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SOME DERIVATIVES OF PHENOTHIAZINE. II.[1]

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This article reports the preparation of some additional derivatives of phenothiazine needed in a systematic study of heterocyclic compounds of potential antioxidant activity. Derivatives with substituents in positions 1, 2, and 4 are described in the experimental part.

3-Formyl-10-methylphenothiazine (1) was used as a starting material for a number of 10-methyl-3-phenothiazinyl derivatives with a carbon side chain. Its oxime was dehydrated with acetic anhydride to 3-cyano-10-methylphenothiazine which was hydrolyzed to 3-carboxy-10-methylphenothiazine. This acid could also be obtained by oxidation of the aldehyde with silver oxide. Reduction of the aldehyde with lithium aluminum hydride led to 3-(10-methylphenothiazinyl)methanol. A Knoevenagel reaction of the aldehyde with malonic acid gave β-[3-(10-methylphenothiazinyl)]acrylic acid which could be reduced to β-[3-(10-methylphenothiazinyl)]propionic acid, and oxidized with alkaline permanganate to 3-carboxy-10-methylphenothiazine-5,5-dioxide. Condensation of 3-formyl-10-methylphenothiazine with nitromethane yielded 1-nitro-2-[3-(10-methylphenothiazinyl)]ethene.

A Friedel and Crafts reaction with 10-methylphenothiazine and acetyl chloride furnished 3-acetyl-10-methylphenothiazine. Its structure follows from its oxidation to 3-carboxy-10-methylphenothiazine-5,5-dioxide.

At the time this work was carried out the only 4-substituted phenothiazine derivative on record was 4-carboxy-10-ethylphenothiazine which Gilman, Van Ess, and Shirley (2) had obtained in low yield by carbonating lithium 10-ethylphenothiazine. Only very recently an abstract of a thesis by Nelson (3) was published in which the carbonation of 10-ethylphenothiazine-5-oxide to the same acid in much higher yield was revealed. Since we had been unaware of this thesis, we undertook a total synthesis of derivatives of 4-carboxyphenothiazine. 2-Bromo-3-nitrobenzoic acid was converted to its anilide, and this was condensed in alkaline medium with 2-bromobenzenethiol. The resulting 2-bromo-2′-nitrodiphenylsulfide-6′-carbanilide was reduced to the 2′-amino derivative, and this was dehydrobrominated to phenothiazine-4-carbanilide under the conditions of the Ullmann reaction.

EXPERIMENTAL[2]

Purification of phenothiazine. Practical grade phenothiazine (Eastman Kodak) was purified by distillation in an electrically-heated distilling apparatus at about 15 mm. pressure. The pale yellow product, m.p. 180–182°, could be used directly for the syntheses de-

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[1] Paper I by Burger and Clements, *J. Org. Chem.*, **19**, 1113 (1954). 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] All melting points are corrected. Microanalyses by Miss Patricia L. Paynter.

scribed. The melting point of the pale yellow leaflets can be raised to 184–185° by two recrystallizations from hexane-acetone (5:1) with the aid of Norit, or better by sublimation at atmospheric or reduced pressure.

10-Methylphenothiazine. As a substantial improvement over methods previously reported, 20 g. (0.5 mole) of sodamide was added in portions to a stirred refluxing solution of 100 g. (0.5 mole) of phenothiazine in 300 ml. of dry xylene. After refluxing the mixture for five hours, 71 g. (0.5 mole) of methyl iodide was dropped into the yellow suspension. As the solid slowly became white refluxing was continued for three hours, the mixture was filtered hot, the inorganic salt washed with hot xylene, and the solvent distilled. The residue solidified on cooling. Recrystallization from ethanol (Norit) gave 80 g. (80%) of almost colorless needles, m.p. 99–100°.

10-Methylphenothiazine-3-aldoxime. A mixture of 10 g. (0.042 mole) of 3-formyl-10-methylphenothiazine (1) and 10 g. (0.143 mole) of hydroxylamine hydrochloride was warmed with 50 ml. of pyridine for 30 minutes. The mixture was poured into water and the yellow-green oil crystallized from 70% ethanol. Fine yellow granules, m.p. 160–161.5°, were obtained in quantitative yield.

Anal. Calc'd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72.

Found: C, 65.30; H, 4.85.

Reduction of the aldoxime with lithium aluminum hydride gave a yellow gum which could not be characterized.

