[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

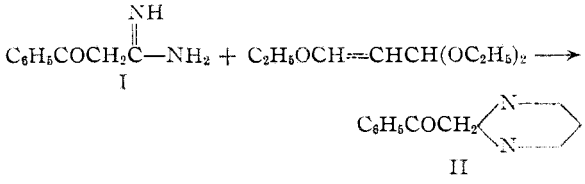
Phenacylpyrimidines

BY BARBARA ROTH AND JAMES M. SMITH, JR.

A preceding paper[1] described a series of phenacylpyridines and -quinolines and their α-amino derivatives, some of which showed moderate analgesic activity in preliminary tests on animals. It seemed of interest to investigate the corresponding phenacylpyrimidines, and therefore certain 2- and 5-phenacylpyrimidines have been prepared using benzoylacetamidine and α-phenacylacetoacetic ester as intermediates. Phenacylpyrimidines previously reported in the literature include 1- and 5-derivatives obtained by treatment of a barbituric acid derivative with phenacyl bromide[2a] or alloxan with ethyl benzoylacetate.[2b]

Benzoylacetamidine (I) was prepared from benzoylacetonitrile through the imino ester hydrochloride. Haller[3] described the latter, which was treated with ammonia to obtain the free imino ester, but apparently no attempt was made to convert it to an amidine. Due to the presence of the benzoyl group, this amidine is unusual in regard to its stability and lack of strongly basic properties. The free amidine (I), rather than a hydrochloride, is the product isolated from the reaction of the imino ester hydrochloride with alcoholic ammonia. This can be recrystallized from water without decomposition.

To prepare 2-phenacylpyrimidine (II), benzoylacetamidine was condensed with β-ethoxyacrolein acetal. Condensation of I with acetylacetone

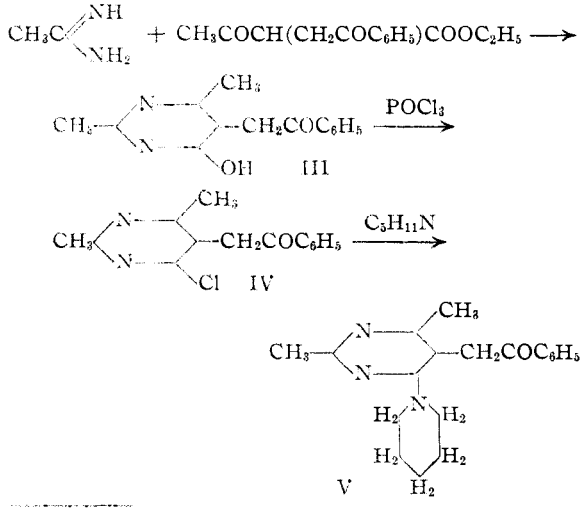


gave 4,6-dimethyl-2-phenacylpyrimidine, and with ethyl acetoacetate, 4-hydroxy-6-methyl-2-phenacylpyrimidine. These condensations were carried out by the method of Tuey[4] for the preparation of sulfadiazine from sulfaguanidine and β-ethoxyacrolein acetal.

Since it was found that phenacylpyridines and -quinolines brominated very readily on the methylene group, yielding α-bromo derivatives which reacted readily with amines,[1] similar bromination reactions were carried out with 2-phenacylpyrimidine. A monobromo derivative was thereby formed which was very stable and had the properties expected for 5-bromo-2-phenacylpyrimidine, rather than an α-bromo derivative. For example, it was unattacked by heating several hours with sodium hydroxide solution. It is not surprising that apparently a 5-bromopyrimidine was formed, since pyrimidines as a rule brominate very readily in this position. However, attempts to introduce a second atom of bromine in boiling glacial acetic acid were unsuccessful, even with the addition of acetic anhydride and benzoyl peroxide as catalysts, and in the presence of ultraviolet light.

As further evidence of the unreactivity of the methylene group of 2-phenacylpyrimidine, a Mannich condensation with formaldehyde and piperidine was attempted, to obtain 2-[α-benzoyl-β-(1-piperidyl)-ethyl]-pyrimidine. However, under all conditions tried the starting material was recovered unchanged. Likewise, attempted nitrosation of the methylene group with butyl nitrite in alcoholic sodium methylate solution[5] was unsuccessful. Unreactivity of the keto group was also evidenced by lack of oxime formation by the usual methods.

