of methyl propionate gave no *t*-butyl α-benzoylpropionate. A small amount of *t*-butyl alcohol, unchanged *t*-butyl propionate, and fractions colored deeply yellow, probably consisting of propionin and the corresponding diketone, were isolated. A large tarry residue remained from the fractional distillation of this product.

Condensations Using Diethylaminomagnesium Bromide.—Methyl propionate (0.2 mole) was condensed with methyl benzoate (0.2 mole) in the presence of diethylaminomagnesium bromide according to the procedure described below for diisopropylaminomagnesium bromide condensations. The diethylaminomagnesium bromide solution was prepared as described by Hauser and Walker.[11] Fractional distillation gave, in addition to lower boiling fractions, 16.6 g. of material, b.p. 133–134° (5 mm.), $n^{21}D$ 1.5216. This last fraction corresponds in b.p. to the expected methyl α-benzoylpropionate. Qualitative test, however, indicated the presence of nitrogen, and quantitative determination by the Kjeldahl procedure showed 5.7% nitrogen. Assuming the nitrogen compound to be N,N-diethylbenzamide, this corresponds to the presence of 73.4% of this substance.

Condensations Using Diisopropylaminomagnesium Bromide.—The diisopropylaminomagnesium bromide for these condensations was prepared as described by Frostick and Hauser.[5] A mixture of 27.2 g. (0.2 mole) of methyl benzoate and 17.6 g. (0.2 mole) of ethyl acetate was added dropwise during 30 minutes to a solution of 0.4 mole of diisopropylaminomagnesium bromide in 250 ml. of ether. Stirring was continued for an additional 2 hours. The reaction mixture was poured onto a mixture of 300 g. of cracked ice and 25 ml. of concd. sulfuric acid. The ether layer was separated, and the aqueous layer twice extracted with 100-ml. portions of ether. The ether extracts were combined, washed with water, then with saturated sodium bicarbonate solution, and finally dried over sodium sulfate followed by Drierite. Removal of the drying agents and solvent followed by fractional distillation of the residue gave, after a very small amount of lower boiling material, 18.7 g. (49%) of ethyl benzoylacetate, b.p. 116–122° (2 mm.). This fraction did not give a test for nitrogen. It was characterized by conversion to ethyl α,α′-dibenzoylglutarate, m.p. 91°; reported[12] m.p. 92.5°.

A similar condensation of methyl benzoate (0.2 mole) with methyl propionate (0.2 mole) gave 19.6 g. (51%) of methyl α-benzoylpropionate, b.p. 132–136° (7–8 mm.), $n^{21}D$ 1.5200. This material gave no test for nitrogen and was characterized by conversion to 4-methyl-3-phenylisoxazolone-5, m.p. 121–122°.

Condensation of methyl 2-furoate (0.2 mole) with methyl propionate (0.2 mole) by this same procedure gave 17 g. (47%) of methyl α-2-furoylpropionate, b.p. 114–116° (2 mm.), $n^{25}D$ 1.5006. The product gave a negative nitrogen test and was characterized by conversion to α-furoylpropionamide, m.p. 182–183.5°; reported[10] m.p. 183°.

Condensation of methyl benzoate (0.2 mole) with methyl *n*-butyrate (0.2 mole) by this procedure gave 28.9 g. of material of b.p. 126–130° (2 mm.) corresponding to the expected b.p. of methyl α-benzoyl-*n*-butyrate. Kjeldahl analysis, however, showed the presence of 1.24% nitrogen, indicating contamination of the mixed condensation product with N,N-diisopropylbenzamide. Very little material boiling in the expected range for the self-condensation product of methyl *n*-butyrate was isolated. Another condensation of methyl benzoate (0.2 mole) with methyl *n*-butyrate (0.2 mole) was effected by the technique of adding the ether solution of diisopropylaminomagnesium bromide to the mixture of esters. This condensation led to the formation of 18.2 g. (47%) of methyl α-benzoyl-*n*-butyrate, b.p. 125–132° (3–4 mm.). This material did not give a test for nitrogen. Under these conditions of effecting the condensation, 9.8 g. (56%) of methyl α-*n*-butyryl-*n*-butyrate was also formed by self-condensation of methyl *n*-butyrate.

(11) C. R. Hauser and H. G. Walker, Jr., THIS JOURNAL, **69**, 295 (1947).

(12) F. R. Japp and A. C. Mitchie, *J. Chem. Soc.*, **79**, 1010 (1901).

