

## Synthesis of Thiophthalans \*

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The antidepressant drug 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylthiophthalan (XVII) and related compounds were prepared by alkylation of 3,3-dimethyl-1-phenylthiophthalan (VI) and related compounds.

Compound VI was obtained by an amine-catalyzed addition of hydrogen sulfide to 2-isopropenylbenzophenone (IV) or by cyclization of benzyl-[1-(2-chlorophenyl)-1-methylethyl]sulfide (IX) by a nucleophilic aromatic substitution.

3,3-Dimethyl-1-(3-dimethylaminopropyl)-1-phenylthiophthalan (VIII) was prepared by addition of hydrogen sulfide to 4-dimethyl-amino-1-(2-isopropenylphenyl)-1-phenyl-1-butene (VII).

Compound XVII did not rearrange to 1,1-dimethyl-2-(2-methyl-aminoethyl)-3-phenylindene (XXI) by treatment with 48 % hydro-bromic acid/acetic acid as did 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan (XX).

3,3-Dimethyl-1-phenylthiophthalan-1-ol (V) was obtained by ad-dition of hydrogen sulfide to IV at conditions suggesting that V is an intermediate in the synthesis of VI from IV. Bromination of VI gave V after hydrolysis. Compound V was reduced to VI with formic acid and [3,3-dimethyl-1-phenyl-1-thiophthalyl]acetic acid (XXIV) was prepared by treatment of V with malonic acid.

The sulfone (XXV) and sulfoxides (XXVI) of VI were prepared by oxidation of the parent compounds with hydrogen peroxide.

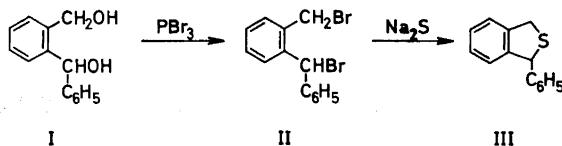
The sulfoxide XXVI could undergo a Pummerer rearrangement to V by treatment with acetyl chloride.

The known antidepressant activity of 3,3-dimethyl-1-(3-methylamino-propyl)-1-phenylphthalan (XX) and related compounds<sup>1</sup> has prompted us to synthesize the analogous thiophthalans. The pharmacological activity of these thiophthalans has been described in a previous paper,<sup>2</sup> and clinical studies suggest that XVII, the sulfur isomer of XX, is a more potent anti-depressant drug than XX.

The most straightforward method of preparing thiophthalans is the reac-tion of  $\alpha,\alpha'$ -dibromo-*o*-xylene or a substituted derivative of this with sodium

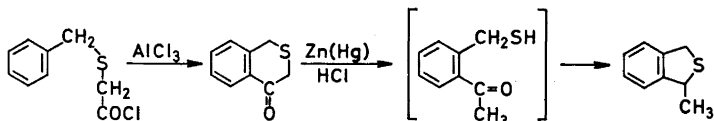
\* Used here for the sake of brevity instead of the systematic name 1,3-dihydro-benzo[c]thiophene.

sulfide.<sup>3</sup> We have used this method for the synthesis of 1-phenylthiophthalan (III) from  $\alpha$ -phenyl-*o*-xylene- $\alpha,\alpha'$ -diol (I) *via*  $\alpha,\alpha'$ -dibromo- $\alpha$ -phenyl-*o*-xylene (II).



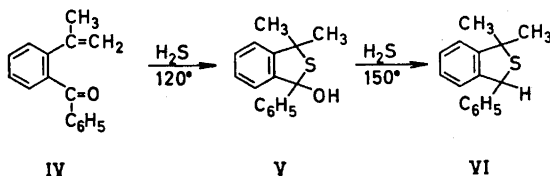
Attempts to prepare 3,3-dimethyl-1-phenylthiophthalan (VI) by this method were unsuccessful and none of the other known methods for preparing thiophthalans could be used here. Cava *et al.*<sup>4</sup> have prepared 1,3-diphenylthiophthalan by reduction of 1,3-diphenylbenzo[*c*]thiophene, which was in turn prepared from the benzo[*c*]furan and  $\text{P}_2\text{S}_5$ , but this method cannot be used for a 1,1-dimethyl-substituted thiophthalan, and any attempt to substitute the oxygen atom in phthalans with sulfur by the action of  $\text{P}_2\text{S}_5$  has been unsuccessful.

von Braun and Weissbach<sup>5</sup> have prepared 1-methylthiophthalan by ring closure of (benzylthio)acetyl chloride to form isothiochroman-4-one, which was transformed in a Clemmensen reduction to the thiophthalan.

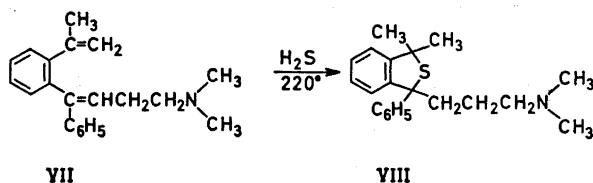


We have tried to prepare 1-methyl-3-phenylthiophthalan by this method from (diphenylmethylthio)acetic acid, but without success.

