurea (1.5 litres) in THF (10 litres) was added to a solution of lithium diisopropylamide [prepared from *n*-butyllithium (2.5*M*, 9.5 litres, 23.8 moles) in hexane and diisopropylamine (3.6 litres, 25.7 moles) in THF (12.5 litres)] in a 10 gallon vessel, maintaining the temperature between -15° and -5°. The dianion solution was aged at this temperature for 40 minutes and then carbon dioxide passed over the surface of the stirred mixture for 3 hours. During this time the temperature was allowed to rise to 10°. Water (30 litres) was added cautiously and the phases separated. The aqueous phase was washed with ethyl acetate (2 x 10 litres), hexane (2.5 litres) was added and the mixture acidified with hydrochloric acid to *p*H 1.5. the suspension was stirred for 3 hours, the precipitate collected, washed with water and dried to give 2.88 kg (99%) of 4-carboxy-2-phenylthiophenylacetic acid (**6**) mp 226-229°; hplc solvent 2, Rt 4.8 minutes, 99%; Rt 12.3 minutes 1%. Recrystallisation from ethyl acetate gave an analytical sample mp 227-229°; ir: 2660, 2550 cm^{-1} (OH,

carboxylic acid), 1690 cm^{-1} (C=O carboxylic acid); nmr: δ 3.88 (s, CH_2, 2H), 7.2-7.4 (m, Ph, 5H), 7.53 (dd, 5-H, 1H, J = 1 and 8 Hz), 7.93 broad s, 3-H, 1H).

Anal. Calcd. for $C_{15}H_{12}O_4S$: C, 62.49; H, 4.20; S, 11.12. Found: C, 62.35; H, 4.33; S, 10.94.

10-Oxo-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylic Acid (**7**).

The phenylacetic acid (**6**) (1152 g, 4 moles) was added in portions to water (290 ml) and polyphosphoric acid (8 kg) stirred at 110°. Water (290 ml) was added slowly causing an exothermic reaction which increased the temperature to 155°. The temperature had fallen to 140° after 30 minutes and the mixture was maintained at 140° for 30 minutes. Ice water (10.4 litres) was added to the mixture and the suspension was stirred for 2 hours. The precipitate was collected, resuspended in hot water (10 litres x 2), filtered and dried to give 1058 g (98%) of 10-oxo-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylic acid (**7**) mp 252-254°; hplc solvent 2, Rt 8.3 minutes 98.7%. Recrystallisation from 2-propanol gave an analytical sample mp 255-257°; ir: 2610, 2500 cm^{-1} (OH, carboxylic acid), 1685 cm^{-1} (C=O, carboxylic acid), 1660 cm^{-1} (C=O, ketone); nmr: δ 4.45 (s, CH_2, 2H), 7.41 (ddd, 8-H, 1H, J = 1.5 and 8 Hz), 7.56 (ddd, 7-H, 1H, J = 1.5 and 7.5 Hz), 7.64 (d, 1-H, 1H, J = 8 Hz), 7.70 (dd, 6-H, 1H, J = 1 and 7.5 Hz), 8.03 (dd, 2-H, 1H, J = 1.5 and 7.5 Hz), 8.11 (dd, 9-H, 1H, J = 1 and 8 Hz), 8.24 (d, 4-H, 1H, J = 1 Hz).

Anal. Calcd. for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73; S, 11.86. Found: C, 66.62; H, 3.93; S, 11.68.

10-Hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylic Acid (**8**).

The ketoacid **7** (1.08 kg, 4 moles) was dissolved in a solution of sodium hydroxide (185 g, 4.6 moles) in water (7.2 litres) and ethanol (690 ml). Sodium borohydride (80 g, 2.1 moles) was added in portions during 10 minutes and the mixture stirred at room temperature for 2 hours. The reaction mixture was added slowly to well stirred hydrochloric acid (1*N*, 16 litres), (**Caution** evolution of hydrogen). The precipitate was collected, washed with water and dried to give 1.06 kg (97%) of 10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylic acid (**8**) mp 185-187°; hplc solvent 2, Rt 5.8 minutes 98%; Rt 4.8 minutes 2%. Recrystallisation from aqueous *N,N*-dimethylformamide gave an analytical sample mp 215-216°; ir: 3320, 3240 cm^{-1} (OH), 2640, 2520 cm^{-1} (OH, carboxylic acid), 1680 cm^{-1} (C=O, carboxylic acid); nmr: δ 3.35 (m, 11-H, 1H), 3.63 (m, 1-H, 1H), 5.52 (m, 10-H, 1H), 7.18 (ddd, 7-H, 1H, J = 1.5 and 7.5 Hz), 7.30 (ddd, 8-H, 1H, J = 1.5 and 7.5 Hz), 7.36 (d, 2-H, 1H, J = 8 Hz), 7.46 (dd, 6-H, 1H, J = 1 and 7.5 Hz), 7.65 (dd, 9-H, 1H, J = 1 and 8 Hz), 7.81 (dd, 1-H, 1H, J = 1.5 and 8 Hz), 8.05 (d, 4-H, 1H, J = 1.5 Hz).