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Action of Hydrochloric and Nitric Acids on Some Derivatives of Phenothiazine[1]

BY A. CHANDLER SCHMALZ AND ALFRED BURGER

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The formation of 3-chloro-10-methylphenothiazine (IV) by reductive chlorination of 10-methylphenothiazine-5-oxide (I) has been confirmed by synthesis of IV. Under similar conditions 10-(3-diethylaminopropyl)-phenothiazine-5-oxide gave 3(?)-chloro-10-(3-diethylaminopropyl)-phenothiazine while 10-(3-diethylaminopropyl)-phenothiazine-N,5-dioxide gave a dichlorophenothiazine. 3,7-Dichloro-10-methylphenothiazine-5-oxide furnished a tetrachlorophenothiazine as well as 3,7-dichloro-10-methylphenothiazine. Nitration of 10-methylphenothiazine and of I under ordinary conditions gave 3-nitro-10-methylphenothiazine and not the expected sulfoxide. Mechanisms for these and allied reactions are proposed.

The product obtained by heating 10-methylphenothiazine-5-oxide (I) with hydrochloric acid was recognized by Page and Smiles[2] as a chloro-10-methylphenothiazine, but the position of the chlorine atom was not established. In a similar "reductive chlorination" of 3-nitrophenothiazine-5-oxide, the chlorine atom was assumed to have entered the 7-position, but no proof for the structure of the resulting compound was offered.[3] We have now synthesized 3-chloro-10-methylphenothiazine (IV) in order to establish the structure of the product from the reaction of 10-methylphenothiazine-5-oxide with hydrochloric acid. 4-Chlorodiphenylamine was fused with sulfur in the presence of iodine, and the 3-chlorophenothiazine from this reaction was methylated with sodamide and methyl iodide. The product was identical with that from the above reaction.

A mechanism for the first phase of the reductive chlorination has been suggested by Page and Smiles.[2] It was based on the observation that 10-methylphenazothionium chloride can be isolated from the reaction of 10-methylphenothiazine-5-oxide (I) with hydrochloric acid,[4] and the same conditions initiate the reduction of this sulfoxide. Indeed, the *o*-quinonoid phenazothionium salts[5] are believed to be the materials undergoing a rearrangement underlying the reaction, and the protonation of the sulfoxide I with formation of the sulfonium base II should therefore be the first in this sequence of steps. It now appears that in the strongly acid medium required for the rearrangement the diacid

(1) This study was carried out under Contract AF33 (038)-22947 between the University of Virginia and Wright Air Development Center, U. S. Air Force, Wright–Patterson Air Force Base, Dayton, Ohio.

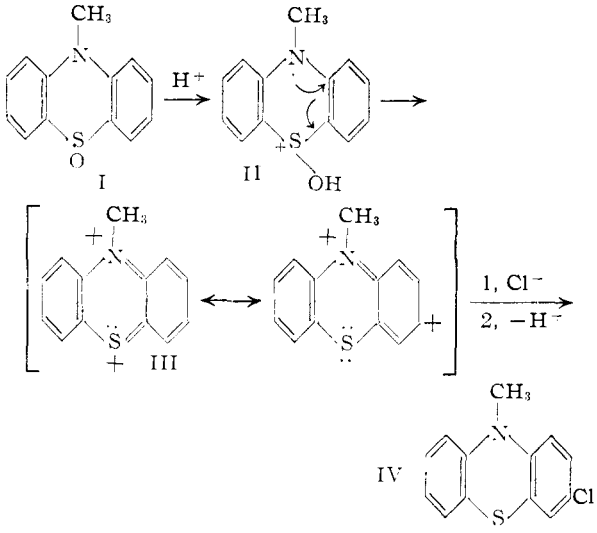
(2) H. J. Page and S. Smiles, *J. Chem. Soc.*, **97**, 1112 (1910).

(3) F. Kehrmann and O. Nossekno, *Ber.*, **46**, 2809 (1913).

(4) E. de B. Barnett and S. Smiles, *J. Chem. Soc.*, **97**, 186 (1910).

(5) F. Kehrmann, *Ann.*, **322**, 1 (1902).

salt III must be formed, and its 3-position can be thought to be attacked by chloride ion, leading to 3-chloro-10-methylphenothiazine.

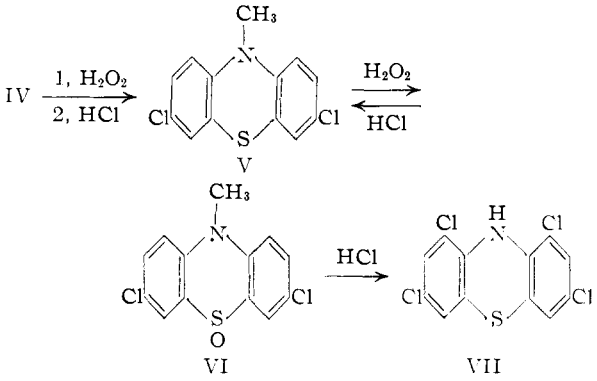


Using phenothiazine-5-oxide, Page and Smiles[2] tried to effect a similar reductive halogenation with hydrobromic and hydriodic acid, respectively, but could isolate only from the reaction with hydrobromic acid a very small amount of an ill-defined material which seemed to be a bromophenothiazine. In our hands, 10-methylphenothiazine-5-oxide did not furnish identifiable substances with these two acids, but 48% hydrofluoric acid reduced the sulfoxide to 10-methylphenothiazine in 47% yield without introducing a fluorine atom into the nucleus.