A few other methods are found in the literature,<sup>6</sup> but none of them are suited for the type of compound we wanted to prepare, so we had to develop new methods. We found that the treatment of 2-isopropenylbenzophenone (IV) with an excess of hydrogen sulfide in a steel autoclave at temperatures from 180 to 250°C gave 1,1-dimethyl-3-phenylthiophthalan (VI) in a yield of 70–80%. The reaction was accelerated by a small amount of amine. With diethylamine as catalyst, the yield of thiophthalan was near 100% after 2 h at 150–155°C. At temperatures from 100 to 120°C there was still near 100% addition of hydrogen sulfide in the amine-catalyzed reaction, but the main product was now 3,3-dimethyl-1-phenylthiophthalan-1-ol (V). When this was heated further with hydrogen sulfide to higher temperature, it was reduced to the thiophthalan (VI).

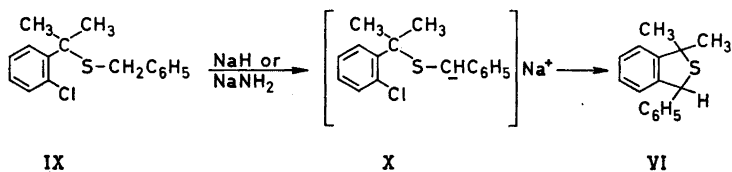


We have also tried to add hydrogen sulfide to the diene VII in order to get 3,3-dimethyl-1-(3-dimethylaminopropyl)-1-phenylthiophthalan (VIII). The reaction did proceed at 200–220°C, but the yield was low (18 %).

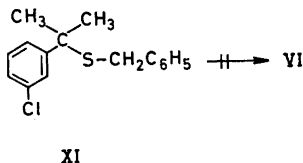


The most reasonable interpretation of these results is that the initial step is an amine-catalyzed addition of hydrogen sulfide to the carbonyl double bond followed by ring closure by electrophilic addition to the double bond in the isopropenyl group. The other possibility – that the initial step is an electrophilic addition of hydrogen sulfide to the carbon-carbon double bond in accordance with Markovnikov's rule – is unlikely in the amine-catalyzed reaction because this addition should not be base-catalyzed and the following ring closure of the first formed mercaptan should be fast and not rate determining. Whether the first step in the noncatalyzed reaction is an addition to the carbonyl group or the olefine double bond cannot be said at present.

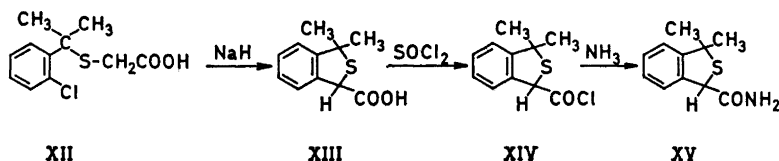
Another method of preparing VI was an intramolecular ring closure of benzyl-[1-(2-chlorophenyl)-1-methylethyl]sulfide (IX) by treatment with sodium hydride or sodium amide in dimethyl sulfoxide, DMSO. The reaction proceeded at room temperature within a few minutes giving a good yield of VI.



This ring closure could not be performed with benzyl-[1-(3-chlorophenyl)-1-methylethyl]sulfide (XI) as starting material, not even with 3 mol NaH per mol XI. This, together with the fact that the ring closure of the *ortho*-chloro compound IX proceeded well with only a little more than 1 equiv. of NaH, suggests that a benzyne intermediate is not involved in this reaction. We assume that direct displacement of the chlorine may occur with a carbanion (X) as an intermediate.

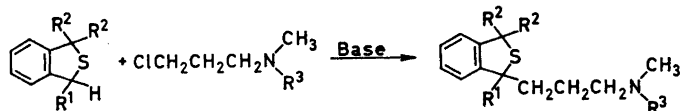


Treatment of {[1-(2-chlorophenyl)-1-methylethyl]thio} acetic acid (XII) with sodium hydride as described above gave 3,3-dimethylthiophthalan-1-carboxylic acid (XIII). By treatment of XIII with thionyl chloride and ammonia 3,3-dimethylthiophthalan-1-carboxamide (XV) was obtained.



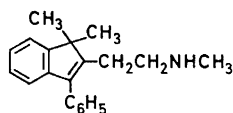
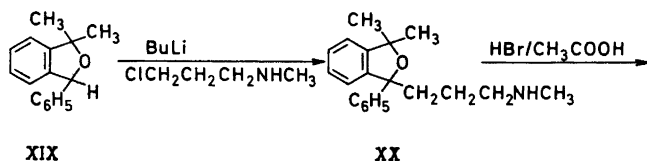
The compounds III, VI, and XV were alkylated at the 1-position with *N,N*-dimethyl-3-chloropropylamine, or *N*-methyl-3-chloropropylamine, by treatment with butyllithium, sodium amide or sodium hydride. Table 1 shows the reactions.

