

than of the corresponding acyclic or small ring carbonyl derivatives which give appreciable amounts of products derived from carbenoid insertion and rearrangement processes.<sup>3a</sup> The possibility that **5** is formed in the reaction, but is rearranged to **3** during chromatographic resolution of the reaction mixture may not, however, be excluded.

A comparison of the ultraviolet spectrum of **3** with that of **4** (Fig. 1) provides a particularly striking demonstration of the absence of conjugation between the ethylenic bond and the cyclopentadienyl ring in **3**.

#### Experimental

**$\alpha$ -Keto-1,1'-trimethyleneferrocene *p*-Toluenesulfonylhydrazone (2).**—A solution of 240 mg. (1.0 mmole) of the ketone and 190 mg. (1.0 mmole) of *p*-toluenesulfonylhydrazine in 30 ml. of ethanol containing a few drops of acetic acid was heated on the steam bath for 0.5 hr. On cooling, the hydrazone separated as lustrous golden rods, m.p. 198.5–200.0°, with darkening, yielding 337 mg. (82%). An analytical sample (from ethanol) melted at 201–202°.

*Anal.* Calcd. for  $C_{20}H_{20}FeN_2O_2S$ : C, 58.83; H, 4.94; N, 6.86. Found: C, 58.90; H, 4.83; N, 7.02.

**Dehydro-1,1'-trimethyleneferrocene (3).**—Sodium hydride (180 mg., 7.5 mmoles) was added to a solution of 500 mg. of the tosylhydrazone (1.2 mmoles) in 50 ml. of cyclohexane. The solution was heated at reflux, in an atmosphere of nitrogen, for 12 hr., then cooled, poured into water, and extracted with ether. The combined ether–cyclohexane extract was washed to neutrality and dried over magnesium sulfate. Removal of solvent left a crude crystalline product which was taken up in Skellysolve B and chromatographed on an alumina column. Three bands appeared. The first gave 45 mg. (22%) of **3**, m.p. 100.5–102.5°, after further chromatographic purification followed by sublimation.

The second band afforded 19 mg. of  $\alpha$ -keto-1,1'-trimethyleneferrocene (**1**), and the third 120 mg. of starting material. With sodium methoxide as base **3** was obtained in 14% yield.

*Anal.* Calcd. for  $C_{18}H_{12}Fe$ : C, 69.68; H, 5.40. Found: C, 70.05; H, 5.28.

**Reduction of Dehydro-1,1'-trimethyleneferrocene.**—The olefin (25 mg., 0.1 mmole) was taken up in 10 ml. of methanol and hydrogenated at atmospheric pressure and room temperature in the presence of platinum oxide catalyst. At the end of 36 hr., the catalyst was filtered off, solvent was removed, and the product was chromatographed on a short alumina column using Skellysolve B as eluent. In this manner, 11.4 mg. of 1,1'-trimethyleneferrocene, m.p. 100.5–104.0°, was obtained. Its infrared spectrum was identical with that of an authentic sample, and its mixture melting point with a sample of **4** (m.p. 107.5–108.5°) was 105–106°.

## A New Phenothiazine Synthesis. The Halogen-Induced Smiles Rearrangement<sup>1</sup>

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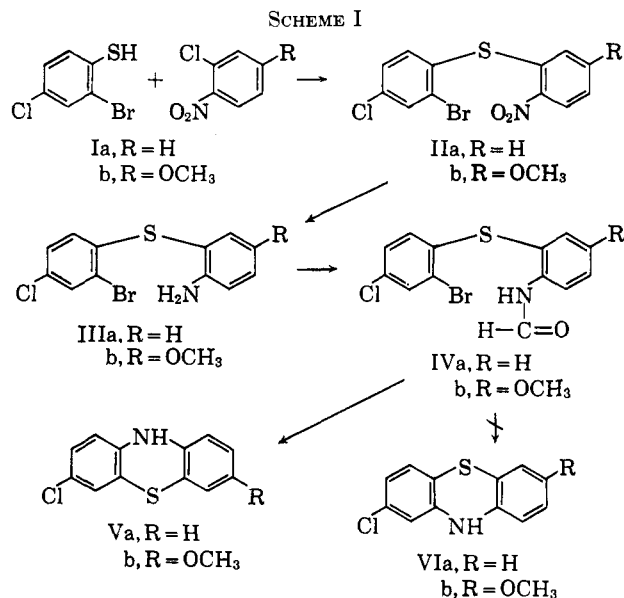
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Bonvicino, Yogodzinski, and Hardy have reported a new Smiles-type rearrangement in which bromo replaces nitro as the activating group.<sup>2</sup> They encountered this rearrangement in the synthesis of phenoxazines by dehydrohalogenation of *o*-bromo-*o'*-alkylaminodiphenyl ethers in benzene in the presence of sodamide. Bonvicino, *et al.*, considered the possibility that the same rearrangement could take place with potassium carbonate in *N,N*-dimethylformamide (DMF), but they minimized this possibility on theoretical grounds.