Oxidation of 3-chloro-10-methylphenothiazine with hydrogen peroxide gave 3-chloro-10-methylphenothiazine-5-oxide. Refluxing of this compound with hydrochloric acid led, by way of a deeply colored phenazothionium chloride, to 3,7(?)-dichloro-10-methylphenothiazine (V). The position of the second chlorine atom is inferred by analogy with the mechanism proposed for the formation of the 3-chloro derivative IV (*vide supra*).

The acceptance of *o*-quinonoid structures as intermediates in these reactions facilitates the explanation of the excellent yields of reaction products carrying halogen in *para* and, as will be seen below, *ortho* to the cyclic nitrogen. An alternative simple explanation of the formation of IV and V would be the reduction of the respective sulfoxides by hydrochloric acid with production of one mole of chlorine, followed by chlorination of the phenothiazine nucleus. The orientation into the 3- and 7-positions obviously parallels that observed in nitration[3,6] and formylation.[7]

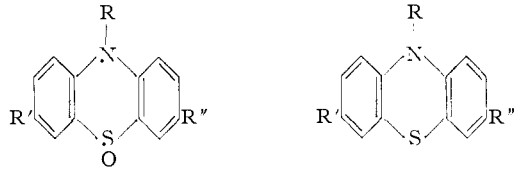
When 3,7-dichloro-10-methylphenothiazine-5-oxide (VI), obtained by oxidation of V with hydrogen peroxide, was heated with hydrochloric acid, two products could be fractionated from the reaction mixture. One of them, obtained in 46% yield, proved to be 3,7-dichloro-10-methylphenothiazine



(V). The other substance (34% yield) represented a tetrachlorophenothiazine (VII) of melting point 235–236°, apparently identical with the tetrachlorophenothiazine previously prepared by two different and independent methods.[2,8]

Reductive chlorination of VI should, according to the mechanisms elaborated for the two comparable cases above, yield 1(?),3,7-trichloro-10-methylphenothiazine. A molecular scale model of this compound indicates that the chlorine atom entering position 1 interferes sterically with the 10-methyl group and must therefore weaken its carbon–nitrogen linkage. The slower rate of discoloration of the phenazothionium intermediate observed, and the fact that almost one-half of the reduced sulfoxide could be isolated without having been chlorinated further (V), indicates that the one mole of chlorine produced in the reaction was now available for the chlorination of less than one-half of V. Thus the formation of the tetrachlorophenothiazine (VII) finds a ready explanation; loss of the 10-methyl group by acid hydrolysis from its crowded position can serve as evidence for chlorine substitution in the sterically significant positions 1 and 9 in VII.

The reduction of the phenothiazine-5-oxides with hydrochloric acid may follow a course similar to the reduction of 3-nitrophenothiazine-5-oxide (VIII) to 3-nitrophenothiazine (IX) with ethanol and dilute sulfuric acid which was first reported by Kehrmann and Nossenko.[3] In order to explore further



VI	R = CH_3; R′, R″ = Cl	V
VIII	R, R′ = H; R″ = NO_2	IX
X	R = CH_3; R′ = NO_2; R″ = H	XI
XII	R = $(CH_2)_3N(C_2H_5)_2$; R′, R″ = H	
	R = $(CH_2)_3N(C_2H_5)_2$; R′ = Cl; R″ = H	XIII
XIV	R = $(CH_2)_3N(O)(C_2H_5)_2$; R′, R″ = H	
	R = H; R′, R″ (unassigned) = Cl	XV

the scope of this reaction, we studied the behavior of 3-nitro-10-methylphenothiazine-5-oxide (X) under the same conditions and found that here also the sulfoxide was reduced readily to the corresponding 3-nitro-10-methylphenothiazine (XI). When we tried to synthesize the sulfoxide X by the method of Kehrmann and Zybs[9] who had isolated it

(6) A. Bernthsen, *Ann.*, **230**, 76 (1885); E. de B. Barnett and S. Smiles, *J. Chem. Soc.*, **95**, 1261 (1909); F. Kehrmann and F. Ringer, *Ber.*, **46**, 3014 (1913).

(7) Ng. Ph. Buu-Hoï and Ng. Hoán, *J. Chem. Soc.*, 1834 (1951).

(8) O. Unger and K. A. Hofmann, *Ber.*, **29**, 1362 (1896).