Table 1. Alkylation of the thiophthalans III, VI, and XV.



| Reactant | Product   | R <sub>1</sub>                | R <sub>2</sub>  | R <sub>3</sub>  | Base              | Solvent | Yield, % |
|----------|-----------|-------------------------------|-----------------|-----------------|-------------------|---------|----------|
| III      | XVI, HCl  | C <sub>6</sub> H <sub>5</sub> | H               | CH <sub>3</sub> | NaH               | DMSO    | 38       |
| VI       | VIII, HCl | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub> | CH <sub>3</sub> | NaH               | DMSO    | 58       |
| VI       | XVII, HCl | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub> | H               | BuLi              | Ether   | 46       |
| VI       | XVII, HCl | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub> | H               | NaNH <sub>2</sub> | DMSO    | 86       |
| VI       | XVII, HCl | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub> | H               | NaH               | DMSO    | 88       |
| XV       | XVIII     | CONH <sub>2</sub>             | CH <sub>3</sub> | CH <sub>3</sub> | NaNH <sub>2</sub> | Ether   | 46       |
| XV       | XVIII     | CONH <sub>2</sub>             | CH <sub>3</sub> | CH <sub>3</sub> | NaH               | DMSO    | 55       |

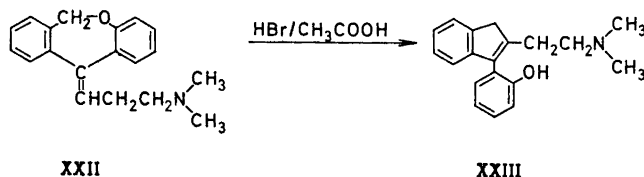
The metallation of VI with butyllithium in ether proceeded with a reasonable rate only at temperatures above 15°C. The same reaction between 3,3-



XXI

dimethyl-1-phenylphthalan (XIX), butyllithium and *N*-methyl-3-chloropropylamine gave 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan (XX) in good yields only at reaction temperatures below 0°C.

By treatment of XX with a boiling mixture of 48 % hydrobromic acid and glacial acetic acid overnight 1,1-dimethyl-2-(2-methylaminoethyl)-3-phenylindene (XXI) was obtained. This reaction was similar to the rearrangement of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[*b,e*]oxepin (XXII) to yield 2-(2-dimethylaminoethyl)-3-(2-hydroxyphenyl)indene (XXIII) described by Bickelhaupt *et al.*<sup>7</sup>

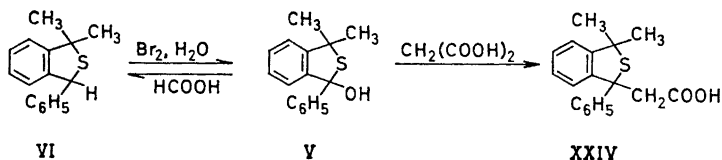


Compound XVII was unchanged after treatment with HBr/CH<sub>3</sub>COOH.

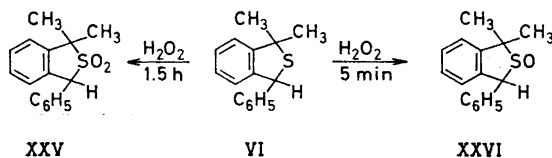
The thiophthalan VI reacted with bromine in chloroform with evolution of hydrogen bromide. We were unable to isolate the compound directly formed because of its instability, but after extraction of the chloroform solution with strong hydrochloric acid and neutralization of the acid solution the thiophthalanol V was isolated in good yield.

This is soluble in strong acid forming a yellow carbonium ion just as described for 3,3-dimethyl-1-phenylphthalan-1-ol,<sup>8</sup> but the thiophthalanol showed a better solubility in acid than the phthalanol. In 6 N hydrochloric acid the thiophthalanol could form a 0.5 M solution and the phthalanol only a 0.1 M solution.

The thiophthalanol was reduced by formic acid to VI by heating on a steam bath for 2.5 h, as described for the analogous phthalanol.<sup>9</sup>



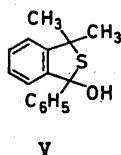
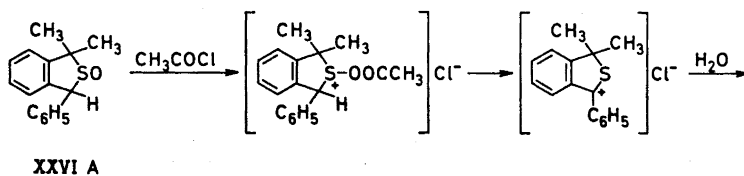
Compound V was not reduced with lithium aluminium hydride and did not react with methylmagnesium iodide or 3-dimethylaminopropylmagnesium chloride, contrary to 3,3-dimethyl-1-phenylphthalan-1-ol. [3,3-Dimethyl-1-phenyl-1-thiophthalyl]acetic acid (XXIV) was obtained from V by treatment with malonic acid, as described for 3,3-dimethyl-1-phenylphthalan-1-ol.<sup>10</sup>



