A New Synthesis of "D"-Ring Phenothiazine Dioxides Employing a Modified Smiles Rearrangement (1)

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Phenothiazines are known to exhibit a broad spectrum of pharmacologic activity. These compounds and their derivatives have been extensively synthesized and structurally modified. One modification of the basic structure involves the addition of a fourth (or D-ring) attached through a *N*-atom to an adjacent ring. Although several of these compounds have been synthesized, the methods (2-12) are usually compound specific and the yields are generally poor. All of these prior methods start with an intact phenothiazine nucleus and proceed to construct the D-ring by alkylation of the *N*-atom followed by a ring closure. It was felt that an alternative synthetic scheme to these compounds, which would permit the easier introduction of different substituents, would be beneficial in that the pharmacologic activity of a variety of derivatives of this class of compounds could be more fully evaluated.

The method to be elucidated here is unique because the phenothiazine nucleus is generated in the final step, the initial steps being concerned with the formation of the D-ring already fused to a benzenoid nucleus. Another feature of this synthetic scheme is that it presents an interesting extension of the Smiles Rearrangement; one in which the attacking anion (amine) is incorporated in a

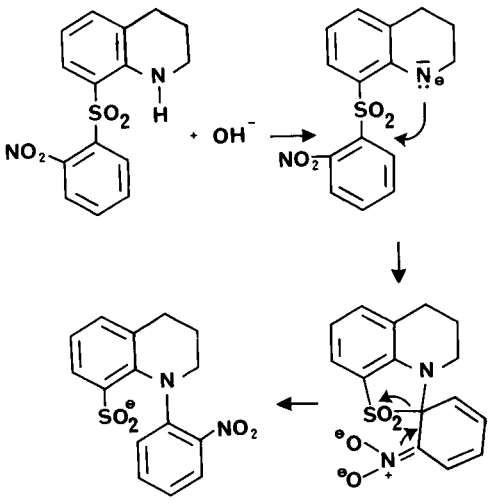


Figure 1

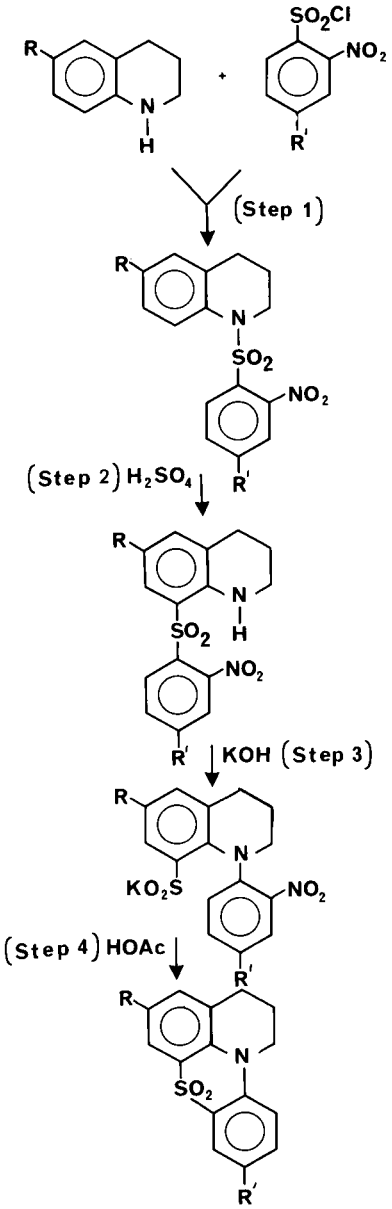


Figure 2

ring. The Smiles Rearrangement can be illustrated by any of a series of intramolecular aromatic nucleophilic displacements (13). The rearrangement depicted in Figure 1 is an extension of the work by Warren and Smiles (14) on the rearrangement of *o*-aminodiarylsulfones. Neither Smiles nor any of the more recent workers have reported using an attacking nucleophile which is incorporated into a ring. Concerning possible extensions of this modification, it would appear that only a tricovalent species such as a cyclic amine or amide could be utilized as the nucleophile for this reaction.