Our work on the preparation of the isosteric phenothiazines by dehydrohalogenation of *o*-bromo-*o'*-formamidodiphenyl sulfides (IVa and IVb) has shown that the halogen-induced Smiles rearrangement can indeed take place in DMF–potassium carbonate.

The intermediates (IVa and IVb) were prepared by the routine reaction sequence<sup>3</sup> outlined in Scheme I.



Cyclizations of IVa and IVb were effected by heating under reflux, in *N,N*-dimethylformamide, in the presence of anhydrous potassium carbonate and copper–bronze catalyst. Instead of the anticipated 2-chlorophenothiazine (VIa, m.p. 198.5–199.5°)<sup>4–6</sup> and 2-

(1) This rearrangement was first described in our Sixth Progress Report (April 30, 1963) to the Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md., under Contract SA-43-ph-3758.

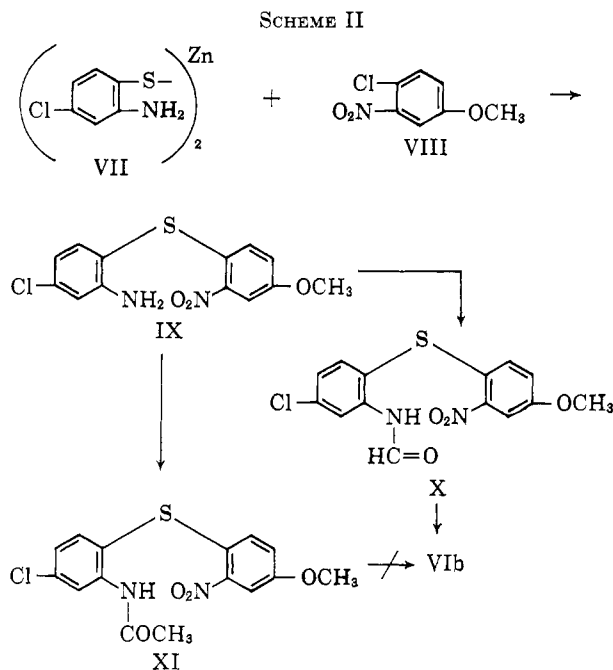
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chloro-7-methoxyphenothiazine (VIb, m.p. 174.5–175°), IVa and IVb yielded, respectively, 3-chlorophenothiazine (Va, m.p. 201–201.5°)<sup>5,6</sup> and 3-chloro-7-methoxyphenothiazine (Vb, m.p. 202–203°).

To permit mixture melting point and infrared comparison, an authentic sample of 2-chloro-7-methoxyphenothiazine (VIb) was prepared as shown in Scheme II.

Adaptations of literature procedures<sup>7–9</sup> provided the 2-nitro-2'-acylamino-diphenyl sulfides (X and XI). Application of the Clarke modification<sup>10</sup> of the Smiles rearrangement to the formamido compound (X) gave a 44% yield of 2-chloro-7-methoxyphenothiazine (VIb). This compound was identical with that obtained by thionation of 3-chloro-4'-methoxydiphenylamine.<sup>11,12</sup>

The Clarke modification was ineffective with the acetamido derivative (XI). Attempts to use standard conditions<sup>9,13</sup> for the conversion of X and XI to VIb were unsuccessful. Starting material, deacylated starting material, and intractable oils were obtained.

Authentic 3-chloro-7-methoxyphenothiazine (Vb) was obtained in very low yield by thionating 4-chloro-4'-methoxydiphenylamine (XII) under very carefully controlled conditions. The major product of this thionation was the dehalogenated compound 3-methoxyphenothiazine. (Similar loss of halogen during thionation of 4-halodiphenylamines has been reported previously.<sup>7,12,14</sup>) Efforts to improve the yield of Vb by eliminating catalyst, by using solvents, and by varying time, temperature, and concentration were to no avail.