3-(10-Methylphenothiazinyl)methanol. A solution of 4.82 g. (0.02 mole) of 3-formyl-10-methylphenothiazine in 300 ml. of dry ether was dropped into a well-stirred suspension of 0.76 g. (0.02 mole) of lithium aluminum hydride in 100 ml. of dry ether at such a rate as to maintain gentle reflux. The resulting suspension was stirred for one hour after addition was complete, and decomposed with a little water followed by 100 ml. of 10% sulfuric acid. The ether layer was dried over sodium sulfate, the solvent removed, and the residue recrystallized from 70% ethanol (Norit). The soft pale yellow needles, m.p. 130.5–131.5°, weighed 4.2 g. (90%).

Anal. Calc'd for $C_{14}H_{13}NOS$: C, 69.10; H, 5.38.

Found: C, 68.96; H, 5.58.

β-[3-(10-Methylphenothiazinyl)]acrylic acid. A mixture of 48.2 g. (0.2 mole) of 3-formyl-10-methylphenothiazine, 39.6 g. (0.38 mole) of malonic acid, 155 ml. (0.2 mole) of pyridine, and 4 ml. of piperidine was warmed at 90° for 3.5 hours and refluxed for 30 minutes. During this process the clear solution, yellow at first, became reddish and orange; it was cooled, poured into a stirred mixture of 300 g. of crushed ice and 200 ml. of concentrated hydrochloric acid, and the precipitated orange solid was filtered, washed with dilute hydrochloric acid, and then with water. Recrystallization from ethanol (Norit) gave 48.0 g. (86%) of fine, light, orange needles, m.p. 230–230.5°.

Anal. Calc'd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62.

Found: C, 67.87; H, 4.92.

β-[3-(10-Methylphenothiazinyl)]propionic acid. A suspension of 10.2 g. (0.036 mole) of β-[3-(10-methylphenothiazinyl)]acrylic acid and 1.0 g. of platinum oxide catalyst in 250 ml. of acetone-ethanol (4:1) was shaken for 24 hours under a pressure of three atmospheres of hydrogen. The mixture was filtered, the filtrate concentrated to 20 ml., and the product was precipitated dropwise with water. Recrystallization from 50% ethanol gave 9.5 g. (95%) of colorless leaflets, m.p. 144.5–145.5°.

Anal. Calc'd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30.

Found: C, 67.30; H, 5.20.

The *methyl ester* was obtained in 90% yield by refluxing the acid with methanol in the presence of sulfuric acid for 1.5 hours. The mixture was worked up, the residual yellow oily methyl β-[3-(10-methylphenothiazinyl)]propionate solidifying on cooling. Recrystallization from ethanol (Norit) gave colorless flakes, m.p. 58.5–59.5°.

Anal. Calc'd for $C_{17}H_{17}NO_2S$: C, 68.19; H, 5.72.

Found: C, 67.97; H, 5.51.

The *hydrazide* was obtained quantitatively by refluxing an ethanolic solution of the ester with excess 64% hydrazine hydrate for 28 hours. The product, which crystallized on cooling, was recrystallized from ethanol as glittering colorless plates, m.p. 163–164°.

Anal. Calc'd for $C_{16}H_{17}N_3OS$: C, 64.20; H, 5.72.
Found: C, 64.43; H, 5.50.

1-Nitro-2-[3-(10-methylphenothiazinyl)]ethene. A mixture of 2.5 g. (0.01 mole) of 3-formyl-10-methylphenothiazine, 1.0 g. of ammonium acetate, 2.5 ml. of nitromethane and 20 ml. of glacial acetic acid was refluxed for two hours and poured into 500 ml. of ice-water. The precipitated lumpy solid was washed repeatedly with water and was recrystallized from 70% ethanol. The glittering maroon needles, m.p. 134–135°, weighed 0.7 g. (25%).

Anal. Calc'd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.26.
Found: C, 63.44; H, 4.35.

Treatment of an ether solution of this compound with lithium aluminum hydride remained inconclusive.

Phenothiazine-1-carboxhydrazide. 1-Carboxyphenothiazine was prepared by the method of Gilman, Shirley, and Van Ess, but in 89% yield, m.p. 264°. A mixture of 17.0 g. (0.07 mole) of this acid, 500 ml. of methanol, and 40 ml. of concentrated sulfuric acid was refluxed with stirring for 48 hours. Excess methanol was distilled off, and the residual oil was extracted with ether, washed with potassium carbonate solution, dried over sodium sulfate, and the ether was distilled. Crystallization of the residue from ethanol gave 14.4 g. (80%) of glittering orange leaflets, m.p. 114.5–115.5°. This compound had been prepared in 32% yield, m.p. 113–113.5°, by the action of methyl sulfate on an alkaline solution of the acid (4).