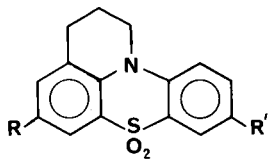
The general synthesis developed in this research is outlined schematically in Figure 2. The initial tetrahydroquinolines are available *via* the Skraup synthesis (15), followed by reduction of the heterocyclic ring. Thus the preparation of the proper starting material with any of a variety of substituents presents no great synthetic problem as many of the *o*-nitrobenzenesulfonyl chlorides used as intermediates are available commercially. The synthesis of the *o*-nitrobenzenesulfontetrahydroquinolinides (step 1) and their rearrangement to tetrahydroquinoline-8-sulfones (step 2) is detailed in a previous paper (16). The sulfonamides are easily prepared by any of the standard methods and the rearrangement in concentrated sulfuric acid goes smoothly and in reasonably good yield. Isolation and product work-up are also facile. The Smiles Rearrangement (step 3) is carried out in a mixture of 60% aqueous potassium hydroxide and methanol. If methanol is not used to solublize the sulfone, the rearrangement product is a red gum which is contaminated with much unrearranged material. As the mixture is heated to boiling, methanol distills off, and the sulfinate salt separates as red crystals which are usually of sufficient purity to proceed directly to the final step. In those cases where purification was a problem, the salt was extracted with water to separate it from any unrearranged sulfone. The ring closure (step 4) is carried out in glacial acetic acid. As the suspension of sulfinate salt in acid is gradually warmed, solution occurs and, as the boiling point is reached, there is a sudden evolution of nitrogen dioxide. The product is isolated by the addition of excess water and is usually recrystallized from glacial acetic acid. Table I lists the physical properties and analyses of the phenothiazine dioxides prepared. Since it is the phenothiazines rather than their oxides which are usually pharmacologically active, several attempts to reduce the oxides to the parent phenothiazines were made. These compounds proved to be unusually resistant to reduction even when lithium aluminum hydride was utilized (17). Other reductive methods are still under investigation.

The Smiles Rearrangement of 6-Chloro-8-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroquinoline.

A solution of 0.42 g. of the above named sulfone in 10 ml. of methanol was mixed with 5 ml. of a 50% aqueous potassium hydroxide solution in a beaker. The beaker was heated on a hot plate to boiling. As the methanol was slowly distilled off, brilliant orange-red crystals separated. Heating was continued until approximately half the methanol was lost. The mixture was then filtered to give 0.37 g. of the potassium salt of 1-(*o*-nitrophenyl)-6-chloro-1,2,3,4-tetrahydroquinoline-8-sulfinic acid. The yield of sulfinate salt was 80% but in other runs ranged as high as 99%.

TABLE I

D-Ring Phenothiazine Dioxides



	R	R′	M.p., °C	Formula	% Yield	Analyses Calcd. (Found) C	H	N	S	Cl
Ia	Cl	H	232-233	$C_{15}H_{12}ClNO_2S$	43	58.92 (59.00)	3.96 (3.97)	4.58 (4.43)	10.49 (10.30)	11.60 (11.64)
Ib	H	H	205-205.5	$C_{15}H_{13}NO_2S$	59	66.40 (66.67)	4.83 (4.89)	5.16 (4.94)	------ ------	------ ------
Ic	CH_3	H	175-177	$C_{16}H_{15}NO_2S$	79	67.20 (67.12)	5.28 (5.38)	4.90 (4.92)	------ ------	------ ------
Id	CH_3	Cl	275-276	$C_{16}H_{14}ClNO_2S$	35	60.05 (59.92)	4.41 (4.28)	4.38 (4.34)	------ ------	------ ------

The Ring Closure of 1-(*o*-Nitrophenyl)-6-chloro-1,2,3,4-tetrahydroquinoline-8-sulfinic Acid, Potassium Salt.

The sulfinate salt (0.37 g.) was added to 10 ml. of glacial acetic acid. On heating solution occurred but as the temperature approached the boiling point crystals began to separate. Occasionally a sudden evolution of gas was observed. The mixture was cooled and filtered to give 0.19 g. (66%) of brownish-yellow crystals, m.p. 228-229°. On recrystallization from glacial acetic acid or acetone, the m.p. was raised to 232-233°.

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