Anal. Calcd. for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44; S, 11.77. Found: C, 65.96; H, 4.56; S, 11.70.

Dibenzo[*b,f*]thiepin-3-carboxylic Acid (**9**).

Concentrated sulphuric acid (320 ml) was added dropwise during 1 hour to a stirred suspension of the alcohol **8** (440 g, 1.6 moles) in acetic acid (1.8 litres). The temperature of the mixture rose to 45° and solution occurred. The solution was heated to 75°, allowed to cool to 55° during 1 hour and then cooled to 15°. The precipitate was collected, washed with acetic acid, water and then stirred in water before being recollected and dried. The solid was stirred in boiling acetone (600 ml), cooled, the solid collected and dried to give 353 g (86%) of the acid **9** mp 248-250° hplc solvent 2 Rt 11.6 minutes 99%. Recrystallisation from aqueous *N,N*-dimethylformamide gave an analytical sample mp 253-255°; ir: 2630, 2510 cm^{-1} (OH, carboxylic acid), 1675 cm^{-1} (C=O, carboxylic acid); nmr: δ 7.14 (d, 11-H, 1H, J = 12 Hz), 7.19 (d, 10-H, 1H, J = 12 Hz), 7.35 (m, 7-, 8-, 9-H, 3H), 7.44 (d, 1-H, 1H, J = 8 Hz), 7.51 (m, 6-H, 1H), 7.92 (dd, 2-H, 1H, J = 1.5 and 8 Hz), 8.06 (d, 4-H, 1H, J = 1.5 Hz).

Anal. Calcd. for $C_{15}H_{10}O_2S$: C, 70.84; H, 3.96; S, 12.61. Found: C, 70.55; H, 4.09; S, 12.41.

Dibenzo[*b,f*]thiepin-3-carboxylic Acid 5,5-Dioxide (**10**) (Using Hydrogen Peroxide).

A suspension of the sulphide **9** (615 g, 2.4 moles) in acetic acid (4.8 litres) was heated to 95° and hydrogen peroxide solution (50%, 386 ml) added dropwise during 1 hour, the exothermic reaction maintaining a gentle reflux. The solution was concentrated by distillation of acetic acid (2.5 litres) and then water (4.5 litres) was added slowly to the hot suspension. The mixture was cooled to 20° to complete crystallisation. The solid was collected washed with water and dried to give 644 g (93%) of the sulphone **10** mp 263-265°; hplc solvent 1, Rt 6.5 minutes 99.9%. Recrystallisation from methanol gave an analytical sample mp 266-268°; ir: 2640, 2500 cm^{-1} (OH, carboxylic acid), 1680 cm^{-1} (C=O, carboxylic acid), 1310 and 1170 cm^{-1} (SO_2, sulphone); nmr: δ 7.50 (d, 11-H, 1H, J = 14 Hz), 7.57 (d, 10-H, 1H, J = 14 Hz), 7.8 (m, 7-, 8-, 9-H, 3H), 7.93 (d, 1-H, 1H, J = 8 Hz), 8.22 (m, 6-H, 1H), 8.29 (dd, 2-H, 1H, J = 1.5 Hz), 8.82 (d, 4-H, 1H, J = 1.5 Hz).

Anal. Calcd. for $C_{15}H_{10}O_4S$: C, 62.92; H, 3.52; S, 11.29. Found: C, 62.93; H, 3.61; S, 11.09.

Dibenzo[*b,f*]thiepin-3-carboxylic Acid 5,5-Dioxide (**10**) (Using Sodium Perborate).

A suspension of the sulphide **9** (544 g, 2.14 moles) in acetic acid (2.2 litres) was heated to 72° and the source of heat removed. Sodium perborate tetrahydrate (815 g, 5.3 moles) was added in portions (*ca.* 50 g) during 1 hour. The reaction temperature initially dropped to 60° but reached reflux (115°) after 500 g sodium perborate had been added. The reaction mixture was allowed to cool to 65°, water (1 litre) was added and the mixture cooled to 20° to complete crystallisation. The solid was collected, washed with water (2.4 litres) and dried to give 582 g (95%) of sulphone **10** mp 162-165°; hplc solvent 1, Rt 6.4 minutes 98.9%.

3-Hydroxymethyldibenzo[*b,f*]thiepin 5,5-Dioxide (**13**).