The hydrazide was prepared by refluxing an ethanolic solution of the ester with excess 64% hydrazine solution for 28.5 hours. The product precipitated on evaporation of about one-half of the solvent and cooling. Recrystallization from 50% ethanol gave glistening yellow flakes in quantitative yield, m.p. 148–149.5°.

Anal. Calc'd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31.
Found: C, 60.67; H, 4.53.

3-Cyano-10-methylphenothiazine. A mixture of 2.56 g. (0.01 mole) of 10-methylphenothiazine-3-aldoxime and 15 ml. of acetic anhydride was refluxed for two hours and poured into 75 ml. of ice-water. A dark oil precipitated and crystallized on further cooling. Recrystallization from 70% ethanol (Norit) gave 2.2 g. (92%) of fine yellow granules, m.p. 121–122°.

Anal. Calc'd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23.
Found: C, 70.25; H, 4.17.

3-Carboxy-10-methylphenothiazine. (*a*). A suspension of 1.20 g. (5 millimoles) of 3-formyl-10-methylphenothiazine and 1.47 g. (12 millimoles) of moist silver oxide in 100 ml. of ethanol was refluxed with stirring for five hours, filtered hot, and the residue was washed well with water. The red filtrate was evaporated to a dark oil which was taken up in ether, and extracted with 10% sodium hydroxide solution; the alkaline extract was acidified and the precipitated solid was recrystallized from ethanol. The yield of fine yellow granules, m.p. 244–245°, was 0.35 g. (30%).

Anal. Calc'd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31.
Found: C, 65.12; H, 4.41.

(*b*). A solution of 1.1 g. (4.6 millimoles) of 3-cyano-10-methylphenothiazine in 50 ml. of ethanol was refluxed with 10 ml. of 20% sodium hydroxide solution for seven hours. The hot mixture was diluted with 10 ml. of water, the ethanol removed, the solution was acidified and the precipitated fine yellow granules (1.1 g., 92%) were recrystallized from ethanol to m.p. 248–249°. A mixture melting point with a sample prepared by method *a* was 245–248°. The nitrile could not be hydrolyzed with boiling hydrochloric acid in six hours.

3-Carboxy-10-methylphenothiazine-5,5-dioxide. A solution of 0.5 g. (1.67 millimoles) of β-[3-(10-methylphenothiazinyl)]acrylic acid in excess dilute potassium hydroxide was stirred with a solution of 0.8 g. of potassium permanganate at 90° for 30 minutes, filtered hot, and the residue was washed with water. The filtrate was acidified with hydrochloric acid and the precipitated solid was recrystallized from 70% ethanol. A yield of 0.3 g. (62%) of fine yellow flakes, m.p. 287.5–288°, was obtained.

Anal. Calc'd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83.
Found: C, 58.11; H, 3.83.

3-Acetyl-10-methylphenothiazine. A stirred solution of 10.65 g. (0.05 mole) of 10-methylphenothiazine and 4.0 g. (0.05 mole) of acetyl chloride in 200 ml. of carbon disulfide was treated at 25° with 20.0 g. (0.15 mole) of anhydrous aluminum chloride in small portions. The mixture quickly turned red and began to boil. It was refluxed with stirring until no further hydrogen chloride was evolved (22.5 hours). The carbon disulfide solution was decanted from a dark oily residue and evaporated whereby 6.7 g. of unchanged 10-methylphenothiazine was recovered. The insoluble oily complex was decomposed with one liter of acidified ice-water. The precipitated yellow solid weighed 3.35 g. (71% based on unrecovered starting material), m.p. 182–187°. Recrystallization of a sample from ethanol-glacial acetic acid (1:1) gave fine yellow needles, m.p. 205–206°, of the hemihydrate of the ketone.

Anal. Calc'd for $C_{15}H_{13}NOS \cdot \frac{1}{2}H_2O$: C, 68.15; H, 5.34.
Found: C, 68.15; H, 5.00.

The *oxime* was obtained as the monohydrate from 50% ethanol as a yellow powder, m.p. 264–265° (dec.).

Anal. Calc'd for $C_{15}H_{14}N_2OS \cdot H_2O$: C, 62.47; H, 5.59.
Found: C, 62.37; H, 5.24.

The ketone was oxidized to 3-carboxy-10-methylphenothiazine-5,5-dioxide with alkaline potassium permanganate as described for the oxidation of β-[3-(10-methylphenothiazinyl)] acrylic acid. The product, obtained as small yellow flakes, melted at 286–287°. A mixture melting point with a sample prepared from the acrylic acid was 286–287°.

