[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FISK UNIVERSITY]

Ring Derivatives of Phenothiazine. The Synthesis of 1-Substituted Phenothiazines by Thionation

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The preparation of some 1-derivatives of phenothiazine by thionation and their 10-acetyl derivatives are described.

The preparation of phenothiazines by thionation of diarylamines was discussed recently as a part of the review of the chemistry of phenothiazines.[2] The thionation reaction is being systematically studied in this laboratory, with particular emphasis on the use of catalysts, solvents, and temperature, and this paper describes some observations on the results obtained using solvents in the preparation of 1-substituted phenothiazines.

The comparison of the thionation reaction of diphenylamine in various solvents showed that pyridine and dimethylformamide were completely unsatisfactory, benzene and naphthalene gave highly impure products, and xylene and *o*-dichlorobenzene were most suitable. Using the last mentioned solvent there were obtained good yields of rather pure 1-methyl- and 1-methoxy-phenothiazines. The 1-chlorophenothiazine presented difficulties because of the simultaneous formation of phenothiazine. A similar observation has been made by Roe and Little[3] in the preparation of 1-fluorophenothiazine from 2-fluorodiphenylamine.

1-Carboxyphenothiazine, previously prepared by metalation[4] was obtained in low yield by the thionation of N-phenylanthranilic acid in *o*-dichlorobenzene. The larger part of the acid was decarboxylated so that a 75% yield of phenothiazine was obtained. Previous attempts[4] to obtain this compound by thionation gave neither the phenothiazine acid nor phenothiazine; only starting material was recovered. The formation of 1-carboxyphenothiazine, even in small yield, suggests that if a catalyst could be found which lowers the reaction temperature, the anthranilic acid might give the carboxyphenothiazine directly. Studies in this direction are in progress.

The necessary diphenylamines were prepared by decarboxylation of the corresponding anthranilic acids; these were prepared in good yields by the use of large amounts of the corresponding anilines and *o*-chlorobenzoic acid.[5]

The acetyl derivatives were prepared by heating the phenothiazines with acetic anhydride and pyridine; it is of interest to note that in the case of 1-chlorophenothiazine, if the acetic anhydride mixture was poured into water, the acetylated product was hydrolyzed; it was shown conclusively to be the starting material by mixture melting point and analysis. To obtain the desired acetyl derivative, it was necessary to work up the reaction mixture using anhydrous solvents.

It is also of interest to compare the melting points of the various ring derivatives of phenothiazine: the 1- and 4- have low melting points, and the 2- and 3- have relatively high melting points (Table I).

TABLE I

MELTING POINTS OF SIMPLE RING DERIVATIVES OF PHENOTHIAZINE

Substituent	1	2	3	4
Chloro	92–93°[a]	196–197°[c]	199°[d]	116°[c]
Fluoro	81.5–82°[b]	199°[b]	178–179°[b]	—
Methyl	137.5–138.5°[a]	187–188°[c]	166–168°[e]	114–118°[c]
Methoxy	99°[a]	179–180°[c]	159°[e]	—

[a] This work. [b] Roe and Little, *J. Org. Chem.*, **20**, 1577 (1955). [c] Charpentier, *et al.*, *Compt. rend.*, **235**, 59 (1952) [d] Evans and Smiles, *J. Chem. Soc.*, 1263 (1935). [e] Gilman and Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944).

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EXPERIMENTAL[6]

Thionation of diphenylamine. The results of the thionation of diphenylamine (0.1 mole), sulfur (0.2 mole), and 0.7 g. of iodine in 20 ml. of various solvents at their reflux temperatures are given in Table II.

Preparation of the anthranilic acids. These acids were prepared as described in *Organic Syntheses*[5] for the synthesis of N-phenylanthranilic acid, in the total synthesis of acridone. It was found quite necessary to use an excess (3–4 equivalents) of the aniline, which was easily removed by steam-distillation. Copper powder was used rather than copper oxide. The addition of potassium iodide as an additional

(1) Former papers by this author are in the name of (Miss) K. S. Pankajamani.

