

Monsanto Research Corporation, Boston Laboratory

1-Substituted Phenothiazine Derivatives (II)

Richard H. Nealey and John S. Driscoll

An improved synthesis of phenothiazine-1-carboxaldehyde and several new 1-substituted phenothiazine derivatives are reported. A 1-substituted thionine dye is described.

This work extends the chemistry of 1-substituted phenothiazines and thionine dyes previously reported (1,2). Phenothiazine derivatives have been intensively investigated owing to their properties as photopolymerization initiators, drugs and dyes. Relatively few 1-substituted phenothiazines are known.

In our previous work, 1-hydroxymethylphenothiazine (III) was prepared from 1-carboxyphenothiazine (II). All attempts to convert this alcohol to a halomethyl phenothiazine as a carbon chain-extension intermediate yielded only 1,1'-(oxydimethylene)diphenothiazine (IV). However, a successful scheme has now been devised (Table I) based on the reduction of the acid chloride, V.

1-Phenothiazinecarbonyl chloride (V) was obtained from the reaction of phenothiazine-1-carboxylic acid (II) with oxalyl chloride. The acid chloride (V) was converted to phenothiazine-1-carboxaldehyde via the Rosenmund reduction (5). The aldehyde was condensed with (carbethoxymethylene)triphenylphosphorane to yield ethyl 3-(1-phenothiazine)propenoate (XIII) in 49% yield, and with malonic acid to yield 3-(1-phenothiazine)propenoic acid (VII). The latter olefin was reduced via the triethylammonium salt to 3-(1-phenothiazine)propanoic acid (VIII).

Nitration of 3-(1-phenothiazine)propanoic acid in glacial acetic acid yielded 3-[1-(3,7-dinitrophenothiazine sulfoxide)]propanoic acid (IX). The assignment of the nitro groups to the 3,7-positions is based on the following evidence. Elemental analysis of the product was in agreement for dinitro substitution, as was the nmr data. The visible and ultraviolet spectrum of XII, the disodium salt of IX [λ max (log E) 499 (4.57), 231 (4.29), 349 (3.82) and 267 (4.07)] is very similar to that of the aci-nitro sodium salt of 3,7-dinitrophenothiazine sulfoxide, [λ max (log E), 483 (4.50), 343 (3.66), 262 (3.95) and 225 μ (4.30)] and also to that previously reported (2) for the disodium salt of 1-carboxy-3,7-dinitrophenothiazine sulfoxide [λ max (log E), 500 (4.47), 352 (3.87), 265 (4.01) and 225 μ (4.30)].

The synthesis of a thionine dye from a dinitrophenothiazine sulfoxide involves two steps. First, the nitro groups must be reduced to amino groups and the sulfoxide group

reduced to a sulfide. Second, the diamino leuco-base must be oxidized to the phenazathionium form. The first step is accomplished by hydrogenation at three atmospheres over platinum. The insolubility of IX in methanol was overcome by the use of the triethylammonium salt. The reduction proceeded smoothly and the clear solution of the unisolated diamino leuco-base X, obtained after filtration, began to turn blue immediately upon exposure to air.

The oxidation step was facilitated by the slow bubbling of oxygen through the cold methanol solution. The desired product was deposited as shiny green crystals. The product, 3-[1-(3,7-diaminophenazathionium hydroxide)]propanoic acid, inner salt, XI, is a thionine type dye with a visible and ultraviolet spectrum [λ max (log E), 602 (4.66), 284 (4.53)] very similar to that of thionine [λ max (log E), 599 (4.56), 282 (4.48)].

This work has provided an entry into the phenothiazine system substituted in the 1-position by various alkyl groups. The straight-forward synthesis of phenothiazine-1-carboxaldehyde is an improvement of the only other reported synthesis of this compound (4). This work also indicated that the presence of an alkyl group in the 1-position does not alter the position of nitration of the phenothiazine ring relative to unsubstituted phenothiazine.

EXPERIMENTAL

Melting points are corrected. Elemental analyses were carried out by Galbraith Laboratories. Infrared spectra were determined in potassium bromide pellets on a Perkin-Elmer Model 30 spectrophotometer. Visible and ultraviolet spectra were recorded with a Cary Model 14 spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained with a Varian A-60 spectrometer.