For synthesizing 5-phenacylpyrimidines, α-phenacylacetoacetic ester[6] was employed. Reaction with acetamidine in aqueous or alcoholic medium produced 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine (III). Chlorination of the latter proceeded in normal fashion with phosphorus oxychloride to yield the 6-chloro derivative (IV), which reacted readily with piperidine, giving 2,4-dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine (V). Compound III brominated readily in glacial acetic acid at 70°, but a mixture of products was obtained. These included the hydrobromide of the starting material and a dibrominated pyrimi-



(1) Smith, Stewart, Roth and Northey, THIS JOURNAL, **70**, 3997 (1948).

(2) (a) Kraeh and Hill, *ibid.*, **48**, 2743 (1926); Hultquist and Poe, *Ind. Eng. Chem., Anal. Ed.*, **7**, 398 (1935); Henze and Spurlock, THIS JOURNAL, **63**, 3360 (1941). (b) Kuhling, *Ber.*, **43**, 2406 (1910).

(3) Haller, *Bull. soc. chim.*, [2] **48**, 24 (1887).

(4) Tuey, British Patent 569,140, May 7, 1945.

(5) Meyer and Oetkers, *Ber.*, **21**, 1303 (1888).

(6) Paal, *ibid.*, **16**, 2866 (1883).

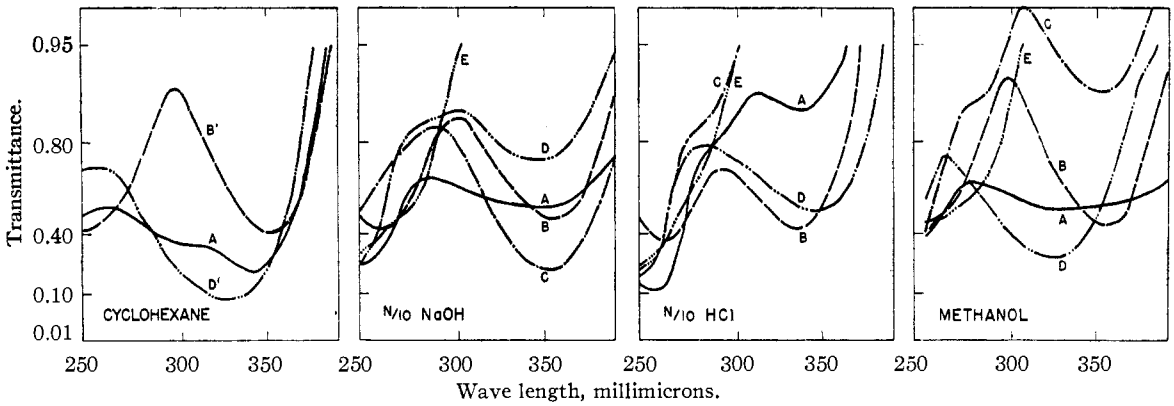


Fig. 1.—Ultraviolet absorption spectra[a] of 10 mg./l. solutions: A—, 2-phenacylpyridine; B– –, 2-phenacylpyrimidine hydrochloride; B'– –, 2-phenacylpyrimidine; C–·–, 4-phenacylpyridine hydrochloride; D–···, 2-phenacyl-4,6-dimethylpyrimidine hydrochloride; D'–···, 2-phenacyl-4,6-dimethylpyrimidine; E–···, 2,4-dimethyl-5-phenacyl-6-hydroxypyrimidine hydrochloride.

[a] Data were obtained on a Beckman quartz spectrophotometer using 1-cm. cells. Readings were made at 5 mμ intervals except at points of inflection where they were made at 1 mμ intervals.

dine base. No monobrominated derivative was isolated from the mixture.

Pharmacological data on these compounds will be reported elsewhere.

In an effort to explain the difference in behavior of the 2-phenacylpyrimidines from the 2- and 4-phenacylpyridines and quinolines in regard to reactivity of the methylene group, a spectrophotometric study was carried out by Miss Ruth Abbott of this Laboratory on samples of 2- and 4-phenacylpyridine, 2-phenacylpyrimidine and its 4,6-dimethyl derivative, and 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine to see whether any differences in type of structure were indicated. While the data obtained do not definitely prove the structures of the phenacylpyrimidines, there is no indication that these structures are incorrect.