3,3-Dimethyl-1-phenylthiophthalan-2-dioxide (XXV) was prepared by treatment of VI with 30 % hydrogen peroxide and glacial acetic acid at 80–100°C for 1.5 h. IR maximum at 1300  $\text{cm}^{-1}$  indicates the formation of a sulfone.<sup>11</sup>

If the same reaction was stopped after 5 min at 60°C the product was a mixture of the two isomers XXVI A and XXVI B of 3,3-dimethyl-1-phenylthiophthalan-2-oxide (XXVI) with IR maximum at 1060  $\text{cm}^{-1}$  as expected for sulfoxides.<sup>11</sup>

The sulfoxide XXVI A reacted violently with acetyl chloride in chloroform and gave after hydrolysis the thiophthalanol V in a yield of 80 %. This is analogous with the Pummerer rearrangement,<sup>12</sup> but the conversion of XXVI A to V could not be brought about by hydrochloric acid or acetic



anhydride, the reagents mostly used for the Pummerer rearrangement. This is in accordance with the observation of Horner and Kaiser<sup>12c</sup> that dibenzylsulfoxide reacts more slowly with acetic anhydride than dimethyl sulfoxide,

Table 2. NMR data at 60 MHz in deuteriochloroform at room temperature with TMS as a standard. d, doublet. t, triplet. m, multiplet.

|                       | S—C—CH <sub>3</sub><br>ppm | NCH <sub>3</sub><br>ppm | <i>J</i> <sub>H—H</sub><br>Hz | SCH<br>ppm | NH<br>ppm |
|-----------------------|----------------------------|-------------------------|-------------------------------|------------|-----------|
| V <sup>b</sup>        | 1.75 1.81                  |                         |                               |            |           |
| VI <sup>a</sup>       | 1.75 1.83                  |                         |                               | 5.75       |           |
| VIII,HCl <sup>b</sup> | 1.65 1.76                  | 2.72 d                  | 5.4                           |            | 12.3      |
| XV <sup>b</sup>       | 1.75 1.80                  |                         |                               | 5.15       | 6.4 6.8   |
| XVI,HCl <sup>b</sup>  |                            | 2.70 d                  | 5.0                           | 4.30       | 12.2      |
| XVII,HCl <sup>b</sup> | 1.65 1.76                  | 2.48 t                  | 5.7                           |            | 9.5       |
| XXV <sup>a</sup>      | 1.68 1.71                  |                         |                               | 5.45       |           |
| XXVI A <sup>b</sup>   | 1.60–1.70 (m)              |                         |                               | 5.20       |           |
| XXVI A+B <sup>b</sup> | 1.47–1.73 (m)              |                         |                               | 5.17 5.51  |           |

<sup>a</sup> Recorded on a Varian A-60 instrument.

<sup>b</sup> Recorded on a Perkin-Elmer R12 instrument.

presumably because the electron-attracting phenyl groups render the oxygen atom less nucleophilic.

In Table 2 NMR data of a number of substituted thiophthalans are given. The two methyl groups at the 3-position gave two sharp signals, except the sulfoxides XXVI A and XXVI B which gave rise to multiplets at 1.43–1.74 ppm. NMR spectra of VI and XXV were recorded both at room temperature and at  $-50^{\circ}\text{C}$ . The spectra showed the same signals at these temperatures, but the spectra at room temperature showed sharp signals, and the spectra at  $-50^{\circ}\text{C}$  showed a slight broadening of the signals. This indicates that the 5-membered ring undergoes "movements" even at  $-50^{\circ}\text{C}$ .

The *N*-methyl signals of the tertiary amines VIII,HCl and XVI,HCl showed up as doublets at approx. 2.70 ppm with coupling constants  $J_{\text{H-H}} = 5.0 - 5.5$  Hz. The N–H signals of the same compounds appeared as a broad signal at 12.2–12.3 ppm. The spectrum of the secondary amine XVII,HCl showed a triplet at 2.48 ppm with  $J = 5.7$  Hz assignable to the *N*-methyl group and a broad signal at 9.5 ppm assignable to the two protons attached to nitrogen. This is in agreement with the results of Pansare.<sup>13</sup> The proton at the 1-position in the thiophthalans appeared as a singlet at chemical shifts ranging from 5.15 ppm to 5.75 ppm.

#### EXPERIMENTAL

60 MHz NMR spectra were recorded in  $\text{CDCl}_3$  solutions on a Varian A-60 instrument or a Perkin-Elmer R12 instrument using TMS as standard. Microanalyses were made by Dr. A. Bernhardt.