(9) F. Kehrmann and P. Zybs, *ibid.*, **52**, 130 (1919).

from the nitration of 10-methylphenothiazine with "fuming" nitric acid in acetic acid solution, we obtained 3-nitro-10-methylphenothiazine (XI) instead. Since Gilman and Shirley[10] had nitrated 10-ethylphenothiazine oxidatively to 3-nitro-10-ethylphenothiazine-5-oxide by the action of concentrated nitric acid in acetic acid medium directly, we applied these conditions to our lower homolog but again obtained only 3-nitro-10-methylphenothiazine in excellent yield. Repetition of the experiment of Gilman and Shirley with the 10-ethyl derivative fully confirmed the results of these authors. Only when 99.5% nitric acid[11] was used could we convert 10-methylphenothiazine to 3-nitro-10-methylphenothiazine-5-oxide directly; a considerable amount of 3,7-dinitro-10-methylphenothiazine-5-oxide[9] was isolated also. The difference in the behavior of the two homologous 10-alkyl derivatives remains unexplained. Even the nitration of 10-methylphenothiazine-5-oxide (I) did not give the nitro sulfoxide X, but surprisingly 3-nitro-10-methylphenothiazine (XI) was obtained from this reaction in 91% yield. An explanation of this unexpected result may be initial protonation of I, reduction by the medium to 10-methylphenothiazine and nitration of this intermediate.

The best way to prepare the sulfoxide X was to oxidize 3-nitro-10-methylphenothiazine (XI) with one mole of hydrogen peroxide while oxidation with two moles of this reagent furnished the corresponding sulfone in good yield.

Since 10-dialkylaminoalkylphenothiazine derivatives such as Diparcol, promethazine, pyrathiazine[12] and Thorazine[13] are used widely for the correction of functional disorders, a study of the behavior of some of their sulfoxide derivatives toward hydrochloric acid was undertaken. The sulfoxide XII was prepared from 10-(3-diethylaminopropyl)-phenothiazine oxalate with hydrogen peroxide; hydrochloric acid treatment gave 3(?)chloro-10-(3-diethylaminopropyl)-phenothiazine (XIII). Oxidation of 10-(3-diethylaminopropyl)-phenothiazine with hydrogen peroxide in ethanol solution led to the N,5-dioxide XIV, which on prolonged boiling with hydrochloric acid furnished a dichlorophenothiazine (XV) in 46% yield with the loss of the basic side chain. While the nature of the aliphatic nitrogen atom of the 10-substituent thus seems to influence the course of the reaction, the reductive chlorination of the sulfoxides XII and XIV follows the same pattern as that of the 10-methyl derivatives, I and VI, respectively.

Experimental[14]

3-Chlorophenothiazine.—An intimate mixture of 6.1 g. (0.03 mole) of 4-chlorodiphenylamine,[15] 2.1 g. (0.06 g. at.) of sulfur and 0.2 g. of iodine was fused at 145–155° for one hour when the evolution of hydrogen sulfide ceased. The cooled melt was extracted with ether and the ether evaporated. From the solid residue (4.1 g.) the chloro derivative was extracted with benzene, purified with Norit and crystallized from about 25 ml. of the solution. The green-tan powder weighed 2.3 g. (33%), m.p. 193–195°. A sample purified by vacuum sublimation at 165° (0.1 mm.) melted at 200–201°. The literature reports m.p. 199°.[16]

Anal. Calcd. for $C_{12}H_8ClNS$: C, 61.67; H, 3.45. Found: C, 61.97; H, 3.40.

10-Methylphenothiazine-5-oxide (I).—To a hot solution of 21.3 g. of 10-methylphenothiazine in 500 ml. of 95% ethanol and 100 ml. of acetone was added 100 ml. of 30% hydrogen peroxide. The colorless mixture was refluxed for 15 minutes and allowed to stand at 25° for 14 hours. It was concentrated to about 100 ml. and diluted to 1 l. with water. Colorless needles separated after a short time. They were recrystallized from about 400 ml. of ethanol to give 20.4 g. (90%) of pure product, m.p. 193–194°. The literature[4] reports m.p. 193°.

3-Chloro-10-methylphenothiazine (IV). (a).—In accordance with the general directions of Page and Smiles,[2] a mixture of 22.9 g. (0.1 mole) of 10-methylphenothiazine-5-oxide and 150 ml. of concentrated hydrochloric acid was shaken briefly until a deep red-violet clear solution resulted. After refluxing for 30 to 60 minutes the liquid became pale-pink, and a green oil separated. The cooled mixture was extracted with four 125-ml. portions of ether, the pale-green ether extract was washed free from acid with carbonate solution and water and the solvent was removed. The oily residue readily solidified and was recrystallized from methanol or ethanol to colorless needles, m.p. 105–106°; literature melting point 107°; the yield was 23.3 g. (93%).