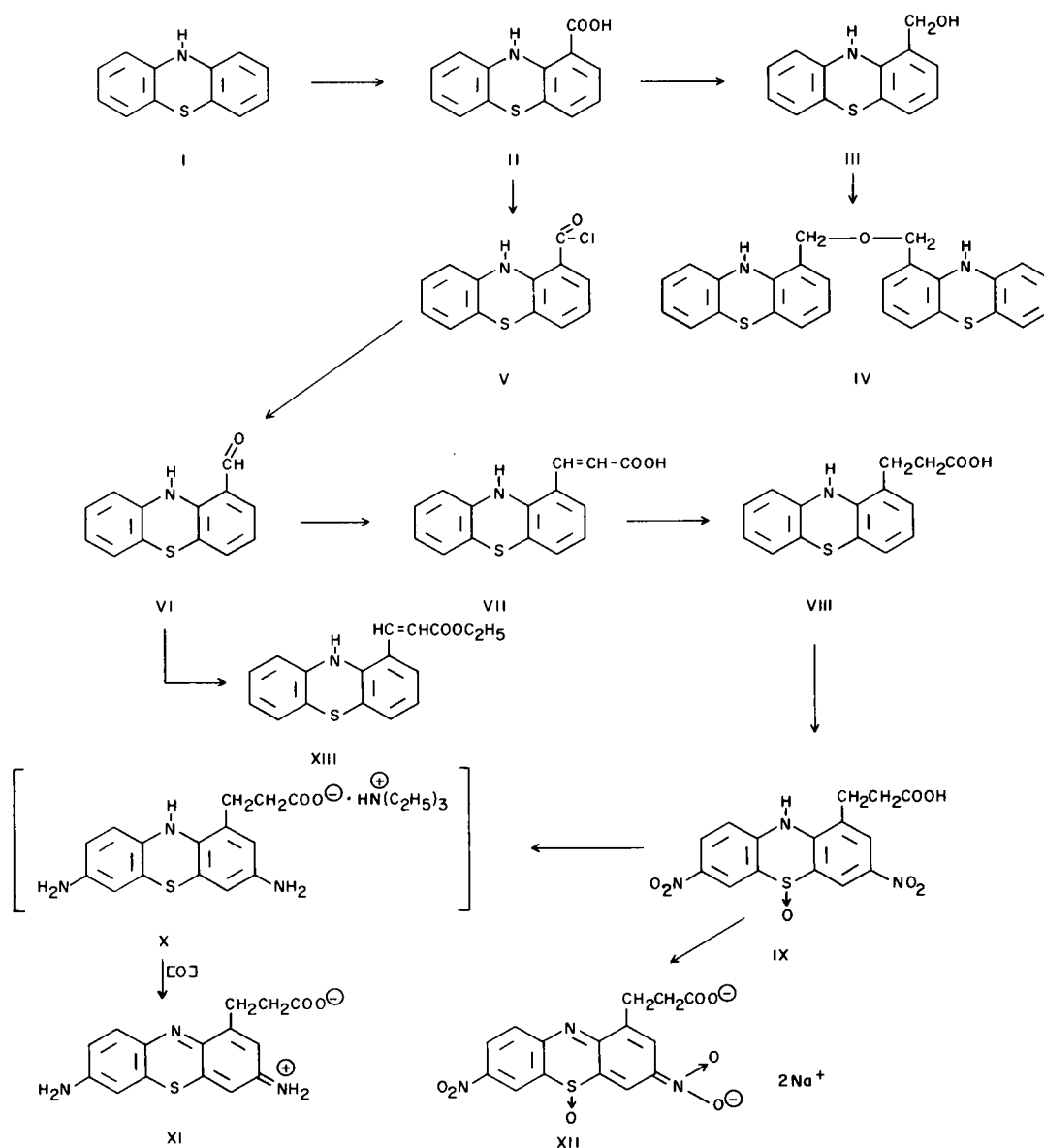
1-Carboxyphenothiazine (II).