Ethyl chloroformate (110 ml, 1.15 moles) was added dropwise during 20 minutes to a solution of the acid **10** (300 g, 1.15 moles) and pyridine (93 ml, 1.15 moles) in THF (5 litres). The mixture was stirred for 1 hour and the solution filtered to remove pyridine hydrochloride. The solution of the mixed anhydride was added dropwise during 90 minutes to sodium borohydride (150 g, 4.0 moles) in water (1 litre) and THF (2 litres) cooled at 20°. The mixture was stirred for 1 hour and then allowed to separate into an upper organic phase and a lower aqueous phase. The aqueous layer was washed with THF and then acidified to give 31.5 g (11%) of recovered acid **10**. The combined organic layer was distilled under reduced pressure at 45°, adding water (750 ml) when most of the THF had been removed. Distillation was continued to remove the remaining THF, then the aqueous mixture was cooled to give 255 g (89%) of the crude product. The solid was stirred in boiling methanol (2.5 litres), the mixture concentrated to 500 ml and then cooled. The solid was collected and crystallised from ethanol to give 230 g (82%) of the alcohol **13** mp 161-163°; hplc solvent 1, Rt 5.1 minutes 99.7%; ir: 3480 cm^{-1} (OH), 1295, 1160 cm^{-1} (SO_2, sulphone); nmr (perdeuterioacetone): δ 4.80 (s, CH_2, 2H), 7.38 (d, 10-H, 1H, J = 13 Hz), 7.42 (d, 11-H, 1H, J = 13 Hz), 7.6-7.8 (m, ArH's, 5H), 8.20 (m, 4-H, 1H), 8.24 (broad s, 6-H, 1H).

Anal. Calcd. for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44; S, 11.77. Found: C, 66.21, H, 4.51; S, 11.68.

Methyl 10-Oxo-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylate (**15**).

10-Oxo-10,11-dihydrodibenzo[*b,f*]thiepin-3-carboxylic acid (**7**) (50 g, 0.19 mole) suspended in methanol (500 ml) was treated with concentrated sulphuric acid (20 ml) and the mixture stirred at reflux for 4 hours. The mixture was cooled (ice-bath) and the yellow solid collected, washed with water, and dried to give 50 g of crude product, which was crystallised from ethyl acetate to give 34.2 g (63%) of the methyl ester **15** mp 160.5-162.5°; ir: 1725 cm^{-1} (C=O, ester), 1670 cm^{-1} (C=O, ketone); nmr: δ 3.85 (s, OCH_3, 3H), 4.83 (s, CH_2, 2H), 7.42 (ddd, 7-H, 1H, J = 2 and 8 Hz), 7.58 (ddd, 8-H, 1H, J = 2 and 8 Hz), 7.68 (d, 1-H, 1H, J = 6 Hz), 7.70 (dd, 6-H, 1H, J = 1.5 and 6 Hz), 8.01 (dd, 2-H, 1H, J = 2 and 8 Hz), 8.09 (dd, 9-H, 1H, J = 2 and 8 Hz), 8.21 (d, 4-H, 1H, J = 2 Hz).

Anal. Calcd. for $C_{16}H_{12}O_3S$: C, 67.59; H, 4.26; S, 11.28. Found: C, 67.58; H, 4.30; S, 11.13.

3-Hydroxymethyl-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (**18**).

10-Oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-3-carboxylic acid (**7**) (108 g, 0.4 mole) was dissolved in THF (1 litre) and triethylamine (58 ml, 0.42 mole) added. The solution was cooled (ice-bath) and ethyl chloroformate (40 ml, 0.42 mole) added dropwise during 13 minutes maintaining the temperature between 5° and 7°. The mixture was aged at 5° for 15 minutes and then allowed to warm to 15° for 45 minutes. The reaction mixture was filtered and the solids washed with THF (3 x 100 ml). The combined filtrate and washings were added, over 1 hour to a vigorously stirred solution of sodium borohydride (54 g, 1.43 moles) in water (400 ml) and THF (800 ml) cooled between 12° and 15° (ice-water bath). After 1.5 hours sodium borohydride (5 g, 0.13 mole) and ethanol (200 ml) were added and the reaction mixture stirred and heated at 40° for 4 hours. Ethanol (400 ml) and water (200 ml) were added, and the mixture stirred for 18 hours at 20°. The aqueous phase was separated and extracted with THF (3 x 100 ml). The combined organic phases were treated with aqueous sodium hydroxide solution (90 g in 300 ml water) and the solvent reduced by evaporation under reduced pressure. Water (300 ml) was added during the distillation. When the majority of the organic solvent had been removed, the precipitated solid was collected, washed well with water and dried to give 91.9 g (89%) of the diol **18**, mp 164-165°; hplc solvent 1, Rt 4.0 minutes 99%. Recrystallisation from methanol gave an analytical sample mp 165-166°; ir: 3280, 3350 cm^{-1} (OH); nmr: δ 3.28 (m, 11-H, 1H), 3.52 (m, 11-H, 1H), 4.50 (d, CH_2, 2H, J = 7 Hz), 4.72 (t, OH, 1H, J = 7 Hz), 5.20 (m, OH, 1H), 5.45 (m, 10-H, 1H), 7.14 (m, 8-H, 1H), 7.2 (m, 1-, 9-H, 2H), 7.31 (ddd, 7-H, 1H, J = 1.5 and 7.5 Hz), 7.43 (m, 2-, 4-H, 2H), 7.63 (m, 6-H, 1H).