Anal. Calcd. for $C_{13}H_{10}ClNS$: C, 63.02; H, 4.07. Found: C, 63.26; H, 4.05.

(b).—A mixture of 0.5 g. (2.14 millimoles) of 3-chlorophenothiazine and 0.084 g. (2.14 millimoles) of sodamide in 75 ml. of dry xylene was refluxed with stirring for 5.5 hours. To the resulting yellowish mixture was added 1 g. (6.5 millimoles) of methyl iodide, and heating and stirring was continued for three hours. The hot suspension was filtered, the precipitated sodium iodide was washed with hot xylene and the solvent was removed from the filtrate. The residual greenish oil crystallized from dilute ethanol, m.p. 107.5–108°. The yield was 0.88 g. (83%). A mixture melting point with a sample obtained by method a was 105–107°. Both products gave the same red-violet color with cold concentrated sulfuric acid.[2]

Anal. Found: C, 62.99; H, 3.94.

Reduction of 10-Methylphenothiazine-5-oxide (I) with Hydrofluoric Acid.—A mixture of 4.6 g. (0.02 mole) of 10-methylphenothiazine-5-oxide and about 150 ml. of 48% hydrofluoric acid was boiled gently in a copper flask for 4 hours and poured into 1 l. of water. The solid material was separated, extracted with 200 ml. of acetone in small portions and the solvent removed. Extraction of the residual solid with ether followed by evaporation of the solvent left a red oil which was washed with dilute potassium hydroxide to destroy any excess acid. The oil solidified on cooling and was recrystallized from ethanol–benzene (10:1) with the aid of Norit to give 2.0 g. (47%) of colorless to pale yellow needles, m.p. 99–100°. A mixture melting point with an authentic sample of 10-methylphenothiazine was 99–100°.

Anal. Calcd. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20. Found: C, 73.19; H, 5.37.

The reaction could be carried out also in a Pyrex flask provided the boiling was interrupted before the flask disintegrated.

3-Nitro-10-methylphenothiazine (XI). (a).—A warm solution of 10 g. (0.047 mole) of 10-methylphenothiazine in 250 ml. of glacial acetic acid was cooled to 25° and treated with a solution of 10 ml. (*ca.* 0.167 mole) of nitric acid (d. 1.42) in 40 ml. of glacial acetic acid. The reddish-brown reaction mixture was allowed to stand at 25° for two days and poured into 2 l. of ice-water. The cold supernatant liquid was decanted, the remaining yellow suspension of the nitro compound was neutralized partially with sodium carbonate, and the now solid precipitate was filtered and washed with water. Recrystallization from benzene furnished 11.2 g. (90%) of yellow crystals, m.p. 118–120°.

(10) H. Gilman and D. A. Shirley, THIS JOURNAL, **66**, 888 (1944).

(11) J. W. Mellor, "Inorganic and Theoretical Chemistry," Vol. VIII, Longmans, Green and Co., New York, N. Y., 1928, p. 558.

(12) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 452; P. Marquart and H. Schumacher, *Arzneimittelforschung*, **4**, 223 (1954).

(13) *Cf.* P. Viaud, *J. pharm. pharmacol.*, **6**, 361 (1954).

(14) All melting points are corrected. Microanalyses by Miss Patricia L. Paynter.

(15) F. Ullmann, *Ann.*, **355**, 322 (1907), p. 338.

(16) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).

Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90. Found: C, 60.64; H, 4.13.

(b).—When a solution of 5 ml. of nitric acid (d. 1.5) in 20 ml. of glacial acetic acid was added dropwise to a solution of 5 g. of 10-methylphenothiazine in 25 ml. of acetic acid at 25°, and the red mixture was worked up as above after standing overnight at 25°, 6.25 g. (97%) of a yellow material, m.p. 115–118°, containing a very small amount of residue melting at 172–173° was obtained. Recrystallization from benzene raised the melting point to 119–121° without appreciable loss of yield. A mixture melting point with a sample obtained by method a was 119–121°.

Anal. Found: C, 60.56; H, 4.18.

(c).—To a solution of 2.29 g. (0.01 mole) of 10-methylphenothiazine-5-oxide in 50 ml. of glacial acetic acid was added a mixture of 2 ml. of nitric acid (d. 1.42) and 8 ml. of glacial acetic acid at 25°. The yellow solution turned dark orange on standing for 48 hours. It was worked up as above and yielded, after recrystallization from benzene, 2.5 g. (91%) of product, m.p. 120.5–122°. A mixture melting point with a sample prepared by method a showed no depression.

Anal. Found: C, 60.27; H, 4.07.

(d).—A solution of 0.5 g. of 3-nitro-10-methylphenothiazine-5-oxide (*vide infra*) in 20 ml. of 95% ethanol and 12.5 ml. of 30% sulfuric acid was refluxed for six hours, poured into 250 ml. of water and cooled to deposit 0.37 g. (80%) of yellow crystals, which were recrystallized from benzene and melted at 120–121°. A mixture melting point with a sample prepared by method a was undepressed.