The major difference between 2-chloro-7-methoxyphenothiazine and 3-chloro-7-methoxyphenothiazine, in the infrared, lies in the possession by the latter of a single, strong, broad band (12.3  $\mu$ ) in the region between 12.0 and 13.1  $\mu$ .<sup>7</sup> 2-Chloro-7-methoxyphenothiazine has two strong peaks in this region, one at 12.3 and another at 12.6  $\mu$ .

#### Experimental<sup>15</sup>

**2-Bromo-4-chloro-5'-methoxy-2'-nitrodiphenyl Sulfide (IIb).**—A solution of sodium ethoxide, prepared by adding 1.92 g. (0.084 g.-atom) of sodium metal to 62 ml. of absolute ethanol, was cooled to 10° and treated dropwise with 18.4 g. (0.082 mole) of 2-bromo-4-chlorobenzenethiol.<sup>16</sup> The resulting solution was added to 15.5 g. (0.075 mole) of 3-chloro-4-nitroanisole (Ib)<sup>17</sup> dissolved in 62 ml. of ethanol and the mixture was stirred at room temperature for 20 hr. The yellow solid which separated was washed with water and dried *in vacuo*, m.p. 81–85° (15.6 g., 56%). This material was used in the subsequent reduction without additional purification. An analytical sample was prepared by crystallization from methanol, m.p. 96–97°.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_9\text{BrClNO}_2\text{S}$ : C, 41.65; H, 2.40; N, 3.75. Found: C, 41.22; H, 2.58; N, 3.53.

**2-Bromo-4-chloro-2'-nitrodiphenyl Sulfide (IIa).**—The reaction between 2-bromo-4-chlorobenzenethiol (0.20 mole) and 2-chloro-nitrobenzene (0.22 mole) was carried out essentially as described for IIb. After heating the reaction mixture under reflux for 3 hr., a 72% yield of IIa was obtained as pale yellow crystals, m.p. 120–121°. Crystallization from ethanol provided an analytical sample, m.p. 123–124°.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_7\text{BrClNO}_2\text{S}$ : C, 41.80; H, 2.03; N, 4.07. Found: C, 42.54; H, 2.34; N, 4.09.

**2'-Amino-2-bromo-4-chloro-5'-methoxydiphenyl Sulfide (IIIb).**—Hydrogen chloride gas was passed into a suspension of 42 g. (0.19 mole) of stannous chloride dihydrate in 192 ml. of glacial acetic acid until the suspension cleared. This solution was added dropwise to a solution of 10 g. (0.027 mole) of IIb in 36 ml. of glacial acetic acid previously heated to 85°. The temperature was maintained at 80–95° during addition and for 1 hr. afterwards. The mixture was allowed to stand at room temperature overnight, cooled with ice, and treated with 1 l. of 10% sodium hydroxide solution. The resulting off-white solid was triturated with 10% sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate and evaporated under reduced pressure to give 6.3 g. (66%) of tan solid (m.p. 102–106°) sufficiently pure for formylation. An aliquot was crystallized three times from ethanol to yield a tan, crystalline analytical sample, m.p. 107.5–109.5°.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{11}\text{BrClNO}_2\text{S}$ : C, 45.39; H, 3.19; N, 4.14. Found: C, 45.47; H, 3.26; N, 4.18.

**2-Amino-2'-bromo-4'-chlorodiphenyl Sulfide (IIIa).**—A suspension of 49.2 g. (0.15 mole) of IIIa in 640 ml. of absolute ethanol was warmed to 55° and a solution of 120 g. (0.53 mole) of stannous chloride dihydrate in 64 ml. of concentrated hydrochloric acid was added in several portions. The mixture was heated under reflux for 1 hr., cooled to room temperature, and poured into 2 l. of cold water. The yellow oil which separated on standing was extracted with ether. The ether was dried over magnesium sulfate and concentrated under reduced pressure to leave 44.5 g. of yellow oil. This oil was formylated without additional treatment.

**2-Bromo-4-chloro-2'-formamido-5'-methoxydiphenyl Sulfide (IVb).**—A mixture of 6 g. (0.017 mole) of IIIb and 60 g. of 90% formic acid was heated under reflux for 6.5 hr. and allowed to stand at room temperature overnight. Tan crystals separated (4.64 g., 72%), m.p. 87–89°. Crystallization from ethanol raised the melting point to 134–137°. The same melting point increase was also produced by maintaining the tan crystals at 85° for 1 hr. The infrared spectra (Nujol) of the high- and low-melting materials were almost identical. Some peaks in the spectrum of the high-melting form were displaced slightly toward longer wave lengths. These differently melting solids were most

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likely polymorphic forms of IVb. (The presence of polymorphism among diphenyl sulfides has been reported previously.<sup>3</sup>) The analytical sample (ethanol) was a white crystalline solid, m.p. 137–138°.