Experimental[7,8]

Benzoylacetamidine.—Ten grams (0.069 mole) of benzoylacetonitrile[9] was dissolved in 50 ml. of dry benzene and 12.1 ml. (0.207 mole) of absolute alcohol added. The mixture was cooled to 0° and dry hydrogen chloride gas bubbled in until the mixture was saturated. It was kept at 0° over-night and then allowed to warm to room temperature, at which time only a small amount of crystalline material was present in the liquor. After two hours at room temperature, it had practically solidified. The product was filtered, washed with benzene, and dried in the vacuum desiccator; weight, 11.9 g. This was then mixed with 50 ml. of alcoholic ammonia, which had been saturated at 0°. The mixture stood for three days at room temperature, and was then filtered from ammonium chloride. The alcohol was distilled off, and ether added to the sirupy residue, resulting in the precipitation of 7 g. of benzoylacetamidine as a white solid. After two recrystallizations from water (1 g./20 ml.) the substance melted at 188–189°. It contained no halogen, and the *p*H of a saturated aqueous solution was 8.3. Upon warming with sodium hydroxide solution, ammonia was evolved.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.6; H, 6.22; N, 17.3. Found: C, 66.1; H, 6.2; N, 16.7.

2-Phenacylpyrimidine.—A mixture of 16 g. (0.099 mole) of benzoylacetamidine, 17.8 g. (0.102 mole) of β-ethoxyacrolein acetal,[10] 38 ml. of amyl alcohol (b.p. 124–128°, from Pentasol) and 10 ml. of glacial acetic acid was refluxed for ten hours, and the ethyl acetate and amyl alcohol were then distilled off at atmospheric pressure. Upon cooling the residue, 10 g. of tan oily solid crystallized. After distillation of the mother liquor under vacuum to remove remaining solvents, and recrystallization of the dark residue from isopropyl acetate, an additional 2.1 g. of product was obtained. The resultant 12.1 g. was recrystallized from 65 ml. of isopropyl acetate, yielding 7.2 g. (49%) of yellow solid melting at 146–148°. Upon further recrystallization for analysis, the melting point was raised to 147.8–148.5°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.69; H, 5.09; N, 14.14. Found: C, 73.0; H, 5.3; N, 13.9.

An attempt to prepare an oxime by the usual method was unsuccessful.

5-Bromo-2-phenacylpyrimidine.—To 1.00 g. (0.005 mole) of 2-phenacylpyrimidine in 5 ml. of glacial acetic acid was added dropwise a solution of 0.808 g. (0.005 mole) of bromine in 2 ml. of glacial acetic acid at 20°. The bromine was taken up immediately. The mixture was poured into water, resulting in the precipitation of a yellow solid, which, upon recrystallization from alcohol, melted at 144.8–145.6°.

Anal. Calcd. for $C_{12}H_9BrN_2O$: C, 52.0; H, 3.28; Br, 28.9; N, 10.1. Found: C, 51.9; H, 3.4; Br, 28.8; N, 10.0.

The above reaction proceeded equally well in chloroform. The product was isolated by evaporating off the solvent and slurrying the resultant sirup in water, which resulted in the precipitation of the above-described 5-bromo-2-phenacylpyrimidine as a yellow solid. When the chloroform solution stood for some time, a small amount of light tan crystalline material separated which melted with decomposition at 246.5–249.0°. This was apparently the hydrobromide salt of the 5-bromo derivative, which completely hydrolyzed in water to the pyrimidine base.

When the above product was heated on the steam-bath for several hours in 5 *N* sodium hydroxide solution containing a little alcohol, the original material was recovered unchanged. Similarly, the bromo compound did not react with piperidine.

(7) All melting points are corrected.

(8) We are indebted to Mr. O. Sundberg and assistants for the microanalyses.

(9) Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932); Long, *ibid.*, **69** 990 (1947).

(10) Claisen, *Ber.*, **36**, 3670 (1903); Price and Moos, THIS JOURNAL **67**, 207 (1945).

Addition of Two Moles of Bromine to 2-Phenacylpyrimidine.—A solution of 3.23 g. (0.02 mole) of bromine in 4 ml. of glacial acetic acid was added dropwise to a refluxing solution of 2 g. (0.01 mole) of 2-phenacylpyrimidine in 10 ml. of glacial acetic acid. At first the bromine was rapidly taken up, but the solution turned a dark red after approximately half had been added, and no more reaction appeared to take place. The mixture was refluxed for two hours after the addition was complete. The product was then cooled and poured into water. A quantitative yield of 5-bromo-2-phenacylpyrimidine was obtained. The reaction was repeated with the addition of 1 ml. of acetic anhydride and a few crystals of benzoyl peroxide. The same results were obtained, except for some darkening of the product in this case.

