temperature. The analytical sample was evaporatively distilled at 0.1 mm. pressure.

Anal. Calcd. for $C_4H_7O_2PCl_4$: Cl, 54.6. Found: Cl, 52.0.

Repetition of this preparation on a larger scale yielded similar results and gave material with an identical infrared spectrum. When such material stood 8 days in a closed container at room temperature it became dark red and more viscous, and an altered infrared spectrum was observed.

Hydrolysis of isopropyl trichloromethylphosphonochloridate was carried out by heating on a steam bath for 90 min. a 1.0-g. sample of the oily ester acid chloride with 20 ml. of water. The oil was insoluble in cold water but the mixture became homogeneous as soon as heated. Freeze-drying of the reaction mixture left a semisolid residue weighing 0.74 g. A solution of this residue in 20 ml. of dry ether was treated dropwise with *N*-methylaniline until precipitation was complete. The precipitate was collected by suction filtration, washed with dry ether, and dried. The colorless solid, weight 0.68 g., was recrystallized from absolute alcohol to yield colorless plates, m.p. 220–223° (dec.). The m.p. reported[8] for *N*-methylanilinium trichloromethylphosphonate is 224–225° (dec.).

Anal. Calcd. for $C_8H_{11}O_3NPCl_3$: equiv. wt., 153. Found: equiv. wt., 155.

N-(2-chloroethyl)pyrrolidine was prepared by a published method for preparing amino halides.[9] To a solution of 18 g. (0.16 mole) of *N*-(2-hydroxyethyl)pyrrolidine (b.p. 72–73°/10 mm., n_D^{25} 1.4716) in 75 ml. of benzene, there was added dropwise during 0.5 hr. a solution of 20 g. (0.17 mole) of thionyl chloride in 50 ml. of benzene. The reaction was cooled in ice during the addition and a subsequent 1-hr. period of stirring. The mixture was poured into ice and water containing 25 g. of sodium hydroxide, and the product extracted with ether. Distillation yielded 15.2 g. (72%) of product, b.p. 60–63°/23 mm.

The relatively unstable *N*-(2-chloroethyl)pyrrolidine was characterized by conversion to the *picrate* in anhydrous ether. After crystallization from ethanol, the m.p. was 107.3–107.8°.

Anal. Calcd. for $C_{12}H_{15}N_4O_7Cl$: C, 39.73; H, 4.17; N, 15.45. Found: C, 39.83; H, 4.28; N, 15.67.

Attempts to convert this halide to a phosphorothioate (V) by reaction with diethyl potassium phosphorothioate[10] yielded a resinous undistillable material.

Ethylene phosphorochloridite. Commercial ethylene glycol (150 g.) was added dropwise with stirring to 450 g. of phosphorus trichloride, as the reaction mixture was maintained at 0–5°. After addition was complete, the solution was stirred at room temperature for 1 hr. and at 80–90° for 2 hr. The mixture was then distilled through a Claisen head, and the product collected in the range 60–80°/45 mm. was fractionated through a half-meter Vigreux column with heated jacket and partial reflux head. After a small fore-run, there was collected 121.0 g. (39.5%) of product, b.p. 65–66°/42 mm., n_D^{25} 1.4897; lit.,[11,12] b.p. 66–68°/47 mm., n_D^{20} 1.4894; b.p. 71.3°/50 mm., n_D^{25} 1.4878.

There has been reported[12] a more elaborate method of preparation which gives a better yield.

Ethyl ethylene phosphite (VI). To a stirred solution of 63 g. (0.5 mole) of ethylene phosphorochloridite in 200 ml. of anhydrous ether, there was added during 1 hr. at 10° a solution of 23 g. (0.5 mole) of absolute ethanol and 51 g. (0.5 mole) of triethylamine in 50 ml. of anhydrous ether. After stirring had been continued for an additional 0.5 hr. at room temperature, the mixture was diluted with 200 ml. of ether and the precipitated amine salt removed by filtration. Distillation of the filtrate and washings through a Claisen head yielded 56 g. (83%) of phosphite, b.p. 54–55°/16 mm., n_D^{20} 1.4411; lit.[5,12] b.p. 50.5–51°/15 mm., n_D^{20} 1.4395; b.p. 60–61°/21 mm., n_D^{25} 1.4390.

