Notes

A department for short papers of immediate interest.

Ring Derivatives of Phenothiazine. IV. Further Studies on the Thionation Reaction, and the Synthesis of Phenothiazinols

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The synthesis of 2-, 3-, and 4-derivatives of phenothiazine by the thionation of diphenylamines in a solvent was studied and found to offer some advantages over thionation without solvent. The 1-, 2-, and 3-phenothiazinols were prepared by cleavage of the corresponding methyl ethers with pyridine hydrochloride. The phenols were further characterized, by the preparation of suitable derivatives.

The synthesis of 1-substituted ring derivatives of phenothiazine has been studied using *o*-dichlorobenzene as a solvent,[3] and this procedure was shown to afford certain advantages. It, therefore, seemed desirable to extend these studies to the syntheses of ring derivatives of phenothiazine with substituents in other positions by thionation of the corresponding diphenylamines.

It has been found that the use of solvent makes the process quite convenient in the isolation and purification of the products, particularly, where isomers are formed. However, as in the case without solvent,[4] 3-methoxydiphenylamine gave only 2-methoxyphenothiazine, no 4-isomer being isolated. Derivatives containing substituents in both rings also thionated smoothly using solvent.

The phenothiazinols were prepared by smooth demethylation of the corresponding methoxy derivatives, using pyridine hydrochloride.[5] These phenols were further identified through the diacetyl derivatives, both the amino hydrogen and the phenolic hydrogen being replaced by acetyl groups.

Although xanthydrol reacts with phenothiazine in hot glacial acetic acid to yield the 10-(9-xanthenyl) derivative, the susceptibility of the latter to heat, and its high melting point made it unsuitable as a derivative.

The use of isopropenyl acetate,[6] with boron trifluoride as a catalyst, was found to give better results as an acetylating agent than acetic anhydride and pyridine in the case of 1-substituted phenothiazines, where difficulties were encountered earlier in the preparation of 1-chloro-10-acetylphenothiazine.[3]

These compounds were submitted to the Sloan-Kettering Institute and the Upjohn Drug Company for physiological testing; results will be reported elsewhere.

EXPERIMENTAL[7]

Anthranilic acids.[8] The *meta*- and *para*-chloro-, and methoxy- and methylanthranilic acids were prepared in the usual manner[3,9] from the corresponding anilines and *o*-chlorobenzoic acid in 50–60% yields. The *m*-anisidine needed for the synthesis of *N*-*m*-anisylanthranilic acid was prepared by the direct methylation of *m*-aminophenol.[10]

The *N*-*p*-anisyl-*m*-chloroanthranilic acid was prepared from the corresponding potassium salt.[11]

Diphenylamines. These were prepared in good yield by decarboxylation of the corresponding anthranilic acids at 210–260° for 1–2 hr. The liquid diphenylamines were then distilled directly; in the case of the solids, they were taken up in ether, the ethereal solutions extracted with 10% sodium carbonate solution, the ether removed, and the residues crystallized from ethanol, benzene, or benzene-petroleum ether.

Thionation of diphenylamines. The reaction was carried out in the usual manner,[3] by heating a mixture of the diphenylamine (0.1 mole), sulfur (0.2 mole), and 0.7 g. of iodine in 20 ml. of refluxing *o*-dichlorobenzene for 1 hr. On cooling, a crystalline mass separated from the reaction mixture, and was filtered and recrystallized from petroleum ether-benzene mixture. In some cases further purification was effected by sublimation or a second crystallization.

In cases where isomers were present, petroleum ether was added to the reaction mixture. The 2-isomer separated, and was filtered from the mixture. The 4-isomer was recovered from the filtrate. The results are given in Table I.

Anal. Calcd. for $C_{13}H_{10}ONSCl$: S, 12.17. Found: S, 12.23

1-Hydroxyphenothiazine.[12] A mixture of 22.9 g. (0.1 mole) of 1-methoxyphenothiazine[3] and 57.8 g. (0.5 mole) of pyridine hydrochloride was heated for 5 hr. in a flask surrounded by an oil bath maintained at 200°. The melt was cooled, poured into an excess of cold water, and extracted with ether. After treatment with Norite, the ethereal solution was dried over anhydrous magnesium sulfate, and the ether was

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(3) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).

(4) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. rend.*, **235**, 59 (1952).

(5) V. Prey, *Ber.*, **75**, 445 (1942).

(6) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(7) All melting points are uncorrected. Analyses are by Midwest Microlab, Inc., Indianapolis, Ind.

(8) Some of these acids were prepared by Helen Peoples.

(9) C. Allen and G. McKee, *Org. Syntheses*, Coll. Vol. II, 15 (1943).

(10) P. K. Kadaba and Samuel P. Massie, *J. Org. Chem.*, **22**, 333 (1957).

(11) This salt was purchased from the Winthrop Chemical Co., New York, N.Y.

(12) Some of this work was carried out by Eugene A. White.