4-Benzyloxydiphenylamine. Following the general procedure by Houston (5) a mixture of 7.40 g. (0.04 mole) of *p*-hydroxydiphenylamine, 5.06 g. (0.04 mole) of benzyl chloride, and 36 ml. (0.06 eq.) of 10% ethanolic potassium hydroxide was refluxed with stirring for three hours, diluted with water, acidified, and cooled to 0°. The precipitated orange solid was recrystallized from ethanol (Norit) and gave 6.4 g. (60%) of glittering silvery plates, m.p. 94.5–95.5°.

Anal. Calc'd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22.
Found: C, 82.75; H, 6.51.

3-Benzyloxyphenothiazine. A mixture of 4.13 g. (0.015 mole) of 4-benzyloxydiphenylamine, 0.96 g. (0.031 g.at.) of powdered sulfur, and 0.1 g. of iodine was fused at 160–170° for one hour. The cooled melt was ground to a fine olive-green powder and extracted exhaustively with hexane. The solid from the extract was recrystallized from hexane containing a little benzene and gave 2.3 g. (50%) of a light tan powder which became purple on standing; m.p. 144–147°.

Anal. Calc'd for $C_{19}H_{15}NOS$: C, 71.00; H, 4.70.
Found: C, 70.73; H, 4.57.

2-Bromo-3-nitrobenzoyl chloride. This compound was prepared from 49.2 g. (0.2 mole) of 2-bromo-3-nitrobenzoic acid (6) and 41.6 g. (0.2 mole) of phosphorus pentachloride in the usual manner and was recrystallized from 800 ml. of hexane. The yield of colorless needles, m.p. 66–66.5°, was 50.6 g. (96%).

Anal. Calc'd for $C_7H_3BrClNO_3$: C, 31.79; H, 1.14.
Found: C, 32.00; H, 1.15.

2-Bromo-3-nitrobenzamide. A stirred mixture of 2.65 g. (0.01 mole) of 2-bromo-3-nitrobenzoyl chloride and 5 g. (0.05 mole) of finely ground ammonium carbonate was warmed at 90° for 45 minutes, extracted with water, and filtered. The residual solid was recrystallized from 30% ethanol and gave 2.4 g. (98%) of colorless blades, m.p. 170–171°.

Anal. Calc'd for $C_7H_5BrN_2O_3$: C, 34.31; H, 2.06.
Found: C, 34.17; H, 1.87.

2-Bromo-3-nitrobenzanilide. This compound was prepared from 26.45 g. (0.1 mole) of 2-bromo-3-nitrobenzoyl chloride and 18.6 g. (0.2 mole) of aniline. Recrystallization from 70% ethanol gave 31.75 g. (99%) of fine yellow needles, m.p. 162.5–163.5°.

Anal. Calc'd for $C_{13}H_9BrN_2O_3$: C, 48.62; H, 2.82.

Found: C, 48.94; H, 2.95.

2-Bromo-3-aminobenzamide. Reduction of the nitro derivative with stannous chloride in glacial acetic acid solution gave a 54% yield of colorless needles, m.p. 140° (after recrystallization from 50% ethanol).

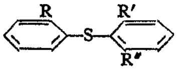
Anal. Calc'd for $C_{13}H_{11}BrN_2O$: C, 53.62; H, 3.81.

Found: C, 53.61; H, 3.85.

Nitrodiphenyl sulfide derivatives. According to the general direction by Bost, Turner, and Norton (7) ethanolic solutions of *o*-bromobenzenethiol (8) or commercial *o*-aminobenzenethiol were neutralized with 13% sodium hydroxide solution and added to ethanolic solutions

