and sublimation (140°/10 μ); m.p. 244–245°; $[\alpha]_D^{25}$ −212° (c, 0.65, methanol).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; CH_3COO—, 12.6. Found: C, 70.3; H, 7.1; CH_3COO—, 13.0.

O^3,O^6-Diacetyl-6-methylmorphine resulted when a solution of 96 mg. of O^6-acetyl-6-methylmorphine, one ml. of acetic anhydride and 2 ml. of pyridine was heated under reflux for 1.5 hr. The reaction mixture was concentrated *in vacuo*, the residue was distributed between chloroform and aqueous phosphate buffer (*p*H 3), and the aqueous phase, after adjustment to *p*H 8.7, was extracted thoroughly with chloroform. The residue from evaporation of the dried chloroform extracts was crystallized from ethyl acetate–hexane to give O^3,O^6-diacetyl-6-methylmorphine, m.p. 166–168°; $[\alpha]_D^{25}$ −200° (c, 0.77, methanol).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.6; C-CH_3, 12.1. Found: C, 69.3; H, 6.4; C-CH_3, 12.3.

Rates of hydrolysis of the O^3-acetyl derivatives prepared above were determined by dissolving 1 mg. of each compound in 10 ml. of 95% ethanol, 0.01*N* in sodium hydroxide. The ultraviolet absorption at 300 mμ, due to the formation of phenolate ion, was followed as a function of time. With O^6-acetyl-6-methylmorphine, the appearance of this peak was instantaneous and did not change with time. With O^3-acetyl-6-methylmorphine and O^3,O^6-diacetyl-6-methylmorphine, this peak appeared as hydrolysis proceeded and the half-time for hydrolysis was 40 sec. for the former and 120 sec. for the latter. Heroin (O^3,O^6-diacetylmorphine), run for comparison, had a half-time for hydrolysis of 100 sec.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Antiparasitic Agents. I. Some New 2,4-Diaminopyrimidines*

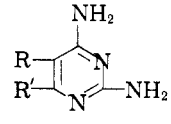
E. F. ROGERS, W. J. LEANZA, AND L. H. SARETT

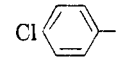
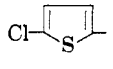
Received July 29, 1957

Six new substituted 2,4-diaminopyrimidines were prepared for chemotherapeutic evaluation. Three of these were found to have activity *vs. S. pyogenes;* one enhances sulfanilamide action *vs. Eimeria spp.*

Various 2,4-diaminopyrimidines and the analogously constituted 2,6-diaminopurines have been found to be folic acid antagonists[1] and, presumably, act in this capacity to inhibit growth of the parasites of malaria[2] and coccidiosis[3] as well as to show antibacterial[4] and antileukemic[5] activity. The most potent of the series in antimalarial activity is pyrimethamine,[2,6] 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (I). In addition to its antimalarial activity it also potentiates sulfaquinoxaline and sulfamezathine.[3] These properties prompted us to prepare some new 2,4-diaminopyrimidines related to pyrimethamine.

The new bases which were made are shown in formulas II–VII. In compounds II–IV, fluoroalkyl or alkoxyalkyl groups replace the 6-ethyl substituent in pyrimethamine; in compounds V–VII the 5-*p*-chlorophenyl is replaced by heterocyclic groups. In each case the bases differ in only one ring substituent.



	R	R′
I		$-C_2H_5$
II	〃	$-CF_3$
III	〃	$-C_2F_5$
IV	〃	$-CH(OCH_3)_2$
V		$-C_2H_5$
VI		$-C_2H_5$
VII		$-C_2H_5$

With the exception of compound VII the syntheses presented no special difficulties. The method is illustrated by the synthesis of 2,4-diamino-5-thienyl-6-ethylpyrimidine. These reactions were exploited most successfully by the Wellcome group in their investigations of 5-aryl-2,4-diaminopyrimi-

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) G. H. Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 467 (1952).

(2) I. M. Rollo, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 474 (1952); L. G. Goodwin, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 485 (1952); G. R. Coatney and W. C. Cooper, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 496 (1952).

(3) R. E. Lux, *Antibiotics and Chemotherapy*, **4**, 971 (1954).

(4) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951); E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

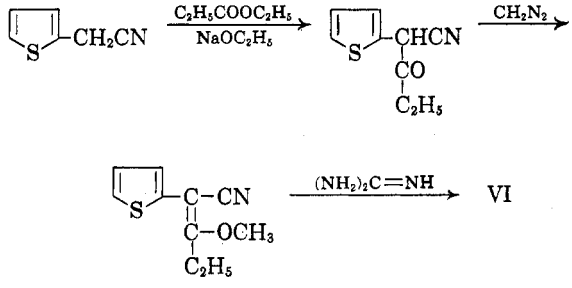
(5) M. L. Murphy, R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *J. Clin. Invest.*, **33**, 1388 (1954).