*1-Phenylthiophthalan (III)*.  $\alpha$ -Phenyl-*o*-xylene- $\alpha,\alpha'$ -diol (I) (74 g) in tetrachloromethane (500 ml) was cooled to  $-5^{\circ}\text{C}$  and phosphorus tribromide (70 g) was added slowly with stirring. The mixture was kept at  $0^{\circ}\text{C}$  for 2 h, left at room temperature overnight and then heated slowly to reflux. After cooling the clear solution was decanted and washed quickly with ice-water, dried ( $\text{MgSO}_4$ ) and evaporated. The crude  $\alpha,\alpha'$ -dibromo- $\alpha$ -phenyl-*o*-xylene (II) was added to anhydrous sodium sulfide (prepared by heating  $\text{Na}_2\text{S}$ ,  $9\text{H}_2\text{O}$  (100 g) in a stream of nitrogen) in anhydrous ethanol (500 ml) at  $60 - 70^{\circ}\text{C}$ . The reaction mixture was refluxed for 1 h, cooled and filtered. The filtrate was evaporated and the residue dissolved in ether. The ether phase was washed with water, dried ( $\text{MgSO}_4$ ) and distilled, yielding 52 g of 1-phenylthiophthalan (III), b.p.  $135 - 140^{\circ}\text{C}/0.1$  mm. The product was crystallized from petroleum ether. Yield 42 g 1-phenylthiophthalan (III), m.p.  $60 - 62^{\circ}\text{C}$ .

*3,3-Dimethyl-1-phenylthiophthalan-1-ol (V) and 3,3-dimethyl-1-phenylthiophthalan (VI)* from IV. A. A suspension of 2-isopropenylbenzophenone (IV) (100 g) in liquid hydrogen sulfide was heated in a steel autoclave at  $180^{\circ}\text{C}$  for 3 h. The product was crystallized from ether petroleum ether. Yield: 85 g of 3,3-dimethyl-1-phenylthiophthalan (VI); m.p.  $71 - 72^{\circ}\text{C}$ . (Found: C 79.86; H 6.80; S 13.46. Calc. for  $\text{C}_{16}\text{H}_{16}\text{S}$  (240): C 80.00; H 6.67; S 13.33.) NMR at  $-50^{\circ}\text{C}$  and room temperature: 1.75 ppm (s) and 1.83 ppm (s)  $\text{C}(\text{CH}_3)_2$  5.75 ppm (s) CH; 6.8–7.4 ppm (multiplet) 9 aryl-H.

B. A mixture of IV (10.0 g), diethylamine (0.7 g) and liquid hydrogen sulfide (5–10 ml) was heated in an autoclave at  $115 - 120^{\circ}\text{C}$  for 1 h, yielding 8.3 g of 3,3-dimethyl-1-phenylthiophthalan-1-ol (V), m.p.  $83 - 84^{\circ}\text{C}$  (ether petroleum ether). (Found: C 74.84; H 6.30; O 6.31; S 12.47. Calc. for  $\text{C}_{16}\text{H}_{16}\text{OS}$  (256): C 75.00; H 6.25; O 6.25; S 12.50.) IR maximum (KBr):  $3310\text{ cm}^{-1}$ . NMR in  $\text{CDCl}_3$ : 1.75 ppm (s) and 1.81 ppm (s)  $\text{C}(\text{CH}_3)_2$  3.02 ppm (s) OH and 6.9–7.7 ppm (multiplet) 9 aryl-H. The NMR in  $\text{CDCl}_3$  containing a drop of  $\text{D}_2\text{O}$  showed no OH signal. From the filtrate was isolated 1.2 g of VI identical with the above described specimen.

C. 2-Isopropenylbenzophenone (IV) (10.0 g) was treated in the autoclave as described under B and then heated for additional 2 h at  $150 - 155^{\circ}\text{C}$ . The only isolated product

was 10.7 g of 3,3-dimethyl-1-phenylthiophthalan (VI) identical with the above described specimen.

*3,3-Dimethyl-1-(3-dimethylaminopropyl)-1-phenylthiophthalan (VIII)*. A suspension of 4-dimethylamino-1-(2-isopropenylphenyl)-1-phenyl-1-butene (VII) (5.0 g) (prepared from thionylchloride and 4-dimethylamino-1-(2-isopropenylphenyl)-1-phenylbutanol, which was prepared from 2-isopropylbenzophenone (IV) and 3-dimethylaminopropylmagnesium chloride) and liquid hydrogen sulfide (about 5 ml) in a 100 ml autoclave was heated at 200–220°C for 4 h. The formed amine was isolated as hydrochloride from acetone/ether. Yield 1.1 g of 3,3-dimethyl-1-(3-dimethylaminopropyl)-1-phenylthiophthalan.HCl (VIII.HCl), m.p. 225–227°C. (Found: C 69.60; H 7.94; N 3.70; S 8.87. Calc. for  $C_{11}H_{15}NS.HCl$  (361.5): C 69.71; H 7.75; N 3.87; S 8.85.) IR maximum (KBr): 2300–2700  $cm^{-1}$  (multiplet) and 3420  $cm^{-1}$  (broad). NMR: 1.65 ppm (s) and 1.76 ppm (s)  $C(CH_3)_2$ ; 2.72 ppm (d,  $J = 5.4$  Hz)  $N(CH_2)_3$ ; 1.5–3.3 ppm (multiplet)  $(CH_2)_3$ ; 7.0–7.6 ppm (multiplet) 9 aryl-H; 12.3 ppm (broad) NH.