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.66; H, 5.48; S, 12.27.

3-Hydroxymethyldibenzo[*b*,*f*]thiepin (**21**).

3-Hydroxymethyl-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (**18**) (25 g, 0.1 mole) in acetic acid (100 ml) was cooled (ice-bath) and a solution of concentrated sulphuric acid (6 ml) in acetic acid (25 ml) added during 45 minutes. The reaction mixture initially at 10-15° was warmed to 40° and maintained at this temperature for 18 hours. The reaction mixture was poured into water (1 litre) and the product extracted into ethyl acetate (2 x 200 ml). The combined ethyl acetate extracts were washed with aqueous sodium bicarbonate (3 x 150 ml) and evaporated under reduced pressure to give 26.5 g of the acetate **22**. The oil was dissolved in methanol (300 ml), filtered and an aqueous solution of sodium hydroxide (5.7 g in 100 ml water) was added dropwise. The solution was stirred at 20° for 2 hours, the solvent evaporated under reduced pressure and water (400 ml) added. The precipitate was collected washed with water and dried. The solid was crystallised from aqueous ethanol and then recrystallised from cyclohexane to give 14.5 g (62%) of the alcohol **21**, mp 110-112°; hplc solvent 2, Rt 8.0 minutes 98.5%; ir: 3460 cm^{-1} (OH); nmr δ 4.33 (t, OH, 1H, J = 6 Hz), 4.62 (d, OCH_2, 2H, J = 6 Hz), 7.05 (broad s, 10-, 11-H, 2H), 7.3-7.5 (m, ArH's, 7H).

Anal. Calcd. for $C_{15}H_{12}OS$: C, 74.97; H, 5.06; S, 13.34. Found: C, 75.00; H, 5.16; S, 13.24.

3-Hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-Dioxide (**13**) from 3-Hydroxymethyl-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (**18**).

Concentrated sulphuric acid (22 ml) was added during 15 minutes, to a stirred slurry of 3-hydroxymethyl-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]-thiepin (**18**) (100 g, 0.39 mole) in acetic acid (425 ml) and the reaction mixture stirred at 40-45° for 20 hours. Anhydrous sodium acetate (85 g) was added, causing the temperature to rise to 60°, and the mixture stirred for 10 minutes. Sodium perborate tetrahydrate (155 g, 1.01 moles) was added in portions during 50 minutes, causing a temperature rise to 80°, and the mixture stirred at 80° for 4 hours. The reaction mixture was cooled to 20° diluted with water (1.5 litres) and the aqueous phase decanted from the precipitated yellow gummy solid. The solid was washed twice with water and then dissolved in hot methanol (1 litre). The solution was filtered and aqueous sodium hydroxide (20 g in 200 ml water) added to the filtrate. The dark solution was allowed to stand at 20° for 16 hours, filtered and concentrated under reduced pressure. When 750 ml of distillate had been collected, water (500 ml) was added. The precipitate was collected, washed with water and dried to give 89.9 g of crude product which was crystallised from methanol to give 70.7 g (62%) of 3-hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-dioxide (**13**), hplc solvent 1, Rt 5.1 minutes 97.5%.

3-Hydroxymethyldibenzo[*b*,*f*]thiepin 5,5-Dioxide (**13**) from 3-Hydroxymethyldibenzo[*b*,*f*]thiepin (**21**).

Sodium perborate tetrahydrate (6.2 g, 0.04 mole) was added in two portions during 10 minutes to a warm solution (40°) of 3-hydroxymethyldibenzo[*b*,*f*]thiepin (**21**) (5 g, 0.02 mole) in acetic acid (30 ml). The mixture was stirred at 40° for 1 hour, warmed to 50° and further sodium perborate (3.1 g, 0.02 mole) added. The reaction mixture was heated at 60° for 1 hour and then poured into water. The product precipitated as a yellow gum which solidified on standing. The solid was collected, washed with water and dried to give 5.1 g (91%) of the crude sulphone **13** hplc solvent 1, Rt 5.1 minutes 92.6%.

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