3-Nitro-10-methylphenothiazine-5-oxide (X). (a).—A solution of 1.0 g. (3.9 millimoles) of 3-nitro-10-methylphenothiazine in 40 ml. of 95% ethanol and 10 ml. of glacial acetic acid was refluxed with 0.45 ml. (3.9 millimoles) of 30% hydrogen peroxide for 15 minutes. It was diluted with 100 ml. of water and cooled until 1 g. (94%) of yellow sulfoxide had crystallized. The material was recrystallized from 82 ml. of benzene containing 2 ml. of glacial acetic acid. The fine yellow crystals melted at 176–177°. The literature melting point[9] is 177°.

Anal. Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.68. Found: C, 57.01; H, 3.45.

(b).—To a solution of 5.0 g. (0.0235 mole) of 10-methylphenothiazine in 25 ml. of glacial acetic acid was added a mixture of 5 ml. of 99.5% nitric acid[11] and 20 ml. of glacial acetic acid, and the clear red-brown solution was allowed to stand at 25° for two days. The yellow crystals which separated (3.55 g.) were filtered and melted after recrystallization from ethanol–benzene (2:1) at 311–312° dec. after preliminary darkening at 280°. The literature[9] reports a decomposition point of 280° for 3,7-dinitro-10-methylphenothiazine-5-oxide.

Anal. Calcd. for $C_{13}H_9N_3O_5S$: C, 48.90; H, 2.84. Found: C, 48.95; H, 3.00.

The filtrate was diluted with 1 l. of water and neutralized. The yellow solid which separated weighed 2.62 g. and melted at 116–155°. Repeated recrystallization from ethanol–benzene (2:1) gave pure 3-nitro-10-methylphenothiazine-5-oxide, m.p. 176–177°. A mixture melting point with a sample prepared by method a was 176–177°.

3-Nitro-10-methylphenothiazine-5,5-dioxide. (a).—A solution of 1 g. of 3-nitro-10-methylphenothiazine in 110 ml. of glacial acetic acid was refluxed with 10 ml. of 30% hydrogen peroxide for 1.5 hours and worked up as described in the preparation of the nitro sulfoxide above. The finely divided yellow solid crystallized from acetic acid or a 1:1 benzene–ethanol mixture, m.p. 213–215°. The yield was 0.92 g. (83%).

Anal. Calcd. for $C_{13}H_{10}N_2O_4S$: C, 53.78; H, 3.47. Found: C, 53.57; H, 3.64.

(b).—Oxidation of 1 g. of 3-nitro-10-methylphenothiazine-5-oxide in 50 ml. of acetic acid with 1 ml. of 30% hydrogen peroxide for one hour as described in (a) gave 0.95 g. (85%) of the nitro sulfone, m.p. 211.5–213°. A mixture melting point with a sample prepared by method a was undepressed.

3-Diacetamido-10-methylphenothiazine.—A solution of 2.58 g. (0.01 mole) of 3-nitro-10-methylphenothiazine in 50 ml. of glacial acetic acid and 50 ml. of acetic anhydride was warmed to 90° and treated with 10 g. of zinc dust in small portions. The olive-green mixture was refluxed for 7.5 hours, filtered and the dark filtrate poured into water. The resulting milky suspension was broken by addition of a small quantity of 40% sodium hydroxide. After cooling, a gray solid was filtered. Recrystallization from 50% ethanol with the aid of Darco gave 2.9 g. of a pale blue powder, m.p. 122–124°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5 16. Found: C, 65.64; H, 5.16.

A portion of the diacetamido derivative was hydrolyzed to 3-acetamido-10-methylphenothiazine by refluxing with 10% hydrochloric acid for two hours. The hot solution was filtered, the filtrate diluted with one-half its volume of water and cooled. The precipitated solid was recrystallized from 70% ethanol (Norit) to give fine colorless needles, m.p. 168–169°. The reported melting point[9] is 169°.

3-Chloro-10-methylphenothiazine-5-oxide Hemihydrate.—A mixture of 17.3 g. (0.07 mole) of 3-chloro-10-methylphenothiazine, 250 ml. of ethanol, 60 ml. of acetone and 50 ml. of 30% hydrogen peroxide was refluxed for 24 hours and worked up as described for 10-methylphenothiazine-5-oxide. Recrystallization of the pink solid from 30% ethanol gave a quantitative yield of colorless blades, m.p. 92–93°.

Anal. Calcd. for $C_{13}H_{10}ClNOS \cdot {}^1/_2H_2O$: C, 57.24; H, 4.07. Found: C, 57.14; H, 3.77.