In another experiment, 1.2 g. (0.004 mole) of 5-bromo-2-phenacylpyrimidine was dissolved in 8 ml. of glacial acetic acid, and 0.5 ml. of acetic anhydride and a few crystals of benzoyl peroxide added. To this refluxing mixture was added dropwise a solution of 0.69 g. (0.004 mole) of bromine in 2 ml. of glacial acetic acid, in the presence of light from an ultraviolet lamp. The mixture became almost black, and some hydrogen bromide was given off. The only product which could be isolated from the black mixture was the original 5-bromo-2-phenacylpyrimidine.

Attempted Mannich Reaction with 2-Phenacylpyrimidine.—A mixture of 4.95 g. (0.025 mole) of 2-phenacylpyrimidine, 3.04 g. (0.025 mole) of piperidine hydrochloride, 1.13 g. (0.0375 mole) of paraformaldehyde, and 20 ml. of absolute alcohol was heated to refluxing for five hours. After the initial two hours an additional 0.75 g. of paraformaldehyde was added. Complete solution occurred. The mixture stood overnight at room temperature, and a precipitate of long yellow needles appeared. This proved to be 2-phenacylpyrimidine. Alcoholic hydrogen chloride was added to the solution until it was acid to congo red test paper. Another 0.75 g. of paraformaldehyde was added and the mixture refluxed for another twenty-six hours, small portions of additional paraformaldehyde being added from time to time. At the end of this time, the mixture was cooled and ether added, precipitating an oil which was taken up in water and neutralized with dilute sodium hydroxide solution. A yellow solid formed which after recrystallization from isopropyl acetate melted at 145.5–147.0° and showed no depression of the melting point with 2-phenacylpyrimidine.

Attempted Nitrosation of 2-Phenacylpyrimidine.—2-Phenacylpyrimidine (4.95 g., 0.025 mole) was slurried in 25 ml. of absolute alcohol, and a solution of 1.5 g. (0.028 mole) of sodium methylate in 10 ml. of absolute alcohol added. The solution was cooled to 0°, and 2.58 g. (0.025 mole) of freshly prepared butyl nitrite added dropwise. No change occurred in the appearance of the mixture, and no exothermic reaction took place. The mixture was stoppered and allowed to stand at room temperature for two days. The mixture was then cooled and the solid filtered off, washed with water and dried. The substance weighed 4.6 g., melted at 147.0–148.8° and showed no depression of melting point with 2-phenacylpyrimidine.

4,6-Dimethyl-2-phenacylpyrimidine.—A mixture of 10 g. (0.062 mole) of benzoylacetamidine, 6.2 g. (0.062 mole) of acetylacetone, 20 ml. of mixed amyl alcohols, and 6 ml. of glacial acetic acid was heated under reflux for twelve hours. The solvents were distilled off under vacuum, and the sirupy residue was washed with dilute sodium hydroxide solution and cold water, after which it slowly crystallized. Approximately 12.5 g. of crude 4,6-dimethyl-2-phenacylpyrimidine was obtained. This was purified by dissolving in hot 5 *N* hydrochloric acid, from which a yellow hydrochloride precipitated on cooling. Upon recrystallizing twice more from 5 *N* hydrochloric acid and twice from alcohol, with the aid of decolorizing charcoal, 8 g. of light yellow crystals was obtained which melted between 202–210°.

Anal. Calcd. for $C_{14}H_{14}N_2O \cdot HCl$: C, 64.0; H, 5.75; N, 10.7; Cl, 13.5. Found: C, 64.2; H, 5.64; N, 10.7; 13.6.

From the aqueous solution of the hydrochloride a light yellow base was precipitated on adding dilute sodium hydroxide solution. After drying in the vacuum desiccator, this melted at 74.0–75.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.3; H, 6.24; N, 12.4. Found: C, 74.4; H, 6.32; N, 12.3.

4-Hydroxy-6-methyl-2-phenacylpyrimidine.—This was prepared from benzoylacetamidine and ethyl acetoacetate in a fashion similar to the above, the product being purified by repeated reprecipitation from dilute sodium hydroxide solution. A white product was obtained which melted at 248.5–250.0°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.30; N, 12.3. Found: C, 68.6; H, 5.36; N, 12.2.