The procedure of Gilman *et al.*, gave a 64% yield of II, m.p. 267-268° (dec.) [lit (3) m.p. 264-264.5°] on a 0.2 molar scale.

Phenothiazine-1-carbonyl Chloride (V).

Oxalyl chloride (20 ml., 0.24 mole) was added to a suspension of 1-carboxyphenothiazine (18.26 g., 0.075 mole) in 200 ml. of dry benzene. The reaction mixture was refluxed for 4 hours with stirring during which time the solution became dark red. The mixture was left overnight (drying tube-Drierite). The solvent and excess oxalyl chloride were evaporated *in vacuo*. The resulting

TABLE I



semisolid was triturated with 150 ml. of hexane at 0° and filtered. The crude acid chloride was stored in a vacuum desiccator over Drierite until it was recrystallized. Recrystallization was accomplished by dissolving the crude product in refluxing hexane (180 ml./g.) with charcoal (1 g./20 g. crude product) and filtering the hot solution. The hexane solution was then cooled to -80° in a dry ice-acetone bath and filtered to give a bright red solid. Drying the product at 0.5 mm/ 25° gave 13.88 g. (70%) of red crystals (m.p. $82-86^\circ$).

A small sample of once recrystallized product was recrystallized a second time. This raised the melting point of A-2 to $94-95^\circ$; ν max 1700 (C=O); 3300 (NH). N.m.r. in deuteriochloroform (6) showed peaks at 6.4-7.9 m [6] and 7.80 d [1] (aromatic protons and 9.25 exchangeable [1] (NH).

Anal. Calcd. for $C_{13}H_8ClNOS$: C, 59.65; H, 3.08; S, 12.25;

Cl, 13.55. Found: C, 59.62; H, 3.13; S, 12.42; Cl, 13.67. Phenothiazine-1-carboxaldehyde (VI).

Phenothiazine-1-carboxyl chloride (25.2 g., 0.097 mole) was dissolved in 500 ml. of dry toluene in a 1-liter, 3-necked Morton flask equipped with mechanical stirrer, condenser and drying tube, and hydrogen inlet (6 mm glass tubing). Palladium on barium sulfate (5%) (6.25 g.) was added, and a steady stream of hydrogen was passed through the rapidly stirred solution. An oil bath maintained at 115° was used to heat the mixture. Hydrogen chloride was detected in the off-gases (moist litmus) almost immediately. Hydrogen gas was passed through the refluxing mixture for 4 hours. At this time, no hydrogen chloride could be detected in the vent gases. The bath was removed and the mixture allowed to cool to room temperature. The catalyst was removed by filtration and washed

with 100 ml. benzene. The benzene washings and toluene filtrate were combined and the solvent was removed *in vacuo*. A thick red oil was obtained. This oil was redissolved in a minimum amount of benzene and chromatographed over 400 g. of silica gel packed in 1/1 hexane/benzene solution. The product was eluted with benzene. After a yellow forerun of about 200 ml., three cuts of 500 ml. each were taken that by TLC contained only the aldehyde (VI). These were combined and taken to dryness to yield 17.83 g. (81%) of VI [m.p. 81-83°, lit (4) m.p. 80-81°].

This reaction has been repeated several times with an average

yield of 80%; ν max 3280 (NH); 1660 $\overset{\text{H}}{\text{C}}\text{(O)}$. N.m.r. spectrum in deuteriochloroform (6) showed peaks at 6.5-7.4 m [7.0] (aromatic); 9.77 s [0.8] (aldehyde proton) and 10.08 s [0.9] (NH).

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{NOS}$: C, 68.70; H, 3.99; N, 6.16; S, 14.11. Found: C, 68.61; H, 4.23; N, 5.89; S, 13.86.

3-(1-Phenothiazine)propenoic Acid (VII).