Dry air was bubbled through a 10-g. sample of this phosphite for 70 hr. while it was heated on a steam bath. A Dry Ice–cooled condenser was necessary to prevent sweeping of the phosphite from the flask in the stream of air. Distillation of the resultant product yielded 5.6 g. of starting material, b.p. 54°/15 mm. n_D^{20} 1.4410, and a nonvolatile residue.

Ethyl ethylene phosphorothioate (VIII). Sulfur (2.1 g., 0.066 mole) was added in small portions with stirring to 10 g. (0.066 mole) of ethyl ethylene phosphite. Addition was at such a rate as to keep the temperature of the exothermic reaction at 35–40°. Stirring was continued for 1 hr. after completion of the addition, then a trace of sulfur was removed by filtration and the product distilled to yield 4.4 g. (36%) of VIII, b.p. 79°/0.5 mm., n_D^{25} 1.4857.

Anal. Calcd. for $C_4H_9O_3PS$: C, 28.57; H, 5.39. Found: C, 28.65; H, 5.23.

A sample which had stood overnight had n_D^{25} 1.4861; after heating for 15 min. at 160° the n_D^{25} was 1.5060, and the viscosity had increased markedly.

2-(Diethylamino)ethyl ethylene phosphite (VII). A solution of 50 g. (0.43 mole) of diethylaminoethanol and 50 g. (0.50 mole) of triethylamine was added dropwise with stirring to a solution of 50 g. (0.40 mole) of ethylene phosphorochloridite in 500 ml. of benzene. The temperature of the reaction mixture was maintained at 5–10° with an ice bath, and the addition required about 1 hr. After the mixture had warmed to room temperature the amine salt was removed by filtration, and the product obtained from the filtrate was distilled to yield 29.1 g. (36%) of phosphite VII, b.p. 95–97°/4 mm., n_D^{25} 1.4618–1.4620. A sample redistilled for analysis had b.p. 97°/4 mm., n_D^{25} 1.4620.

Anal. Calcd. for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; N, 6.76. Found: C, 46.57; H, 8.54; N, 6.75.

2-(Diethylamino)ethyl trimethylene phosphite was prepared by the same procedure described for VII, utilizing 45 g. (0.38 mole) of diethylaminoethanol, 38 g. (0.38 mole) of triethylamine and 46.8 g. (0.33 mole) of trimethylene phosphorochloridite (b.p. 67–68°/12 mm., prepared as described for ethylene phosphorochloridite; lit.[12] b.p. 77°/25 mm.). There was obtained a yield of 38.2 g. (52%), b.p. 107–110°/3.5–4.0 mm., n_D^{25} 1.4592–1.4609. The analytical sample had b.p. 110°/4.0 mm., n_D^{25} 1.4609.

Anal. Calcd. for $C_9H_{20}NO_3P$: C, 48.86; H, 9.11; N, 6.33. Found: C, 48.75; H, 8.96; N, 6.23.

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(8) I. S. Bengelsdorf and L. B. Barron, *J. Am. Chem. Soc.*, **77**, 2869 (1955).

(9) D. S. Breslow, R. S. Yost, H. G. Walker, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1921 (1944).

(10) T. W. Mastin, G. R. Norman, and E. A. Weilmuenster, *J. Am. Chem. Soc.*, **67**, 1662 (1945).

(11) P. A. Rossiiskaya and M. I. Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, **1947**, 509; *Chem. Abstr.*, **42**, 2924 (1948).

