bromine in 10 ml. of acetic acid was added dropwise to the boiling solution. After refluxing for 2 hr., the mixture was cooled and sodium hydroxide added to precipitate the product which was then recrystallized from methanol.

1-Benzylthymine. 1-Benzyldihydrothymine (3.0 g., 0.0138 mole) when treated with one molecular equivalent of bromine gave 2.0 g. (67%) of 1-benzylthymine, which melted at 161–163° (lit.[2] 160°); λ_{max} 271 mμ, λ_{min} 236 mμ; ϵ = 10,500.

1-Isopropylthymine. 1-Isopropyldihydrothymine (3.0 g., 0.018 mole) when treated with one molecular equivalent of bromine gave a 75% yield of 1-isopropylthymine. After recrystallization from isopropanol, it melted at 213–216°.

Anal. Calcd. for $C_8H_{12}O_2N_2$: N, 16.66. Found: N, 16.71 λ_{max} 271 mμ, λ_{min} 236 mμ; ϵ = 9830.

1-Methylthymine. 1-Methyldihydrothymine (5.0 g., 0.035 mole) when treated with one molecular equivalent of bromine gave a 75% yield of 1-methylthymine. After recrystallization from methanol,it melted at 288°; (lit.[3,4] 280–282°) λ_{max} 272 mμ, λ_{min} 237 mμ; ϵ = 8000.

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Ring Derivatives of Phenothiazine. III. Esters of 2-Phenothiazinecarboxylic Acid

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The facile synthesis of 2-phenothiazinecarboxylic acid by the basic hydrolysis of the pyridine addition product of 2-chloroacetyl-10-acetylphenothiazine,[3] in contrast to its earlier preparation, which involved hypochlorite oxidation of 2-acetylphenothiazine,[4] and which gave low yields and complex products, has made this acid available for further studies.

Because of the great interest in 2-substituted phenothiazines, as a prototype for physiologically interesting esters[5] of this acid, and as intermediates for other derivatives, some simple alkyl esters of 2-phenothiazinecarboxylic acid have been prepared. These esters were prepared either by direct alkylation of the acid with an alkyl halide or sulfate, or by alcoholysis of the methyl ester. The latter method gave better yield and may be quite valuable in the synthesis of some larger alkyl esters, particularly when the alcohols are more available than the halides.

The need for relatively large amount of this acid led to studies on its preparation. The method of Burger[3] has been improved to give yields of 90–95%. The preparation of the acid by hydrolysis of 2-cyanoacetylphenothiazine[6] could not be improved beyond a 15% yield and was, therefore, not satisfactory.

These compounds have been submitted for physiological testing to the Sloan-Kettering Institute and the Upjohn Drug Co.; results will be published elsewhere.

EXPERIMENTAL[7]

2-Phenothiazinecarboxylic acid. A mixture of 40.2 g. (0.13*M*) of crude 2-chloroacetyl-10-acetylphenothiazine and 266 ml. of anhydrous pyridine was warmed at 90° for 20 min. The mixture was extracted with ether until the odor of pyridine was gone, leaving a gummy yellow solid. Hydrolysis of this solid with 400 ml. of 5% sodium hydroxide solution for 1 hr., treatment with Norit, filtration, and acidification with concentrated hydrochloric acid gave the acid as a yellow solid. Crystallization from acetone-ethanol mixture gave 30 g. (95%) of yellow crystals, melting at 276–278°.

Preparation of esters. (a) Direct alkylation. The esters were prepared by refluxing a mixture of the acid, one to two equivalents of the alkyl halide or sulfate, catalytic amounts of potassium iodide, and an equivalent of anhydrous potassium carbonate in acetone for 24 hr. After cooling, the reaction mixture was poured into water, filtered, dried, and recrystallized from ethanol-acetone mixtures. All of the esters are yellow solids. The results are given in Table I.

TABLE I

Esters of 2-Phenothiazinecarboxylic Acid

		Percentage Yield		Analyses			
		Method		Nitrogen		Sulfur	
Alkyl Group	M.P., °C.	(a)	(b)	Calcd.	Found	Calcd.	Found
Methyl[4]	166–167	93		5.45	5.39	12.47	12.49
Ethyl[4]	151–152	97		5.17	5.10	11.83	11.89
n-Propyl	162–163	69	70	4.91	4.89	11.23	11.20
n-Butyl	161–162	76	Quan.	4.68	4.71	10.72	10.93
n-Amyl	148–150	56	75	4.47	4.57	10.20	10.20

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(2) A portion of this work was taken from the master's thesis of Carlos Smith, Fisk University, May 1957.