2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine.—A mixture of 515 g. (2.08 moles) of α-phenacylacetoacetic ester,[6] 197 g. (2.08 moles) of acetamidine hydrochloride, 84 g. (2.08 moles) of sodium hydroxide pellets dissolved in 830 ml. of water, and 100 ml. of 95% alcohol was stirred at room temperature for one-half hour, after which it was allowed to stand without stirring for two days. A thick crystalline mass formed, which was filtered off and washed well with water. This material, after drying at 50°, weighed 302 g., and contained considerable oily material. Upon recrystallization from 1100 ml. of 95% alcohol, a white crystalline product weighing 80 g. was obtained. This could be further purified by recrystallization from alcohol, benzene or isopropyl acetate, and then melted at 211–212°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.83; N, 11.6. Found: C, 69.2; H, 5.8; N, 11.7.

The original mother liquor, upon standing two more days, deposited an additional 50 g. of somewhat oily crystalline product. After drying, this was dissolved in 250 ml. of absolute alcohol, and an excess of alcoholic hydrogen chloride added. Upon cooling, the hydrochloride precipitated as an almost white solid weighing 30 g. Upon two recrystallizations from 98% alcohol, with charcoal, the hydrochloride gradually sintered and melted with decomposition at 267–268°.

4-Chloro-2,6-dimethyl-5-phenacylpyrimidine.—A mixture of 106 g. of 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine and 265 ml. of phosphorus oxychloride was heated for one hour on the steam-bath. The excess phosphorus oxychloride was distilled off under vacuum, and the residue poured on ice and neutralized with sodium bicarbonate. The substance, which appeared tarry at first, solidified to a tan solid. After drying at 55°, the weight was 111 g. Upon recrystallization from 600 ml. of V.M. and P. naphtha, which served to separate it from some insoluble impurities, the yield was 82 g. or 72%. After two further recrystallizations with the aid of charcoal the melting point of the white product was 103.5–104.5°.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.5; H, 5.03; Cl, 13.6; N, 10.8. Found: C, 64.2; H, 5.0; Cl, 13.7; N, 10.8.

2,4-Dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine.—A mixture of 60 g. (0.23 mole) of 4-chloro-2,6-dimethyl-5-phenacylpyrimidine and 60 g. (0.70 mole) of piperidine was warmed on the steam-bath until an exothermic reaction commenced. Cooling was then necessary for a few minutes to keep the reaction under control, after which it was heated for an additional fifteen minutes on the steam-bath to complete the reaction. The mixture was then cooled, and sufficient benzene added to make a workable slurry. It was filtered from piperidine hydrochloride, and the benzene solution extracted with an excess of dilute hydrochloric acid, followed by clarification of the acid extracts and neutralization with ammonia. A gummy precipitate was formed which soon solidified. This was filtered off and dried at 45°; weight, 68.6 g. Upon recrystallization from 350 ml. of V.M. and P. naphtha with the aid of charcoal the white product weighed 55 g. (78% yield) and melted at 87–89°.

Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.7; H, 7.50; N, 13.4. Found: C, 73.9; H, 7.7; N, 13.7.

The product was converted to the hydrochloride in absolute ether and recrystallized from alcohol–ether mixture. It then melted at 200–201°.

Bromination of 2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine.—2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine (1.00 g., 0.004 mole) was dissolved in 10 ml. of glacial acetic acid and a solution of 0.663 g. (0.004 m.) of bromine in 2 ml. of glacial acetic acid was added dropwise. No reaction occurred until the mixture was heated to 60–70°, when rapid decolorization took place. When a little more than half of the bromine had been added, white crystals began to separate, which redissolved for the most part by the time the remaining bromine had been added. The mixture was allowed to stand and cool for two hours, resulting in the slow formation of a white precipitate again. This was filtered, washed with ether, and dried; weight, 0.4 g. This proved to be a mixture consisting mainly of the hydrobromide of the starting material. On dissolving in water a small amount of insoluble material remained, which was removed by filtration. On neutralization of the filtrate with sodium bicarbonate, a white precipitate formed which, upon drying, melted at 207–209°, contained no halogen, and showed no depression of the melting point with the starting material. The acetic acid liquor yielded a white precipitate upon the addition of ether, but this became sirupy on all attempts at isolation. Upon pouring the acetic acid solution into water, a small amount of white precipitate formed; dry weight, 0.3 g. After purification by recrystallization from alcohol, the substance melted at 167–169°. Analysis indicated it to be a dibrominated base, which was not further identified.