A solution of phenothiazine-1-carboxaldehyde (22.8 g. 0.10 mole), malonic acid (20.8 g., 0.20 mole) and piperidine (4 ml.) in 100 ml. of pyridine was heated with stirring on a steam bath. After 4 hours, carbon dioxide evolution had ceased. The mixture was cooled to room temperature and poured into a mixture of 200 g. of ice and 200 ml. of concentrated hydrochloric acid with rapid stirring. The resulting precipitate was filtered, washed with 2 x 100 ml. of distilled water and dried at 0.5 mm/25° for 24 hours to yield 25.77 g. of an orange solid. This was pulverized and extracted for 48 hours with 1 liter of hexane in a Soxhlet apparatus. The residue in the thimble was dried at 80°/15 mm for 2 hours to give 13.22 g. of orange product, m.p. 210° (dec.). The hexane extracts were taken to dryness to yield 8.41 g. of recovered 1-phenothiazine-aldehyde. The yield of VII based on unrecovered aldehyde was 77%. The analytical sample was twice recrystallized from absolute ethanol (charcoal) and dried at 100°/0.5 mm [m.p. 273-274° dec.; ν max 3380 (NH), 1685 (CO), 1616, 1600, 1563 (C=C). N.m.r. spectrum in deuteropyridine (6) shows peaks 6.7-7.5 m [8] (aromatic ring protons), 8.50 d [0.9] and 6.76 d (olefinic protons), 9.20 s [0.7] exchangeable (NH) and 11.7 s [1.1] exchangeable with deuterium oxide (carboxyl proton). The large coupling constant, $J_{\text{H}} = 16$ cps indicates a trans structure for this acid.

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{NO}_2\text{S}$: C, 66.89; H, 4.12; N, 5.20; S, 11.91. Found: C, 66.83; H, 4.15; N, 5.08; S, 12.06.

Ethyl 3-(1-Phenothiazine)propenoate (XIII).

Phenothiazine-1-carboxaldehyde (4.54 g., 0.02 mole) and (carbethoxymethylene)triphenylphosphorane (7.66 g., 0.022 mole) were dissolved in 100 ml. of benzene and refluxed under a nitrogen atmosphere for 8 hours. The resultant red solution was filtered and chromatographed over 100 g. of silica gel and eluted with benzene. The first six fractions (approximately 400 ml. each) contained the desired product, as determined by TLC on silica gel/benzene. They were combined and taken to dryness. The resulting dark solid was recrystallized from 300 ml. of hexane (charcoal) to give yellow crystals, which were dried at 70°/15 mm for 4 hours to yield 2.92 g. (49%) of product, m.p. 93-95°. The analytical sample was dried at 0.05 mm overnight; ν max 3333 (NH), 1695 (C=O), 1633 (C=C). N.m.r. spectrum in deuteriochloroform (6) shows peaks 1.32 t [2.9] and 4.28 q [1.9] (ethyl ester group); 6.4 to 7.3 m [9.0] (aromatic plus one olefinic proton) and N-H proton and 7.8 d [1.0] (remaining olefinic proton).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.58; H, 5.01; N, 4.81; S, 10.80.

3-(1-Phenothiazine)propenoic Acid (VIII).

Triethylamine (2.4 g., 24 mmoles) was added to a suspension of 3-(1-phenothiazine)propenoic acid (5.4 g., 20 mmoles) in 150 ml. of methanol. After stirring 1 hour, the orange solution was filtered. Platinum oxide (Adams Catalyst, 0.25 g.) was added and the mixture was hydrogenated at 50 psig of hydrogen on a Parr apparatus at 25° for 48 hours. The resulting straw colored solution was filtered through double filter papers to remove the catalyst. The solvent was removed *in vacuo* and the resultant yellow oil was dissolved in 200 ml. of water. Hydrochloric acid (1 N) was added dropwise with stirring until the solution was acid to litmus. The resulting precipitate was filtered, washed with 2 x 100 ml. of water and dried at 80°/15 mm to give 4.50 g. of grey-green solid, m.p. 190-195°. This material was recrystallized from methanol (43 ml./g.) with charcoal by the addition of water to the hot filtrate until cloudiness just persisted. Slow cooling yielded 3.55 g. (65%) of straw colored crystals, m.p. 206-208° dec. The analytical sample was dried at 100°/0.5 mm for 16 hours; ν max 1709 (CO), 3378 (NH). The n.m.r. spectrum in deuteropyridine (6) shows peaks at 2.65-3.3 m [3.9] (-CH₂-CH₂-of side chain), 6.65-7.15 m [7.0] (aromatic protons), 8.26 s [0.9] (NH) and 10.9 s [1.7] (COOH).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.33; H, 4.90; N, 5.10; S, 11.95.