*3,3-Dimethyl-1-phenylthiophthalan (VI) from IX*. A sodium hydride dispersion in oil, 50% (10.0 g) was heated to 80–90°C in DMSO (250 ml). The reaction mixture was cooled, and benzyl-[1-(2-chlorophenyl)-1-methylethyl]sulfide (IX) (56 g) (prepared from 2-hydroxy-2-(2-chlorophenyl)propane and benzylmercaptan, similar to a method of Holmberg<sup>14</sup>) was added at 20–30°C. After stirring at room temperature for 15 min the mixture was poured into ice-water and extracted with ether. The ether extract was dried ( $MgSO_4$ ) and the product crystallized from ether/petroleum ether. Yield: 40 g of 3,3-dimethyl-1-phenylthiophthalan (VI) identical with the specimen described above.

The sodium hydride could be replaced by sodium amide, 50% in toluene, with only a little reduction in yield.

*3,3-Dimethylthiophthalan-1-carboxylic acid (XIII)*. This was prepared in a yield of 83% from {[1-(2-chlorophenyl)-1-methylethyl]thio} acetic acid (XII) (Holmberg<sup>14</sup>) as described above using 2.7 mol sodium hydride per mol XII, m.p. 92–93°C (ether/petroleum ether). (Found: C 63.32; H 5.59; O 15.49; S 15.30. Calc. for  $C_{11}H_{12}O_2S$  (208): C 63.46; H 5.77; O 15.38; S 15.38.) IR maximum (KBr): 1700  $cm^{-1}$  and 2300–3600  $cm^{-1}$  (multiplet).

*3,3-Dimethylthiophthalan-1-carboxamide (XV)*. The acid chloride XIV of 3,3-dimethylthiophthalan-1-carboxylic acid (XIII) was prepared by refluxing the acid in excess of thionyl chloride, and the crude XIV was converted to the amide XV by reaction with liquid ammonia in chloroform. Yield: 86% of 3,3-dimethylthiophthalan-1-carboxamide (XV), m.p. 129–131°C (ether). (Found: C 63.61; H 6.28; N 6.56; O 7.89; S 15.43. Calc. for  $C_{11}H_{13}NOS$  (207): C 63.77; H 6.28; N 6.76; O 7.73; S 15.46.) IR maximum (KBr): 1590  $cm^{-1}$ , 1680  $cm^{-1}$ , 3150  $cm^{-1}$ , 3260  $cm^{-1}$  and 3425  $cm^{-1}$ . NMR: 1.75 ppm (s) and 1.80 ppm (s)  $C(CH_3)_2$ ; 5.15 ppm (s) CH; 6.4 ppm (broad) and 6.8 ppm (broad  $NH_2$ ); 7.2–7.8 ppm (multiplet) 9 aryl-H.

*Alkylations of the thiophthalans III, VI, and XV* are summarized in Table 1. The metallation in DMSO was performed with either sodium hydride or sodium amide in about 15% excess, as described earlier, and was completed after 5 min at room temperature. The alkyl chloride was added under cooling, keeping the temperature below 35°C. In the case of *N*-methyl-3-chloropropylamine we found it practical to use the hydrochloride and 2.5 mol of sodium hydride. The thiophthalan VI was metallated with butyllithium in ether after 5 min at 15–20°C and alkylated at 10–15°C. The phthalan XIX was metallated and alkylated in the same way at –5°C. The amide XV could be alkylated with sodium amide in ether, according to Kaiser and Hauser.<sup>15</sup>

The analyses and physical data of the compounds prepared by these methods are given below:

*1-(3-Dimethylaminopropyl)-1-phenylthiophthalan (XVI)*. Hydrochloride, m.p. 200–202°C. (Found: C 68.05; H 7.33; N 4.28; S 9.52. Calc. for  $C_{15}H_{23}NS.HCl$  (333.5): C 68.37; H 7.20; N 4.20; S 9.60.) IR maximum (KBr): 2300–2700  $cm^{-1}$  (multiplet) and 3420  $cm^{-1}$  (broad). NMR: 2.70 ppm (d,  $J = 5.0$  Hz)  $N(CH_2)_3$ ; 1.5–3.3 ppm (multiplet)  $(CH_2)_3$ ; 4.30 ppm (s)  $S-CH_2$ ; 7.0–7.6 ppm (multiplet) 9 aryl-H; 12.2 ppm (broad)  $HN^+$ .