(12) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

Synthesis of 1-Substituted Thymines

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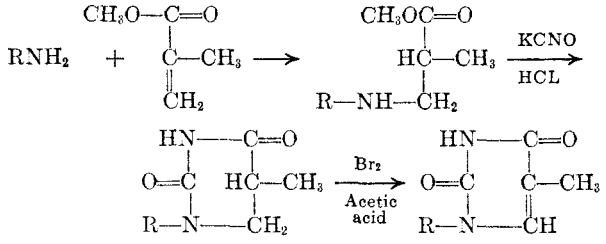
Received July 25, 1958

Gearien and Binkley[1] have recently reported a method for the synthesis of 1-substituted uracils in which ethyl acrylate reacted with a primary

(1) J. E. Gearien and S. B. Binkley, *J. Org. Chem.*, **23**, 491 (1958).

amine to form an *N*-substituted-β-alanine ester which, when treated with potassium cyanate and hydrochloric acid, yields a 1-substituted dihydrouracil. The 1-substituted dihydrouracil was brominated and dehydrobrominated to yield a 1-substituted uracil.

In an attempt to prepare 1-substituted thymines methyl methacrylate was substituted for the ethyl acrylate in the above synthesis. The illustrated series of reactions has been carried out.



R = benzyl, isopropyl, methyl, or furfuryl.

The 1-substituted dihydrothymines and 1-substituted thymines in which the substituent was either benzyl, isopropyl, or methyl were prepared and characterized. The 1-furfuryldihydrothymine was also prepared. Two of these compounds, 1-benzylthymine and 1-methylthymine, have previously been synthesized. Johnson and Derby[2] prepared 1-benzylthymine by the hydrolysis of 2-ethylmercapto-1-benzyl-5-methyl-4-oxypyrimidine. Johnson and Clapp[3] prepared 1-methylthymine by the hydrolysis of 2-ethylmercapto-1,5-dimethyl-4-oxypyrimidine. Shaw and Warrener[4] have prepared the same compound by treating *N*-ethoxycarbonyl-β-methoxy-α-methylacrylamide with methylamine.

The *N*-substituted-β-aminoisobutyric esters were prepared by refluxing the proper primary amine with methyl methacrylate in methanol. The compounds prepared in this manner were converted to the dihydrothymines by treatment with potassium cyanate and hydrochloric acid. When the resulting 1-substituted dihydrothymines were treated with bromine in refluxing glacial acetic acid, the 1-substituted thymines were isolated. This was in contrast to the similar bromination of 1-substituted dihydrouracils[1] in which the brominated uracil was isolated. Under the same conditions the 1-substituted dihydrothymines appear to add bromine and dehydrobrominate spontaneously yielding only the 1-substituted thymines. The treatment of 1-furfuryldihydrothymine with bromine resulted in the production of black tars. Several attempts have been made to dehydrogenate this compound with no success.

The compounds prepared were characterized by melting point comparisons with those compounds previously prepared, by elemental analysis, and in the case of the 1-substituted thymines by ultraviolet absorption spectrum.

EXPERIMENTAL[5]

Preparation of the methyl esters of N-substituted-β-aminoisobutyrates. A mixture of methyl methacrylate and a primary amine was refluxed in methanol for 48 hr. The alcohol was removed under reduced pressure and the product was distilled under vacuum.

Methyl N-benzyl-β-aminoisobutyrate was prepared from 54.7 g. (0.51 mole) of benzylamine and 50.0 g. (0.50 mole) of methyl methacrylate. The product (74.6 g., 72%) was a colorless liquid, b.p. 142–144° at 14 mm.

Anal. Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 6.63.

Methyl N-isopropyl-β-aminoisobutyrate. Isopropylamine (35.1 g., 0.60 mole) and 58.0 g. (0.58 mole) of methyl methacrylate gave 49.6 g. (54%) of a colorless liquid, b.p. 48° at 2 mm.

Anal. Calcd. for $C_8H_{17}O_2N$: N, 8.80. Found N, 8.72.