TABLE I

PHENOTHIAZINES BY THIONATION

Substituent	Yield, %[a]	M.P.
2-Methyl-	38	190–191°[b]
4-Methyl-	3	129–132°[c]
2-Chloro-	26	197–199°[d]
4-Chloro-	Unable to purify	
2-Methoxy-	16	185–188°[e]
4-Methoxy-	Unable to isolate	
3-Methyl-	47	166–167°
3-Methoxy-	48	155–157°[f]
3-Chloro-	[g]	
2-Chloro-7-methoxy	35	173–174°

[a] These yields represent purified yields. For example, in the thionation of 3-methyldiphenylamine, a crude yield of 80% of the 2-isomer, melting at 175–177°, is obtained, and a crude yield of 20% of the 4-isomer, melting at 125–127°. [b] Charpentier *et. al., loc. cit.*, reported a melting point of 187–188°. [c] Charpentier *et al.*, m.p., 114–118°. As noted above, our crude product melted at 125–127°. [d] Charpentier, *et al.*, m.p., 196–197°. [e] Charpentier, *et al.*, m.p., 179–180°. [f] Gilman and Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944) and Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913) report a melting point of 158–159°; Pummerer and Gassner, *Ber.*, **46**, 2322 (1916) report 163°. [g] 3-Chlorophenothiazine could not be obtained by this procedure. Complete loss of chlorine resulted and good yields of phenothiazine were obtained as the only reaction product. A similar loss occurred to some extent in the preparation of 1-chlorophenothiazine.[4]

removed by distillation. There was obtained 20.4 g. (95%) of a yellow product, melting at 135–136°.

An analytical sample was obtained by recrystallization from benzene. Colorless glistening crystals, melting at 136–137°, were obtained. On standing or exposure to air, the compound slowly turned green.

Anal. Calcd. for $C_{12}H_9ONS$: C, 67.0; H, 4.19. Found: C, 66.8; H, 4.25.

1-Acetoxy-10-acetylphenothiazine. A mixture of 0.6 g. of 1-hydroxyphenothiazine, 4 ml. of acetic anhydride, and a few drops of pyridine was refluxed for 4 hr. On cooling the mixture, colorless crystals settled out. Recrystallization from benzene gave 0.4 g. (60%) of colorless crystals, m.p., 208–209°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.34.

1-Ethoxyphenothiazine.[12] A mixture of 3 g. of 1-hydroxyphenothiazine, 3 ml. of ethyl bromide, and 10 g. of anhydrous potassium carbonate in 150 ml. of dry acetone was refluxed for 24 hr. The hot reaction mixture was filtered, and the filtrate evaporated. The residue, which was insoluble in alkali, was recrystallized from ethanol to give 2.1 g. (62%) of colorless crystals, m.p., 81–82.

Anal.[13] Calcd. for $C_{14}H_{13}ONS$: C, 68.8; H, 5.35. Found: C, 68.0; H, 5.36.

2-Acetoxy-10-acetylphenothiazine. A mixture of 2 g. of 2-methoxyphenothiazine and 6 g. of pyridine hydrochloride was heated at 200° for 5 hr. When the melt was worked up as described under 1-hydroxyphenothiazine, an oil was obtained which could not be crystallized. The oil was, therefore, by a procedure similar to that for the 1-hydroxy derivative, converted into 2-acetoxy-10-acetylphenothiazine. This was crystallized with difficulty from benzene–petroleum ether to give 0.6 g. (35%) of colorless crystals, m.p., 138–140°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.23.

(13) Analysis by C. Beames, N. Mexico Highlands University, Las Vegas, N. M.

(14) This compound has been reported to melt at 172–174° by D. F. Houston, E. B. Kester, and F. DeEds, *J. Am. Chem. Soc.*, **71**, 3816 (1949), who prepared it by the thionation of p-anilinophenol.

3-Hydroxyphenothiazine.[14] The demethylation of 3 g. of 3-methoxyphenothiazine with 12 g. of pyridine hydrochloride was carried out as described for the 1-hydroxy derivative. Recrystallization from benzene acetone mixture gave 2.2 g. (76%) of steel-gray crystals, m.p. 187–188°. Because of the ease of oxidation, to a purple colored solid, the product was not analyzed but was converted, as described under the 1-derivative, into 3-acetoxy-10-acetylphenothiazine, which crystallized with difficulty from benzene–petroleum ether mixture to give a white powder, m.p., 111–116°.

Anal. Calcd. for $C_{16}H_{13}O_3NS$: S, 10.70. Found: S, 10.21.

2-Chloro-7-hydroxyphenothiazine. Demethylation of 2 g. of 2-chloro-7-methoxyphenothiazine in the usual manner gave a product which crystallized from benzene to give 1 g. (52%) of light purple crystals, m.p. 224–226°, turning deep purple on standing.

Anal. Calcd. for $C_{12}H_8ONSCl$: S, 12.83. Found S, 13.14.

10-(9-Xanthenyl)-phenothiazine. A mixture of 0.5 g. of phenothiazine, 0.5 g. of xanthydrol and 6 ml. of glacial acetic acid was heated to reflux. On cooling to room temperature, a white crystalline solid separated. Filtration and recrystallization from ethanol-acetone mixture gave a colorless solid, m.p., 205–212°, sintering at 195°. It turned violet on standing.

Anal.[13] Calcd. for $C_{25}H_{17}NOS$: C, 79.2; H, 4.48. Found C, 78.6; H, 4.86.

1-Chloro-10-acetylphenothiazine.[3] To 1.0 g. of 1-chlorophenothiazine was added 1 ml. of isopropenyl acetate[15] and 5 drops of boron trifluoride ethereate. The mixture was heated with stirring in a boiling water for a few minutes. The dark residue was cooled and triturated in ethanol to remove colored impurities. The colorless amide was filtered and recrystallized from ethyl acetate to give 1.3 g. of colorless crystals, m.p., 135–136°. By adapting the same procedure, the 10-acetyl derivatives of 1-methyl phenothiazine and 1-methoxyphenothiazine were also prepared.

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Hexagonal Urea from Acetone-Urea Adduct

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It is reported in the literature that when a urea adduct decomposes, the urea reverts to its natural tetragonal structure.[1] Urea adducts are crystalline molecular compounds of hexagonal structure.[2] We have found that a small part of the urea obtained from the decomposition of an acetone urea adduct existed in the hexagonal form. X-ray dif-

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