*Anal.* Calcd. for  $C_{14}H_{11}BrClNO_2S$ : C, 45.11; H, 2.95; N, 3.76. Found: C, 44.97; H, 3.28; N, 3.77.

**2-Bromo-4-chloro-2'-formamidodiphenyl Sulfide (IVa).**—2-Amino-2'-bromo-4'-chlorodiphenyl sulfide (2.0 g., 0.0064 mole) was heated under reflux for 4 hr. with ten times its weight of 90% formic acid. The mixture was poured into 100 ml. of ice-water and the resulting white emulsion was extracted with ether. The ether was dried ( $MgSO_4$ ) and concentrated under reduced pressure leaving an off-white solid. Several crystallizations from ethanol afforded 1.3 g. (60%) of IVa as a white solid, m.p. 139.5–140.5°.

*Anal.* Calcd. for  $C_{13}H_9BrClNOS$ : C, 45.31; H, 2.63; N, 4.06. Found: C, 45.51; H, 2.58; N, 4.46.

**Cyclization of 2-Bromo-4-chloro-2'-formamido-5'-methoxydiphenyl Sulfide (IVb)**—A mixture of 5 g. (0.013 mole) of IVb, 2.1 g. of anhydrous potassium carbonate, 0.05 g. of copper-bronze catalyst,<sup>18</sup> and 125 ml. of DMF was heated under reflux for 2 hr. and allowed to stand at room temperature overnight. An additional trace of catalyst was added and reflux was continued until carbon dioxide evolution stopped (4 hr.). The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was extracted with 1.5 l. of boiling ligroin (60–90°) and the extracts were concentrated to give 2.5 g. of blue-gray solid. Repeated crystallization from benzene (Darco G-60) provided 3-chloro-7-methoxyphenothiazine (Vb) as very pale green plates, m.p. 202–203°.

*Anal.* Calcd. for  $C_{13}H_{10}ClNOS$ : C, 59.20; H, 3.80; Cl, 13.47; N, 5.31. Found: C, 59.17; H, 3.88; Cl, 13.08; N, 5.30.

**Cyclization of 2-Bromo-4-chloro-2'-formamidodiphenyl Sulfide (IVa).**—A mixture of 2 g. (0.0058 mole) of IVa, 0.83 g. (0.006 mole) of anhydrous potassium carbonate, 0.1 g. of copper-bronze catalyst,<sup>18</sup> and 20 ml. of DMF was heated under reflux for 11 hr. The mixture was filtered and the filtrate was poured into 300 ml. of cold water yielding 0.96 g. of pale green solid. Crystallization from benzene-petroleum ether (b.p. 20–40°) (Darco G-60) followed by crystallization from pure benzene gave 3-chlorophenothiazine (Va), m.p. 205–206°. The identity of Va was verified by mixture melting point and infrared comparison with authentic samples of 2-chlorophenothiazine<sup>6</sup> and 3-chlorophenothiazine.<sup>6</sup>

**2-Amino-4-chloro-4'-methoxy-2'-nitrodiphenyl Sulfide (IX).**—To a solution of 13 g. (0.33 mole) of sodium hydroxide in 195 ml. of ethanol was added 50 g. (0.13 mole) of the zinc salt of 2-amino-4-chlorobenzenethiol<sup>19</sup> and a solution of 52 g. (0.28 mole) of 4-chloro-3-nitroanisole<sup>20</sup> in 325 ml. of ethanol. The mixture was heated under reflux for 5 hr. and poured into 2 l. of cold water. The solid was extracted with ether and the extracts were dried over magnesium sulfate, decolorized, and concentrated to give 44.4 g. (55%) of yellow solid, m.p. 129–138°. This material was used directly in subsequent acylations. An aliquot was crystallized from ethanol to provide the analytical sample, m.p. 141–142°.

*Anal.* Calcd. for  $C_{13}H_{11}ClN_2O_3S$ : C, 50.22; H, 3.57; N, 9.02. Found: C, 50.20; H, 3.57; N, 9.06.

**2-Acetamido-4-chloro-4'-methoxy-2'-nitrodiphenyl Sulfide (XI).**—A mixture of 2.5 g. (0.008 mole) of IX, 0.9 ml. of pyridine, and 11 ml. of acetic anhydride was warmed to effect solution. The deep amber solution was allowed to cool, and a trace of undissolved solid was filtered. The filtrate was diluted with a mixture of 10 ml. of methanol and 150 ml. of water. An oil separated which solidified on standing. Crystallization from methanol (Darco G-60) afforded 1.4 g. (49%) of bright yellow crystals, m.p. 150–151°.