3,7-Dichloro-10-methylphenothiazine (V).—A deep red solution of 12.2 g. (0.05 mole) of 3-chloro-10-methylphenothiazine-5-oxide in 550 ml. of 20% hydrochloric acid was refluxed with stirring for 1.5 hours. The dark green oil which separated was crystallized from 50% ethanol to give 13.15 g. (93%) of long yellow-green needles, m.p. 129–130°.

Anal. Calcd. for $C_{13}H_9Cl_2NS$: C, 55.33; H, 3.22. Found: C, 55.04; H, 3.21.

3,7-Dichloro-10-methylphenothiazine-5-oxide (VI).—This compound was obtained in 95% yield by oxidizing 3,7-dichloro-10-methylphenothiazine in ethanol–acetone solution with 30% hydrogen peroxide for 40 hours. Recrystallization from ethanol gave colorless needles, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.04. Found: C, 52.12; H, 3.34.

Reductive Chlorination of 3,7-Dichloro-10-methylphenothiazine-5-oxide.—A solution of 2.98 g. (0.01 mole) of 3,7-dichloro-10-methylphenothiazine-5-oxide in 150 ml. of 24% hydrochloric acid was refluxed for four hours. The green oil which separated solidified on cooling and was fractionally crystallized from benzene–ethanol (1:1) (Norit) to give 1.15 g. (34%) of soft yellow needles, m.p. 235–236°, which analyzed for a **tetrachlorophenothiazine.**

Anal. Calcd. for $C_{12}H_5Cl_4NS$: C, 42.76; H, 1.50. Found: C, 42.88; H, 1.63.

From the mother liquors was obtained 1.30 g. (46%) of **3,7-dichloro-10-methylphenothiazine,** m.p. 125–126°. A mixture melting point with a sample prepared from 3-chloro-10-methylphenothiazine-5-oxide was 127–129°.

Anal. Calcd. for $C_{13}H_9Cl_2NS$: C, 55.33; H, 3.22. Found: C, 55.16; H, 3.10.

10-(3-Diethylaminopropyl)-phenothiazine Oxalate.—This compound was prepared quantitatively as fine colorless blades, m.p. 176–177° (from absolute ethanol) by treating an ethereal solution of 10-(3-diethylaminopropyl)-phenothiazine[17] with excess ethereal oxalic acid.

Anal. Calcd. for $C_{19}H_{24}N_2S \cdot C_2H_2O_4$: C, 62.66; H, 6.51. Found: C, 62.75; H, 6.51.

10-(3-Diethylaminopropyl)-phenothiazine-5-oxide (XII).—A solution of 20.13 g. (0.05 mole) of 10-(3-diethylaminopropyl)-phenothiazine oxalate in 225 ml. of 85% ethanol and 5.75 g. (0.05 mole) of 30% hydrogen peroxide was refluxed for 25 hours and the solvent removed at the aspirator. The residual oil solidified to a white mass of the sulfoxide oxalate which was recrystallized from absolute ethanol to give 19.8 g. (95%) of colorless blades, m.p. 195–195.5°.

Anal. Calcd. for $C_{19}H_{24}N_2SO \cdot C_2H_4O_2$: C, 60.27; H, 6.26. Found: C, 60.70; H, 6.70.

The sulfoxide (XII) was liberated quantitatively from the warmed aqueous solution of the oxalate with sodium hydroxide solution as an oil which solidified soon. Colorless

(17) P. Charpentier, U. S. Patent 2,519,886 (1950); *C. A.*, **45**, P 673c (1951).

blades were obtained from 50% ethanol, m.p. 118.5–119.5°.

Anal. Calcd. for $C_{19}H_{24}N_2OS$: C, 69.47; H, 7.36. Found: C, 69.69; H, 7.22.

3-Chloro-10-(3-diethylaminopropyl)-phenothiazine (XIII).—A deep red solution of 3.28 g. (0.01 mole) of 10-(3-diethylaminopropyl)-phenothiazine-5-oxide in 75 ml. of concentrated hydrochloric acid was refluxed for 3 hours, diluted with 50 ml. of water and made basic with 20% potassium hydroxide to destroy the red color of the small amount of unreacted phenazothionium salt leaving a pale green oil. The mixture was extracted with ether and worked up to give a pale yellow oil which was converted to the **oxalate** in ether solution. The minute granules (from acetone) weighed 3.8 g. (87%), m.p. 163–164°. The oxalate loses carbon dioxide in a vacuum and cannot be dried above 30°.

Anal. Calcd. for $C_{19}H_{23}ClN_2S \cdot C_2H_2O_4$: C, 57.72; H, 5.77. Found: C, 57.30; H, 6.18.