(2) Massie, *Chem. Revs.*, **54**, 825 (1954).

(3) Roe and Little, *J. Org. Chem.*, **20**, 1577 (1955).

(4) Gilman, Shirley, and Van Ess, *J. Am. Chem. Soc.*, **66**, 626 (1944).

(5) Allen and McKee, *Org. Syntheses*, Coll. Vol. II, 15 (1943).

(6) The nitrogen analyses were by the semi-micro Kjeldahl method and were carried out by Mrs. Helen Peoples of these laboratories.

TABLE II
THIONATION OF DIPHENYLAMINE

Solvent	B.P., °C.	Time (hours)	Results
Benzene	80	7	30%, m.p. 155–165°
o-Dichlorobenzene	180–183	2.5	84%, m.p. 181–182°
N,N-Dimethyl-formamide	153	3	nil
Pyridine	115	5	nil
Naphthalene	218	2.5	33%, m.p. 176–180°
Xylene	144	4	Quant., m.p. 178–180°

catalyst gave no advantage. The yields obtained were N-*o*-chlorophenyl- (77%), m.p. 195-196°; N-*o*-tolyl- (59%), m.p. 191–192°; N-*o*-anisyl- (68%), m.p. 175–176°.

Preparation of the diphenylamines. These were prepared by decarboxylation of the corresponding anthranilic acids (Table III). In the case of 2-methyldiphenylamine the melt was extracted with ether and the ether solution was washed with sodium carbonate, dried, and distilled. In the other cases, the decarboxylation product was directly distilled.

1-Methylphenothiazine.[7] A mixture of 19 g. (0.1 mole) of 2-methyldiphenylamine, 6.4 g. (0.2 mole) of sulfur, and 0.7 g. of iodine in 25 ml. of *o*-dichlorobenzene was refluxed for 1 hour. Hydrogen sulphide was evolved and on cooling the reaction mixture, 1-methylphenothiazine separated out as a green crystalline mass. This was recrystallized from benzene-petroleum ether mixture to give 15 g. (70%) of greenish-yellow glittering crystals, m.p. 137–138°. Sublimation followed by recrystallization from benzene gave pale yellow crystals, m.p. 137.5–138.5°.

Anal. Calc'd for $C_{13}H_{11}NS$: N, 6.57. Found: N, 6.31.

The *1-methyl-10-acetylphenothiazine* was prepared by refluxing 1 g. of 1-methylphenothiazine with 2.5 ml. of acetic anhydride and a few drops of pyridine for 3–4 hours and pouring the reaction mixture into ice-cold water. The acetyl derivative was crystallized from a chloroform-petroleum ether mixture to give 1.2 g. of colorless crystals, m.p. 123.5-124.5°.

Anal. Calc'd for $C_{15}H_{13}NOS$: N, 5.49. Found: N, 5.31.

1-Methoxyphenothiazine. A mixture of 19.92 g. (0.1 mole) of 2-methoxydiphenylamine, 6.4 g. (0.2 mole) of sulfur, and 0.7 g. of iodine was refluxed in 25 ml. of *o*-dichlorobenzene for 1 hour. There was evolution of hydrogen sulphide and the reaction mixture was distilled to remove excess solvent. On cooling, it deposited a dark crystalline solid, which was filtered and dissolved in benzene. The intense green benzene solution was vigorously shaken with excess petroleum ether, when the dark-colored impurities separated out. The yellow supernate on cooling deposited 1-methoxyphenothiazine which was recrystallized from ethanol to yield 12 g. (59%) of glistening yellow crystals, m.p. 99°.

(7) This compound was first prepared in these laboratories by Ivar Cooke, Herman Zittel, and Samuel P. Massie, unpublished observations.

Anal. Calc'd for $C_{13}H_{11}NOS$: N, 6.12. Found: N, 5.94.