*3,3-Dimethyl-1-(3-methylaminopropyl)-1-phenylthiophthalan (XVII)*. Hydrochloride, m.p. 173–174°C. (Found: C 69.25; H 7.48; N 4.18; Cl 10.10; S 9.13. Calc. for  $C_{20}H_{25}NS.HCl$  (347.5): C 69.07; H 7.48; N 4.03; Cl 10.22; S 9.21.) IR maximum (KBr): 2300–2800  $cm^{-1}$  (multiplet) and 3420  $cm^{-1}$  (broad). NMR: 1.65 ppm (s) and 1.76 ppm (s)  $C(CH_3)_2$ ; 2.48 ppm



(t,  $J = 5.7$  Hz)  $\text{NCH}_3$ ; 1.5–3.1 ppm (multiplet)  $(\text{CH}_2)_3$ ; 7.0–7.6 ppm (multiplet) 9 aryl-H; 9.5 ppm (broad)  $\text{NH}_2$ .

*3,3-Dimethyl-1-(3-dimethylaminopropyl)thiophthalan-1-carboxamide (XVIII)*. M.p. of the free base 81–82°C, hydrochloride m.p. 208–210°C. (Found: C 58.27; H 7.51; N 8.38; O 5.00; S 9.57; Cl 10.99. Calc. for  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{OS}\cdot\text{HCl}$  (328.5): C 58.45; H 7.61; N 8.52; O 4.87; S 9.74; Cl 10.81.) IR maximum (KBr): 1590  $\text{cm}^{-1}$ , 1690  $\text{cm}^{-1}$ , 2400–2700  $\text{cm}^{-1}$  (multiplet), 3160  $\text{cm}^{-1}$ , 3260  $\text{cm}^{-1}$  and 3425  $\text{cm}^{-1}$ .

*3,3-Dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan (XX)*. Hydrochloride, m.p. 188–189°C. (Found: C 72.25; H 7.95; O 4.89; N 4.10; Cl 10.77. Calc. for  $\text{C}_{20}\text{H}_{25}\text{NO}\cdot\text{HCl}$  (331.51): C 72.40; H 7.84; O 4.83; N 4.22; Cl 10.71.) IR maximum (KBr): 2400–2800  $\text{cm}^{-1}$  (multiplet) and 3440  $\text{cm}^{-1}$  (broad).

*1,1-Dimethyl-2-(2-methylaminoethyl)-3-phenylindene (XXI)*. A mixture of 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan, HCl (XX, HX1) (50 g), 48 % hydrobromic acid (100 ml) and glacial acetic acid (300 ml) was refluxed for 18 h and poured on ice. Yield: 20 g of 1,1-dimethyl-2-(2-methylaminoethyl)-3-phenylindene, HCl (XXI, HCl), m.p. 150–154°C (acetone). (Found: C 76.54; H 7.60; N 4.59; Cl 11.19. Calc. for  $\text{C}_{20}\text{H}_{23}\text{N}\cdot\text{HCl}$  (313.5): C 76.56; H 7.66; N 4.47; Cl 11.32.) NMR: 1.39 ppm (s)  $\text{C}(\text{CH}_3)_2$ ; 2.15–3.0 ppm (multiplet) 7H ( $(\text{CH}_2)_2$  and  $\text{NCH}_3$ ); 7.1–7.6 ppm 9 aryl-H and 9.5 ppm (broad)  $\text{NH}_2$ .

*3,3-Dimethyl-1-phenylthiophthalan-1-ol (V)*. Bromine (7.4 g) in chloroform (40 ml) was added at room temperature to 3,3-dimethyl-1-phenylthiophthalan (VI) (10.8 g) in chloroform (180 ml). After 0.5 h at room temperature petroleum ether (200 ml) was added and the solution was extracted with conc. hydrochloric acid (200 ml) and 6 N hydrochloric acid (100 ml). The combined water phases were basified with conc. sodium hydroxide solution and extracted with ether. The ether extract was dried ( $\text{K}_2\text{CO}_3$ ) and from ether/petroleum ether crystallized 9.8 g of 3,3-dimethyl-1-phenylthiophthalan-1-ol (V) identical with the above described specimen.

*3,3-Dimethyl-1-phenylthiophthalan (VI)*. 3,3-dimethyl-1-phenylthiophthalan-1-ol (V) (38 g) was dissolved in 98–100 % formic acid (200 ml) and heated on a steam bath for 2.5 h and then poured on ice. Crystals separated and were filtered. Recrystallization from ether/petroleum ether gave 30 g of 3,3-dimethyl-1-phenylthiophthalan (VI) identical with the specimen described above.