Anal. Calcd. for $C_{14}H_{12}Br_2N_2O$: C, 42.0; H, 3.02; Br, 40.0; N, 7.01. Found C, 42.3; H, 2.97; Br, 40.1; N, 7.31.

Summary

A series of 2- and 5-phenacylpyrimidines has been prepared for pharmacological testing purposes. Condensations of benzoylacetamidine, a new compound, with β-ethoxyacrolein acetal, acetylacetone and ethyl acetoacetate yielded 2-phenacylpyrimidine, 4,6-dimethyl-2-phenacylpyrimidine and 4-hydroxy-6-methyl-2-phenacylpyrimidine, respectively. Condensation of α-phenacylacetoacetic ester with acetamidine yielded 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine.

The methylene group of 2-phenacylpyrimidine has been shown to be unusually unreactive. Bromination of 2-phenacylpyrimidine produced the 5-bromo derivative only. Mannich and nitrosation reactions failed. The ketone did not yield an oxime.

2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine was chlorinated to yield the 6-chloro derivative, which reacted with piperidine to form 2,4-dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine. Bromination reactions with the 6-hydroxy compound yielded mixtures, from which no monobrominated product was isolated.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Analogs of Pteroylglutamic Acid. II. 9-Methylpteroylglutamic Acid and Derivatives

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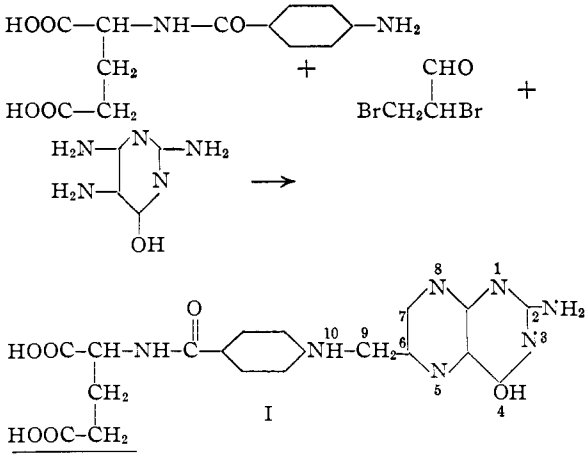
Pteroylglutamic acid (I) was synthesized by Waller, *et al.*,[1] by the simultaneous reaction of 2,4,5-triamino-6-hydroxypyrimidine,[2] 2,3-dibromopropionaldehyde, and *p*-aminobenzoyl-*l*(+)-glutamic acid[3] in aqueous solution at *p*H 4.



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(1) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948); Angier, *et al.*, *Science*, **103**, 667 (1946).

(2) Traube, *Ber.*, **33**, 1371 (1900).

(3) Van der Scheer and Landsteiner, *J. Immunology*, **29**, 373 (1935).

This reaction has proved to be of wide application and a number of derivatives of I have been prepared by varying one or more of the three components.[4] Previous communications from this Laboratory have described N^{10}-alkyl[5] and 4-amino[6] analogs of pteroylglutamic acid. The present paper deals with a series of analogs in which a methyl group has been introduced on the methylene bridge in the 9-position.

When 2,2,3-trichlorobutyraldehyde ("butyl chloral")[7] was reacted with 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid, there was formed N-[4-{[1-(2-amino-4-hydroxy-6-pteridyl)-ethyl]-amino}-benzoyl]-glutamic acid (II), hereafter designated as 9-methylpteroylglutamic acid.

(4) (a) Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947); (b) Hutchings, *et al.*, *ibid.*, **170**, 323 (1947); (c) Martin, Tolman and Moss, *Archives of Biochemistry*, **12**, 318 (1947); (d) Mowat, *et al.*, THIS JOURNAL, **70**, 1096 (1948); (e) Boothe, *et al.*, *ibid.* **70**, 1099 (1948); (f) Smith, Cosulich, Hultquist and Seeger, *Trans. N. Y. Acad. Science*, [II] **10**, 82 (1948); (g) Gordon, *et al.*, THIS JOURNAL, **70**, 878 (1948).

(5) Cosulich and Smith, *ibid.*, **70**, 1922 (1948).

(6) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947).

(7) Pinner, *Ann.*, **179**, 26 (1875). We are grateful to the Westvaco Chemical Corporation for a supply of butyl chloral.