*Anal.* Calcd. for  $C_{15}H_{13}ClN_2O_4S$ : C, 51.07; H, 3.69; N, 7.94. Found: C, 51.43; H, 3.81; N, 7.40.

**4-Chloro-2-formamido-4'-methoxy-2'-nitrodiphenyl Sulfide (X).**—The amino derivative (IX) was formylated on a 0.63 mole scale, as described above for the preparation of IVa, to give a 70% yield of X, m.p. 146–147° (ethanol).

*Anal.* Calcd. for  $C_{14}H_{11}ClN_2O_4S$ : C, 49.61; H, 3.27; N, 8.27. Found: C, 49.49; H, 3.15; N, 8.50.

**2-Chloro-7-methoxyphenothiazine (VIb).**—To a boiling solution of X (2.4 g., 0.0071 mole) in 200 ml. of acetone was added,

in portions, 1.41 g. (0.021 mole) of powdered 85% potassium hydroxide. After reflux for an additional hour, the mixture was concentrated to 15 ml. and diluted with cold water. Two crystallizations from benzene (Darco G-60) gave 0.79 g. (44%) of VIb, m.p. 174–175°. This sample did not depress the melting point of the compound obtained by thionation of 3-chloro-4'-methoxydiphenylamine.<sup>11,12</sup> The infrared spectra of the two samples were identical.

**4-Chloro-4'-methoxydiphenylamine (XII).**—A mixture of 93.5 g. (0.50 mole) of *p*-bromoanisole, 101.7 g. (0.60 mole) of *p*-chloroacetanilide, 48.0 g. (0.35 mole) of anhydrous potassium carbonate, and 1.7 g. of copper-bronze catalyst was heated in an oil bath at 210° for 28 hr. The mixture was allowed to cool and extracted with four 300-ml. portions of boiling acetone. The acetone was removed under reduced pressure and the residue was heated under reflux for 4 hr. with a solution of 145 ml. of concentrated hydrochloric acid in 400 ml. of ethanol. The hydrolysis mixture was poured into 2 l. of cold water, basified with 20% sodium hydroxide solution, and extracted with four 300-ml. portions of ether. The extracts were combined, dried ( $MgSO_4$ ), and concentrated. The black residual oil was distilled with a short column to give 70 g. (60%) of XII, b.p. 150–163° (0.1 mm.), m.p. 50–51°.

*Anal.* Calcd. for  $C_{13}H_{12}ClNO$ : C, 66.71; H, 5.13; N, 5.95. Found: C, 67.19; H, 5.69; N, 5.88.

**3-Chloro-7-methoxyphenothiazine (Vb).**—A mixture of 2.3 g. (0.01 mole) of XII, 0.64 g. (0.02 mole) of sulfur, and 0.06 g. of iodine was heated in an oil bath at 140–145° for 45 min. The brown viscous reaction mixture was extracted with ether and the combined extracts were evaporated under reduced pressure to a dark oil. A good recovery of starting material was effected by trituration of the oil with four 25-ml. portions of petroleum ether (b.p. 20–40°). The petroleum ether-insoluble, green, gummy residue was crystallized repeatedly from benzene (Darco) to give 50 mg. of Vb as very pale green glistening plates, m.p. 195–197°. The infrared spectra of this compound and the compound obtained by cyclization of IVb were identical.

*Anal.* Calcd. for  $C_{13}H_{10}ClNOS$ : C, 59.20; H, 3.80. Found: C, 59.08; H, 4.06.

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## The Synthesis of Thiophene Analogs of Fluorene<sup>1</sup>

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Sometime ago we measured the dipole moments of the three isomeric dithienyls.<sup>3</sup> The values for 2,2'-dithienyl (0.77 D.), 2,3'-dithienyl (1.07 D.), and 3,3'-dithienyl (0.75 D.) indicated that in solution only the 2,3'-isomer could have a coplanar conformation.

It appeared interesting to measure the equilibrium constants of the dithienyl charge-transfer complexes with some electron acceptors in order to gain additional information about the conformation of these dithienyls.<sup>4</sup>

Truly flat (rigid) analogs of the dithienyls, such as I, II, and III, would also be valuable models in this study.

(1) Part II in the series, "Steric Effects in Heterocyclic Systems." For part I, see H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

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