*[3,3-Dimethyl-1-phenyl-1-thiophthalyl]acetic acid (XXIV)*. A mixture of 3,3-dimethyl-1-phenylthiophthalan-1-ol (V) (3.0 g), malonic acid (3.0 g) and a few drops of piperidine was heated at 160–180°C for 0.5 h. The mixture was taken up in 10 % sodium carbonate solution, washed with ether, acidified with diluted hydrochloric acid and extracted with ether. The ether phase was dried ( $\text{MgSO}_4$ ) and evaporated. Crystallization from ether/petroleum ether gave 2.8 g of [3,3-dimethyl-1-phenyl-1-thiophthalyl]acetic acid (XXIV), m.p. 155–157°C. (Found: C 72.68; H 6.17; O 10.77; S 10.80. Calc. for  $\text{C}_{18}\text{H}_{18}\text{O}_2\text{S}$  (298): C 72.48; H 6.04; O 10.74; S 10.74.) IR maximum (KBr): 1720  $\text{cm}^{-1}$  and 2500–3300  $\text{cm}^{-1}$  (multiplet).

*3,3-Dimethyl-1-phenylthiophthalan-2,2-dioxide (XXV)*. 3,3-dimethyl-1-phenylthiophthalan (VI) (30 g) was dissolved in glacial acetic acid (150 ml) and treated with 30 % hydrogen peroxide (30 ml) at 80–100°C for 1.5 h. The reaction mixture was poured on ice and filtered. The crystals were dissolved in chloroform, washed with saturated sodium bicarbonate solution, dried ( $\text{MgSO}_4$ ) and evaporated to crystallization. Yield: 28 g of 3,3-dimethyl-1-phenylthiophthalan-2,2-dioxide (XXV), m.p. 157–158°C. (Found: C 70.48; H 6.06; O 11.88; S 11.80. Calc. for  $\text{C}_{16}\text{H}_{16}\text{O}_2\text{S}$  (272): C 70.59; H 5.88; O 11.77; S 11.77.) IR maximum (KBr): 1300  $\text{cm}^{-1}$ . NMR at  $-50^\circ\text{C}$  and room temperature: 1.68 ppm (s) and 1.71 ppm (s)  $\text{C}(\text{CH}_3)_2$ ; 5.45 ppm (s) CH; 6.9–7.8 ppm (multiplet) 9 aryl-H.

*3,3-Dimethyl-1-phenylthiophthalan-2-oxide (XXVI A and B)*. Prepared as described for XXV, but only heated at 60°C for 5 min. Yield: 86 % of a mixture, containing approximately 90 % of the isomer A of 3,3-dimethyl-1-phenylthiophthalan-2-oxide (XXVI A), and 10 % of the isomer B (XXVI B). Fractioned crystallization gave the pure isomer A (XXVI A), m.p. 123–125°C. (Found: C 74.83; H 6.38; O 6.39; S 12.62. Calc. for  $\text{C}_{16}\text{H}_{16}\text{OS}$  (256): C 75.00; H 6.25; O 6.25; S 12.50.) IR maximum (KBr): 1060  $\text{cm}^{-1}$ . NMR: 1.60–1.70 ppm (multiplet)  $\text{C}(\text{CH}_3)_2$ ; 5.20 ppm (s) CH; 6.8–7.6 ppm (multiplet) 9 aryl-H. A mixture of nearly equal amounts of XXVI A and XXVI B, m.p. 89–97°C, was obtained. (Found: C 74.87; H 6.25; O 6.44; S 12.60. Calc. for  $\text{C}_{16}\text{H}_{16}\text{OS}$  (256): C 75.00; H 6.25; O 6.25; S

12.50.) IR maximum (KBr): 1060  $\text{cm}^{-1}$ . NMR: 1.47–1.73 ppm (multiplet)  $\text{C}(\text{CH}_3)_2$ , 5.17 ppm (s) and 5.51 ppm (s) CH; 6.8–7.6 ppm (multiplet) 9 aryl-H. The content of XXVI A,  $R_F$  0.50–0.54, and XXVI B,  $R_F$  0.59–0.63, was determined by thin-layer chromatography on silica GF<sub>254</sub> Merck precoated plates with 2-butanone:1,2-dichloroethane 10:70 as solvent. The spots were examined under UV light (254 nm).

*3,3-Dimethyl-1-phenylthiophthalan-1-ol (V) from the sulfoxide XXVI A.* To a solution of 3,3-dimethyl-1-phenylthiophthalan-2-oxide (XXVI A) (5 g) in 25 ml of chloroform was added acetyl chloride (1.8 ml). When the reaction had subsided the solution was diluted with ligroin (100 ml) and extracted with 6 N hydrochloric acid (100 ml). The acid solution was neutralized with aqueous ammonia and extracted with ether. The ether phase was dried ( $\text{MgSO}_4$ ) and evaporated. Crystallization from ether/petroleum ether gave 4 g of 3,3-dimethyl-1-phenylthiophthalan-1-ol (V), identical with the above named specimen.

The authors are indebted to Professor B. Bak, Ph.D., Kemisk Laboratorium V, University of Copenhagen, for the NMR spectra on a Varian A-60 instrument, and to Mr. A. Olsson, Chem. eng., Aktiebolaget Leo, Helsingborg, for the NMR spectra on a Perkin Elmer R12 instrument.

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Received January 14, 1971.