Methyl N-methyl-β-aminoisobutyrate. When 17.1 g. (0.55 mole) of methylamine and 58.0 g. (0.58 mole) of methyl methacrylate were heated in a Magne Dash Autoclave at 80° for 24 hr. 28.0 g. (37%) of methyl *N*-methyl-β-aminoisobutyrate were obtained. This colorless liquid boiled at 74° at 0.5 mm.

Anal. Calcd. for $C_6H_{13}O_2N$: N, 10.68. Found: N, 10.82.

Methyl N-furfuryl-β-aminoisobutyrate. Furfurylamine (38.8 g., 0.40 mole) and 39.0 g. (0.39 mole) of methyl methacrylate gave 48.7 g. (64%) of a colorless liquid, b.p. 92–94° at 1 mm.

Anal. Calcd. for $C_{10}H_{15}O_3N$: N, 8.10. Found: N, 7.18.

1-Substituted dihydrothymines. The methyl ester of *N*-substituted-β-aminoisobutyrate was dissolved in water with the aid of hydrochloric acid. This solution was added to potassium cyanate (10% excess) in water and was allowed to stand overnight. The heavy oil which formed was separated and heated at 120° (20 mm.) for 2 hours. Upon cooling the oil solidified and was recrystallized from isopropanol.

1-Benzyldihydrothymine. The methyl ester of *N*-benzyl-β-aminoisobutyric acid (72.1 g., 0.35 mole) and 30.0 g. (0.37 mole) of potassium cyanate gave 52.8 g. (70%) of 1-benzyldihydrothymine melting at 100–102°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: N, 12.84. Found: N, 12.72.

1-Isopropyldihydrothymine was prepared from 49.6 g. (0.31 mole) of methyl *N*-isopropyl-β-aminoisobutyric acid and 28.4 g. (0.35 mole) of potassium cyanate. The product weighed 37.3 g. (70%) and melted at 139–140°.

Anal. Calcd. for $C_8H_{14}O_2N_2$: N, 16.46. Found: N, 16.52.

1-Methyldihydrothymine was prepared from 18.2 g. (0.14 mole) of the methyl ester of N-methyl-β-aminoisobutyric acid and 12.0 g. (0.15 mole) of potassium cyanate. The product weighed 10.1 g. (51%) and melted at 131–133°.

Anal. Calcd. for $C_6H_{10}O_2N_2$: N, 19.71. Found. N, 19.67.

1-Furfuryldihydrothymine. The methyl ester of N-furfuryl-β-aminoisobutyric acid (48.7 g., 0.25 mole) and 21.0 g. (0.26 mole) of potassium cyanate gave 35.0 g. (69%) of 1-furfuryldihydrothymine melting at 98–100°.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.76; H, 5.70; N, 13.42.

1-Substituted thymines. A well stirred, refluxing solution of 3 to 5 g. of the 1-substituted dihydrothymine in 20 ml. of glacial acetic acid was heated to boiling. One equivalent of

(2) T. B. Johnson and J. H. Derby, *Am. Chem. J.*, **40**, 444 (1908).

(3) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 49 (1908).

(4) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 157 (1958).

(5) Analyses were conducted by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points and boiling points are uncorrected. The ultraviolet absorption spectra of the 1-substituted thymines were measured in methanol solution on a Beckmann Ratio Recording Spectrophotometer.

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.

Acknowledgment. The authors wish to express their gratitude to the Research Corp. and U. S. Public Health Service (CY3231) for financial assistance. We also wish to thank Dr. James E. Gearien for helpful advice.

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

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Received July 31, 1958

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.

(3) A. Burger and J. Clements, *J. Org. Chem.*, **19**, 1113 (1954).

(4) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(5) Unpublished studies of these laboratories.

(6) S. P. Massie, I. Cooke, and W. Hills, *J. Org. Chem.*, **21**, 1006 (1956).

(7) All melting points are uncorrected. Analyses are by the Upjohn Laboratories, courtesy, Dr. R. F. Heinzelmann.