(6) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

TABLE I

5,6-DISUBSTITUTED 2,4-DIAMINO PYRIMIDINES

	R	R′	M.P., °C.	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
II	$C_6H_4Cl(4)$	CF_3	243–245	$C_{11}H_8N_4ClF_3$	45.87	2.79	19.41	46.07	2.83	19.58
III	$C_6H_4Cl(4)$	C_2H_5	200–201	$C_{12}H_8N_4ClF_5$	42.55	2.38	16.54	43.39	2.63	16.81
IV	$C_6H_4Cl(4)$	$CH(OCH_3)_2$	264–267	$C_{13}H_{15}N_4O_2Cl$	52.97	5.13	19.01	52.84	4.92	19.40
V	Furyl	C_2H_5	224–226	$C_{10}H_{12}N_4O$	58.81	5.92	27.44	59.39	5.65	27.71
VI	Thienyl	C_2H_5	247–248	$C_{10}H_{12}N_4S$	54.54	5.49	25.44	54.02	5.26	25.44
VII	5-Chloro-thienyl	C_2H_5	240–242	$C_{10}H_{11}ClN_4S$	47.15	4.35	22.00	47.59	4.20	21.83



dines.[6] The guanidine-β-alkoxyacrylonitrile cyclization apparently originated with Huber and Hoelscher[7] who prepared 5-cyano-2,4-diaminopyrimidine from ethoxymethylenemalononitrile and guanidine.

Satisfactory conditions could not be found for the base-catalyzed condensation of ethyl propionate with 5-chlorothienylacetonitrile; polymerization of the nitrile is competitive with the propionate condensation. Only by working at low temperatures could even a poor yield of β-ketonitrile be obtained.

The uncatalyzed condensation of orthoesters with compounds containing active methylene groups has been investigated by Jones[8] who found, for example, that ethyl orthoformate condenses with ethyl acetoacetate and ethyl cyanoacetate in yields approximating 20% after 2–6 hours at 140–150°. Whittaker[9] reacted ethyl orthopropionate with *p*-chlorophenylacetonitrile under similar conditions and the crude α-*p*-chlorophenyl-β-ethoxyacrylonitrile so obtained was converted to pyrimethamine. This method was utilized to secure sufficient α-(5-chloro-2-thienyl)-β-ethoxyacrylonitrile for guanidine condensation and synthesis of compound VII.

The pyrimethamine analogs have been tested for antibacterial, anticoccidial, and antimalarial activities. Activity against *Streptococcus pyogenes* was noted with compounds V–VII at 4 to 15 γ/ml., approximately the same level at which pyrimethamine shows borderline activity.[10] None of the bases showed prophylactic action in coccidiosis when fed at 0.0125%. One compound, the chlorothienyl analog VII, showed sulfaquinoxaline potentiation when fed in a 1:1 ratio (0.0125% of each). Compounds V–VII were tested as antimalarials. They were ineffective in reducing parasitemia at a daily dose of 0.4 mg./kg. in chickens infected with *P. gallinaceum*.[11] The effective pyrimethamine dose in this test was 0.04 mg./kg.

EXPERIMENTAL

In general the procedures of Russell and Hitchings were followed.

α-Acyl-p-chlorophenylacetonitriles. *p*-Chlorophenylacetonitrile was condensed with the appropriate ethyl ester in the presence of ethanolic sodium ethoxide to give the following derivatives: α-trifluoroacetyl, m.p. 95–97°, yield 54%; α-perfluoropropionyl, m.p. 110–111°, yield 47%; and α-dimethoxyacetyl, m.p. 106–108°, yield 61%.

α-Thienyl and furyl-β-ketovaleronitriles. The base VI intermediate, α(2-thienyl)-β-ketovaleronitrile, was prepared by a standard procedure as above. A 55% yield of crude product melting at 90° was obtained.

Anal. Calcd. for C_9H_9OSN: N, 7.82. Found: N, 7.48.

The corresponding furyl compound, α(2-furyl)-β-ketovaleronitrile, was an oxygen-sensitive oil. The compound was prepared and subsequently condensed with guanidine under nitrogen.

α(5-Chloro-2-thienyl)-β-ketovaleronitrile was formed in very low yields when the Claisen condensation was run at −10 to −20° for 1 hr., then permitted slowly to warm to room temperature during 2 additional hr. A very vigorous reaction occurs if 5-chloro-2-thienylacetonitrile is added to a 10% solution of sodium ethoxide in ethanol; considerable heat is generated and sodium chloride and polymeric material are immediately formed. The product from the low temperature condensation melted at 110° after recrystallization from benzene.

Anal. Calcd. for C_9H_8OClSN: C, 50.59; H, 3.77; N, 6.56. Found: C, 50.63; H, 3.70; N, 6.69.

5,6-Disubstituted-2,4-diaminopyrimidines. The ketonitriles were treated with an excess of diazomethane in ether and kept at 0–5° overnight. After evaporation of the ether and unreacted diazomethane, the residual sirup was dissolved in alcohol and added to a solution of guanidine in alcohol. The mixture was heated for 4 hr., then cooled, and the crystalline product collected and recrystallized from alcohol. The compounds prepared are listed in Table I.