The *10-acetyl derivative* was prepared as described for the 1-methyl derivative and was precipitated by adding excess petroleum ether to the reaction mixture. It was recrystallized from an ethyl acetate-petroleum ether mixture, when 0.8 g. of colorless crystals, m.p. 165–166° was obtained.

Anal. Calc'd for $C_{15}H_{13}NO_2S$: N, 5.23. Found: N, 5.24.

1-Chlorophenothiazine.[8] A mixture of 20 g. of 2-chlorodiphenylamine, 6 g. of sulfur, and a few crystals of iodine was heated in 10 ml. of refluxing *o*-dichlorobenzene for 1 hour. Hydrogen sulphide was evolved and the solvent was distilled at the end of the reaction. The residue was repeatedly extracted with boiling hexane and the combined extracts were concentrated and cooled. A small amount of colored oil separated out. The supernatant liquid on further cooling deposited 1 g. of material, m.p. 135–165°. The filtrate was evaporated and the residue was sublimed to give a product which on recrystallization from hexane and resublimation followed by recrystallization from benzene-hexane, gave 3.5 g. (15%) of glistening colorless crystals of 1-chlorophenothiazine, m.p. 92–93°.

Anal. Calc'd for $C_{12}H_8ClNS$: N, 6.00. Found: N, 5.82.

The colored oil and the material of m.p. 135–165° (described above), together with the dark residue from the extraction with hexane were combined and sublimed, when 2 g. of an impure product was obtained. This on crystallization from benzene-hexane followed by recrystallization from benzene gave 0.3 g. of colorless crystals, turning green on standing, m.p. 175–177°. This was shown to be phenothiazine by a mixture melting point of the acetyl derivative (203–204°) and its mixture melting point with an authentic sample.

The *1-chloro-10-acetylphenothiazine*, prepared as described for the 1-methyl derivative, was worked up in the anhydrous condition using petroleum ether to precipitate the amide. It was recrystallized from ethyl acetate-petroleum ether to give 0.6 g. of colorless crystals, m.p. 139–140°.

Anal. Calc'd for $C_{14}H_{10}ClNOS$: N, 5.09. Found: N, 5.14.

1-Carboxyphenothiazine. A mixture of 10.7 g. (0.05 mole) of N-phenylanthranilic acid, 3.2 g. (0.1 mole) of sulfur, and 0.35 g. of iodine in 15 ml. of *o*-dichlorobenzene was refluxed for 2.5 hours; hydrogen sulphide was evolved. The dark green reaction mixture was taken up in ether and the intense green ethereal solution was extracted thrice with 10% sodium carbonate solution. From the ether solution there was obtained 7.5 g. (75%) of yellow crystals, m.p. 182–183°, undepressed by an authentic sample of phenothiazine.

The combined sodium carbonate extracts of acidification yielded 1 g. of yellow material which on crystallization from acetone gave 0.4 g. of yellow crystals, m.p. 264–265°. The *methyl ester* was prepared in 80% yield by refluxing the acid with dimethyl sulphate and anhydrous potassium carbonate in acetone for 18 hours. It was recrystallized from acetone-petroleum ether as golden yellow crystals, m.p. 113–114°. Gilman, *et al.*[4] reported the acid as melting at 264–265° and the methyl ester at 113–113.5°.

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(8) During the writing of this paper, Australian Patent 26,282 was found, which described the synthesis of this compound by ring closure of 2-bromo-2′-amino-3′-chlorodiphenylsulphide. Their compound melted at 92°.

TABLE III
PREPARATION OF THE DIPHENYLAMINES

Anthranilic acid	Time and Temp. of decarboxylation	Diphenylamine	B.P., °C.	Mm.
N-*o*-Tolyl-	200–215° (1.5 hours) 240–255° (0.5 hour)	2-Methyl- (56%)	143–146	4–5
N-*o*-Anisyl-	220–230° (1 hour) 230–250° (0.5 hour)	2-Methoxy- (77%)	156–158	2.5–3
N-*o*-Chlorophenyl-	250–270° (2 hours)	2-Chloro- (89%)	152–153	4