TABLE I

DERIVATIVES OF DIPHENYL SULFIDE

			M.P. °C.	APPEARANCE AND (SOLVENT OF CRYSTALLIZATION)	YIELD, %	MOLECULAR COMPOSITION	ANALYSIS			
							Calc'd		Found	
R	R′	R″					C	H	C	H
Br	CO_2H[a]	NO_2	192–193	Yellow (MeOH-H_2O)	92.5	$C_{13}H_8BrNO_4S$	44.08	2.28	44.03	2.40
Br	CO_2CH_3	NO_2	120–121[b]	Yellow needles (EtOH)	92	$C_{14}H_{10}BrNO_4S$	45.66	2.74	45.76	2.90
Br	$CONHC_6H_5$	NO_2	169–170	Yellow (70% EtOH)	86	$C_{19}H_{13}BrN_2O_3S$	53.16	3.05	53.31	3.12
NH_2	CO_2CH_3	NO_2	98–99	Orange clusters (EtOH)	86	$C_{14}H_{12}N_2O_4S$	55.25	3.98	55.05	3.80
NH_2	$CONHC_6H_5$	NO_2	172–173	Orange needles (75% EtOH)	83	$C_{19}H_{15}N_3O_3S$	62.45	4.14	62.54	4.20
Br	CO_2CH_3	NH_2	90–91	Needles (70% EtOH)	95	$C_{14}H_{12}BrNO_2S$	49.71	3.58	49.88	3.81
Br	$CONHC_6H_5$	NH_2	180–181	Colorless (EtOH)	90	$C_{19}H_{15}BrN_2OS$	57.15	3.79	56.85	3.80
NH_2	CO_2CH_3	NH_2		Oil[c]	100					
NH_2	$CONHC_6H_5$	NH_2	152–153	Colorless (C_6H_6)	100	$C_{19}H_{17}N_3OS$	68.04	5.11	68.28	5.10

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[a] This acid was obtained from one run using two equivalents of sodium hydroxide.

[b] This ester was also obtained from the acid[a] with methanol and dry HCl in 82% yield, m.p. 101.5–102.5° (from methanol). This isomorphous form (*Anal.* Found: C, 45.68; H, 2.56) could be converted to the higher-melting form (m.p. 120–121°) in methanol by seeding.

[c] A colorless hydrochloride salt, m.p. 188–190° (dec.) appeared to be a mixture of the mono- and di-hydrochlorides. *Anal.* Calc'd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86. Calc'd for $C_{14}H_{16}Cl_2N_2O_2S$: C, 48.42; H, 4.64. Found: C, 49.96, 50.15; H, 4.89, 4.93.

of the respective reagents (methyl 2-bromo-3-nitrobenzoate (9), or 2-bromo-3-nitrobenzanilide) at 40°. The mixtures were refluxed for 15 minutes and filtered hot; they deposited the reaction products on cooling or diluting with a little water.

Aminodiphenyl sulfide derivatives. (a). A solution of the nitro derivative in ethanol-acetone (10:1) was hydrogenated under 3 atmospheres of hydrogen over Raney nickel for 30 minutes, and the filtered solution was concentrated.

(b). A solution of the nitro compound in glacial acetic acid was refluxed with stannous chloride for three hours, diluted with much water, and made strongly alkaline with potassium hydroxide solution. The amines were filtered and purified (Table I).

2,2'-Bis-(o-bromophenylthio)-3,3-bis-hydroxymethyleneazobenzene. A dry ether solution of 3.5 g. (9.5 millimoles) of 2-bromo-2'-nitro-6'-carbomethoxydiphenyl sulfide was added to a stirred suspension of 0.95 g. (0.025 mole) of lithium aluminum hydride in 50 ml. of ether. After refluxing for 45 minutes, the mixture was decomposed with water and 50 ml. of 10% sulfuric acid and made basic with potassium hydroxide solution. The residue from the ether layer gave 0.6 g. (21%) of a red solid which crystallized from 70% ethanol, m.p. 179–180°.

Anal. Calc'd for $C_{26}H_{20}Br_2N_2O_2S$: C, 50.66; H, 3.27.
Found: C, 50.38; H, 3.37.

From the mother liquors, 0.9 g. of starting material was recovered unchanged.

Phenothiazine-4-carbanilide. A mixture of 2.0 g. (5 millimoles) of 2-amino-2'-bromodiphenylsulfide-6-carbanilide, 1.0 g. (1.01 mole) of anhydrous sodium carbonate, 0.5 g. of copper bronze, and 100 ml. of diphenyl ether was refluxed with stirring for 48 hours. It was filtered hot, the residue was washed with hot solvent, and the filtrate was distilled under reduced pressure. The dark oil remaining after removal of the solvent was extracted with ten 25-ml. portions of hot acetone, cleared with Norit, and the acetone was removed. The residual dark oil was triturated with ether and gave 0.5 g. of a green solid which after two crystallizations from 50% ethanol appeared as a reddish powder, m.p. 250–252° (dec.).

Anal. Calc'd for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43.
Found: C, 72.36; H, 3.95.

SUMMARY

A number of 3-substituted derivatives of 10-methylphenothiazine have been synthesized from 3-formyl-10-methylphenothiazine. The total synthesis of phenothiazine-4-carbanilide, and several intermediates is reported.

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