3-[1-(3,7-Dinitrophenothiazine Sulfoxide)]propenoic Acid (IX).

A mixture of glacial acetic acid (250 ml.) and VIII (5.4 g., 0.02 mole) was heated on a steam bath for 1 hour in a 500 ml., 3-neck flask equipped with a mechanical stirrer, reflux condenser (Drierite tube) and dropping funnel.

The solution was allowed to remain at room temperature overnight and was then cooled with an ice bath whose temperature was maintained at 10-12°. Concentrated nitric acid (38 ml., 38.2 g., 0.61 mole) was added dropwise to the stirred, cooled suspension over a period of 25 minutes. When the addition was complete, the dark red mixture was stirred for 1.5 hours at 10-15°, for 1 hour at ambient temperature and then allowed to stand for 1 hour. The mixture was poured into three liters of distilled water (stirring) and left standing for three days.

The resulting brown precipitate was filtered and washed with 2 x 150 ml. of water. The red solid was twice stirred with 100 ml. of acetone, filtered, and dried at 80°/15 mm to give 3.73 g. (49%) of crude yellow product, m.p. 243° dec. Two reprecipitations from 5% sodium hydroxide (15 ml./g.) with 1.5 N hydrochloric acid (22 ml./g.) yielded a yellow solid, m.p. 240° dec. The analytical sample was dried at 100°/0.5 mm for 16 hours; λ max (0.1 N sodium hydroxide), 499 m μ (4.57), 231 m μ (4.29), 349 m μ (3.82) and 267 m μ (4.07); ν max 1715 (CO), 1025-1010 (S \rightarrow O), 1500 and 1340-1310 (NO₂) 743 (NO₂). N.m.r. spectrum in a mixture of deuterated pyridine and deuterated DMSO (6) shows peaks at 3.00 τ and 3.4 τ [4] (methylene protons), 8.0-9.2 m [4.9] (aromatic protons).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_7\text{S}$: C, 47.74; H, 2.94; N, 11.14; S, 8.50. Found: C, 47.71; H, 3.04; N, 10.97; S, 8.42.

3-[1-(3,7-Diaminophenazathionium Hydroxide)]propenoic Acid, Inner Salt (XI).

Compound IX (1.89 g., 5 mmoles) was suspended in 100 ml. of methanol and triethylamine (1.00 g., 10 mmoles) was added with stirring. After 1 hour, the solution was filtered, the filter paper was washed with 50 ml. methanol, and the combined filtrate and washings were placed in a hydrogenation bottle. Platinum oxide catalyst (0.20 g.) was added, and the mixture was hydrogenated at 50 psig on a Parr apparatus at 25° for 4 hours. A total of 3.0 lb./in.²

of hydrogen gas was taken up (3.2 lb./in.² theoretical). The clear yellow solution was filtered through double filter papers to remove the catalyst. The filtrate immediately turned deep blue. The combined filtrates from four reductions on the same scale as above were combined and placed in a 1-liter flask equipped with a fritted gas inlet tube, condenser and drying tube. Oxygen gas was bubbled gently through the solution for 8 hours each day. By the third day, a green solid had deposited on the inner walls of the flask. After 5 days, the green crystals were filtered and dried to give 3.71 g. of product, m.p. 180-183° dec. The methanol filtrate was replaced in the flask and oxygen was added for another 7 days. A second crop of green crystals [1.00 g., m.p. 183-187° dec., was obtained. The total yield of product was 4.71 g. (78.5%). The sample sent for analysis was taken from the 1st crop of material. It was dried at 100°/0.5 mm overnight.

Anal. Calcd. for C₁₅H₁₃N₃O₂S: C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found: C, 59.81; H, 4.56; N, 14.07; S, 10.85.

Samples of XI exhibited erratic solubility behavior in methanol and could be completely dissolved only by the addition of a small amount (0.25 ml.) of 6 N hydrochloric acid to the methanol solution; λ max (MeOH), 602 m μ (4.66), 284 m μ (4.53).

REFERENCES

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