2,4-Diamino-5-(5′-chloro-2′-thienyl)-6-ethylpyrimidine. Fifty-two grams of 5-chloro-2-thienylacetonitrile and 30 g. of ethyl orthopropionate were heated under reflux at 160–165° for 20 hr. An additional 30 g. of orthoester was then

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(8) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 4889 (1952).
(9) N. Whittaker, U. S. Patent **2,755,298** (1956).
(10) Personal communication, A. K. Miller, Merck Institute for Therapeutic Research.
(11) Personal communication, A. C. Cuckler and C. Malanga, Merck Institute for Therapeutic Research.

added and the reflux was cut off so that over the next 20 hr. the temperature rose to 185°. The cooled reaction mixture was diluted with 100 ml. of ether and placed in the icebox overnight. The heavy amorphous precipitate was rejected. After ether evaporation the residual oil was pumped out to remove starting materials (2 hr., bath temperature 110–115° at 1–2 mm.). The residual oil, weighing 10.5 g., was carried through the usual guanidine condensation. From the chloroform and 2*N* hydrochloric acid soluble fraction of reaction product 3.2 g. of pyrimidine was obtained. Recrystallization from methanol gave crystals, m.p. 240–242°.

Acknowledgment. The authors are indebted to Drs. Max Tishler and Karl Folkers for their interest and encouragement of this study and to Dr. A. C. Cuckler for helpful advice on biological matters.

RAHWAY, N. J.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structure of *x*-Bromoacetyl-*N*-acetyl-9,10-dihydroacridine*[1]

LEWIS J. SARGENT

Received June 27, 1957

The elucidation of the position occupied by the bromoacetyl group in the title compound has been achieved. This, incidentally, represents the first example of a successful Friedel-Crafts acylation in acridine chemistry.

Some years ago in a study of the plasmodicidal properties of diverse acridine derivatives, a series of amino alcohols derived from *x*-bromoacetyl-*N*-acetyl-9,10-dihydroacridine (I) was synthesized.[2]

It was pointed out at the time that the proof of the structure of this key substance depended upon the availability of certain acridine derivatives then unknown. This deficiency was rectified shortly thereafter by the synthesis of the four requisite ethylacridines by unambiguous routes,[3] and the present communication reports the final phase in arriving at the constitution of I.

The reactions involved in degrading I to an ethylacridine of known constitution are shown in the chart. In the presence of sodium acetate the palladium-charcoal catalyzed debromination step occurred smoothly with hydrogen absorption coming to a virtual halt after the uptake of one mole. On the other hand, when sodium acetate was omitted, the hydrogen bromide formed *in situ* not only induced *N*-acyl cleavage–as evidenced by the isolation of a small amount of *x*-acetyl-9,10-dihydroacridine (III) in one instance–but apparently catalyzed reduction at other sites in the molecule as well. The product isolated from the buffered reduction system, *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II) was a colorless glass that resisted crystallization even after passage through its well-defined semicarbazone. *N*-acyl hydrolysis of II gave *x*-acetyl-9,10-dihydroacridine (III) which was reduced (Wolff-Kishner) to *x*-ethyl-9,10-dihydroacridine (IV). The latter substance proved to be exceedingly air sensitive, more so than the parent 9,10-dihydroacridine. For example, while a pure sample of the latter showed virtually no change in melting point even after one year's keeping in a closed vial, a sublimed specimen of IV exhibited a marked melting point drop after only two days storage in a vial. Potassium dichromate oxidation[4,5] of IV yielded a substance which was identical in all respects with synthetic 3-ethylacridine.[3]

In another approach, *x*-acetyl-9,10-dihydroacridine (III) was oxidized with potassium dichromate to *x*-acetylacridine (VI) which, upon Wolff-Kishner reduction, gave 3-ethylacridine thereby establishing VI as the presently unknown 3-acetylacridine.

After demonstrating that I could be debrominated to *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II), several attempts (five in all) were made to prepare II through Friedel-Crafts acylation of *N*-acetyl-9,10-dihydroacridine by acetyl chloride or acetyl bromide under the conditions utilized in the synthesis of I.[2] Two experiments with acetyl chloride failed to yield any of the desired product; only starting material was recovered. In one of the two acetyl bromide runs (where the reaction mixture was allowed to stand overnight at 25° before workup) it was possible to isolate *ca.* 1.5% of the desired II (as its semicarbazone) from the mother liquors of recovered (85%) starting material. The infrared spectrum of this semicarbazone was identical with that of the corresponding derivative of II obtained *via* the bromoketone. A final acylation with acetyl bromide in nitrobenzene yielded the following three products: (*a*) starting material, 40%, (*b*) acridine, 20%, and (*c*) dihydroacridine, 10%, along with some tarry material. It is of interest that the latter two substances should turn up in this reaction, and

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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(5) *Cf.* ref. 3.