10-(3-Diethylaminopropyl)-phenothiazine-N,5-dioxide (XIV).—A pale yellow solution of 9.36 g. (0.03 mole) of freshly distilled 10-(3-diethylaminopropyl)-phenothiazine, 75 ml. of ethanol and 6.9 g. (0.06 mole) of 30% hydrogen peroxide was refluxed for 17 hours and the solvent removed at the aspirator. The residual pale yellow oil solidified to a colorless mass on cooling. Recrystallization from acetone gave 8.85 g. (80%) of fine colorless granules of the sesquihydrate, m.p. 141–141.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot 1^1/_2H_2O$: C, 61.45; H, 7.33; N, 7.54. Found: C, 61.75; H, 7.26; N, 7.30.

The picrate crystallized from ethanol as fine yellow needles, m.p. 182–183°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot C_6H_3N_3O_7$: C, 52.35; H, 4.75. Found: C, 52.35; H, 4.92.

The pink, granular **hydrochloride**, m.p. 174–176°, crystallized from absolute ethanol.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot HCl$: C, 59.90; H, 6.62. Found: C, 59.48; H, 6.59.

Reductive Chlorination of 10-(3-Diethylaminopropyl)-phenothiazine-N-5-dioxide.—A mixture of 1.64 g. (4.42 millimoles) of the N,5-dioxide and 50 ml. of concentrated hydrochloric acid was refluxed for 47 hours and cooled. The precipitated green solid was extracted with 150 ml. of ethanol, the extract concentrated to 75 ml. and diluted with water. The product was recrystallized from 50% ethanol (Norit) to give 0.55 g. (46%) of light green flakes, m.p. 200–202°.

Anal. Calcd. for $C_{12}H_7Cl_2NS$: C, 53.74; H, 2.63. Found: C, 53.95; H, 2.85.

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p-Nitrophenyl p-Acylphenyl Sulfides and Related Compounds

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The preparation of *p*-(4-nitrophenylmercapto)-benzoic acid and the utilization of this compound in the synthesis of a number of unsymmetrically substituted phenyl sulfides and sulfones is described.

The main purpose of the work described in this paper was the development of a synthetic procedure for the preparation of disubstituted phenyl sulfides containing the nitro and acyl groups in the respective *para* positions. The convenient preparation of such compounds from a simple monosubstituted phenyl sulfide seems unlikely for the following reasons.

The acylation of *p*-nitrophenyl phenyl sulfide fails under ordinary Friedel–Crafts conditions which are successful with phenyl sulfide.[2] This may be so because of the ability of the sulfur atom to transmit the electron-withdrawing effect of the nitro substituent into the other phenyl group—a phenomenon for which there already exists spectroscopic evidence[3]—and thus the unsubstituted phenyl group becomes resistant to electrophilic substitution reactions. Experimental conditions designed to force the Friedel–Crafts reaction of *p*-nitrophenyl phenyl sulfide are being currently investigated.

The nitration of a mono-*p*-acylated phenyl sulfide also fails to give the desired *p'*-nitration product since the nitration reaction is accompanied by the oxidation of the sulfide function[4] as well as by the oxidative degradation of the acyl group. Thus, for example, from the nitration reaction of *p*-phenylmercaptostearophenone[5] there was isolated phenyl sulfoxide 4-carboxylic acid.

In view of the above-mentioned difficulties in the synthesis of *p*-(4-nitrophenylmercapto)-phenyl alkyl ketones from a monosubstituted phenyl sulfide, it was decided to prepare the desired compounds *via* *p*-(4-nitrophenylmercapto)-benzoic acid (I), and two reactions were considered for the preparation of this intermediate.

The first consisted of the reaction of *p*-mercaptobenzoic acid with *p*-chloronitrobenzene under alkaline conditions. While such a reaction was found[6] to take place when a reactive halide such as benzyl chloride is employed, it was possible in our case to isolate only unreacted *p*-chloronitrobenzene and phenyl disulfide *p,p'*-dicarboxylic acid. Apparently the nucleophilic displacement reaction on *p*-chloronitrobenzene is overshadowed by the extremely easy atmospheric oxidation of the *p*-mercaptobenzoate ion. It is noteworthy in this connection that Mann and Turnbull[7] prepared several sulfides by a synthesis similar to the one proposed here except that they first converted the mercaptobenzoic acids to the corresponding esters. The success in the reaction of *p*-chloronitrobenzene with the mercaptobenzoate ester may be explained on the ground that the more electronegative carbomethoxy group would tend to decrease the undesired oxidation as compared to that in the doubly negative charged mercaptobenzoate ion.

These considerations led to the investigation of the alternative synthetic process in which *p*-nitro-

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(4) B. Ciocca and L. Canonica, *Gazz. chim. ital.*, **76**, 113 (1946).

(5) H. H. Szmant and Mien Chao, unpublished work.

(6) W. S. Emerson and R. A. Heimsch, THIS JOURNAL, **73**, 1297 (1951).

(7) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 747 (1951).