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(*b*) *Alcoholysis.* Twenty to thirty ml. of the alcohol were treated with 0.1 g. of sodium. When reaction was completed, one gram of methyl 2-phenothiazinecarboxylate was added, and the mixture was refluxed 4–5 hr. The mixture was poured into water, filtered, dried, and recrystallized from ethanol-acetone mixtures.

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A New Technique in Preparing 2,4-Dinitrophenylhydrazones. Use of Diglyme as Solvent

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An encumberance long associated with the characterization of carbonyl compounds by their 2,4-dinitrophenylhydrazones is the difficulty of obtaining concentrated solutions of 2,4-dinitrophenylhydrazine. The low solubility of the reagent in useful solvents is usually overcome by working with boiling solvents or with highly acidic solutions, since the salts of the reagent are more soluble than the reagent itself. Thus, 2,4-dinitrophenylhydrazones are usually prepared by resorting to one of several techniques now in practice. These are, for example, adding to the carbonyl compound a solution of the reagent in concentrated sulfuric acid, water, and ethanol[1]: adding a solution of the reagent in ethanol containing hydrochloric acid[2]; adding a solution of the reagent in 85% phosphoric acid and ethanol[3]; boiling the carbonyl compound in a methanol solution of the reagent acidified with hydrochloric acid[4]; boiling the carbonyl compound, reagent, and hydrochloric acid in ethanol[5]; uniting the carbonyl compound, reagent and hydrochloric acid in a mixture of ethanol and dioxane[6]; and adding an alcoholic solution of the carbonyl compound to a saturated solution of the reagent in 2*M* hydrochloric acid.[7]

It has now been found that 2,4-dinitrophenylhydrazine is quite soluble in the dimethyl ether of diethylene glycol, for which solvent the name diglyme has been coined.[8] Solutions of the reagent made by warming 1 g. in 25 to 30 ml. of the solvent are stable at room temperature. The neutral solution is deep red in color. Acidification with hydrochloric acid turns the color to yellow. It is not necessary to acidify the reagent solution for storage, however. Solutions of the reagent in diglyme have been found to be admirable for the preparation of derivatives, using, as is customary, hydrochloric acid for catalysis.

Moderate success was also achieved in the use of acetic acid instead of hydrochloric acid for catalysis. The reason for using acetic acid was two-fold. The use of a weak acid for catalysis in solutions at room temperature or lower may be applicable to the preparation of derivatives of sensitive compounds. Also, in the preparation of derivatives of carbonyl compounds formed in the oxidation of glycols by lead tetraacetate the precipitation of the derivative may be complicated by the precipitation of lead chloride, unless the trouble is taken first to separate the carbonyl compounds from lead acetate. If acetic acid can be used for catalysis of 2,4-dinitrophenylhydrazone formation it may be possible to use crude oxidation mixtures in the preparation of derivatives. Results with lead tetraacetate oxidation solutions will be published elsewhere. As can be seen in Table I success was achieved in the four cases tried. However, the formation of the derivatives was slow. In the case of benzaldehyde the derivative crystallized nicely from solution 30 min. after adding the acetic acid. In the cases of methyl *p*-tolyl ketone and 7-ethyl-1-tetralone the derivatives crystallized out overnight. In each case, however, the amount of derivative obtained was much smaller than expected from the amount of compound used. The use of solutions of 2,4-dinitrophenylhydrazine in acetic acid alone or in aqueous acetic acid is to be avoided since acetylation of the reagent occurs when warming to dissolve. No acetylation occurred in a control diglyme experiment.

As might be expected, triglyme[8] and tetrahydrofuran can be used as solvents for 2,4-dinitrophenylhydrazine. Undoubtedly, other solvents may be found. Because tetrahydrofuran needs to be distilled prior to use and because of its volatility, we found diglyme to be preferred. It was found unnecessary to distill the diglyme before use.

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