with 358 mg. of chromic anhydride in 15 ml. of 80% aqueous acetic acid. After the excess oxidizing agent had been destroyed with methanol the mixture was concentrated *in vacuo* and water was added. The product was extracted with ether–chloroform and the organic solution washed with 5% aqueous sodium hydroxide and finally water. The solution was dried over sodium sulfate and evaporated to a small volume to afford 350 mg. of hecogenone. The m.p. and mixed m.p. of this material with authentic hecogenone prepared by chromic anhydride oxidation of hecogenin was 238–241°. The infrared spectra of both samples were identical in all respects; $[\alpha]^{24.5}D$ +23.8° (chf.).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.70; H, 9.35. Found: C, 75.44; H, 9.09.

An additional 200 mg. of hecogenone was obtained from the mother liquors, giving a total yield of 550 mg.

Hecogenin (XII).—A solution of 1.7 g. of hecogenone in 75 ml. of anhydrous tetrahydrofuran was added to a well-stirred solution of 1.5 g. of lithium aluminum hydride in 100 ml. of dry ether. After the mixture had stirred at room temperature for two hours, water and dilute hydrochloric acid were added and the aqueous layer was separated. The aqueous layer was concentrated *in vacuo* to remove the tetrahydrofuran and then extracted with chloroform. The combined organic extracts were washed with water, saturated salt solution, dried and evaporated to give crude XI which was employed as such in the next step.

The crude reduction product (XI) was dissolved in 20 ml. of anhydrous pyridine containing 3.0 g. of succinic anhydride and heated on a steam-bath for 3 hr. in an atmosphere of nitrogen. After the reaction mixture had been concentrated *in vacuo*, water was added and the product was extracted with chloroform and ether. The organic layer was washed with dilute hydrochloric acid, water, saturated salt solution, and finally dried over sodium sulfate. The solvents were evaporated *in vacuo* to give 2.4 g. of the crude 3-hemisuccinate derivative of (XI) which was employed without further purification in the succeeding step.

The above hemisuccinate derivative, 2.4 g., was dissolved in 50 ml. of acetic acid and oxidized at room temperature for 16 hr. with 350 mg. of chromic anhydride in 10 ml. of 80% aqueous acetic acid. The oxidation product was worked up as previously described (see above) to give *ca.* 2.16 g. of crude hecogenin hemisuccinate. Saponification of the latter was effected directly by dissolving it in 75 ml. of methanol containing 4.0 g. of potassium hydroxide and refluxing for 4 hours in an atmosphere of nitrogen. The methanol was removed *in vacuo*, water was added, and the product extracted with chloroform. The chloroform extract was washed with water, saturated salt solution, and dried over sodium sulfate. The residue obtained on removal of the solvent was crystallized from chloroform–ethyl acetate to yield hecogenin as small plates, m.p. 263–266°. A mixed m.p. of this material with an authentic sample was 263–266°; wt. 350 mg. An additional 300 mg. of somewhat lower melting material was obtained from the mother liquors; $[\alpha]^{24.5}D$ +13.5° (chf.).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.35; H, 9.77. Found: C, 75.48; H, 9.94.

The acetate was prepared and crystallized from chloroform–ethyl acetate, m.p. and mixed m.p. with authentic hecogenin acetate was 247–50°, $[\alpha]^{24.5}D$ +92° (chf.).

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.73; H, 9.37. Found: C, 73.52; H, 9.32.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. X. Some 1,3-Oxazolo(5,4-d)pyrimidines

BY ELVIRA A. FALCO, GERTRUDE B. ELION, ELIZABETH BURGI AND GEORGE H. HITCHINGS

RECEIVED MAY 1, 1952

A series of 1,3-oxazolo(5,4-d)pyrimidines has been prepared by treatment of 5-amido-4-hydroxypyrimidines with phosphoryl chloride. With a 5-amido-6-amino-4-hydroxypyrimidine both a purine and an oxazolopyrimidine usually are formed. The relative proportion of the oxazolopyrimidine is increased when a reagent prepared by mixing water with the phosphoryl chloride is used for the cyclization. The latter reagent is superior to phosphoryl chloride in the formation of some other oxazolopyrimidines. The conversion of representative oxazolopyrimidines to purines by heating with amines could be demonstrated. The ultraviolet absorption spectra of the oxazolopyrimidines aid in the differentiation of these substances from certain oxazinopyrimidines previously described.

The preparation and study of some 1,3-oxazolo-5,4-d)pyrimidines in this Laboratory were undertaken for several reasons. Derivatives of condensed pyrimidine systems bearing functional groups in the pyrimidine ring analogous to those of the natural purines are of interest as antimetabolites,[1,2] as are the 5-mono- and 5,7-diamino derivatives.[3] Furthermore, certain derivatives were desired for comparison with the isomeric *p*-oxazino(2,3-d)pyrimidines,[4] to add support to the assignment of the structure of the latter through the elimination of a possible alternative formulation.[4]

Several 1,3-oxazolo(5,4-d)pyrimidines have been reported in the literature. Biltz[5] prepared some acyl and alkyl derivatives of 5,7-dihydroxy-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine by heating uramil and 1-methyluramil with an excess of benzoyl chloride. It appeared possible that the desired derivatives could be obtained by chlorination of the dihydroxy derivative followed by various transformation reactions analogous to those employed by Fischer in the purine series.[6] However, in several attempts a satisfactory preparation of the 5,7-dichloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine from the dihydroxy derivative could not be achieved.

Attention was then turned to the method of preparation of Johnson,[7] which involved cyclization of a 5-amido-4-hydroxypyrimidine by treatment with phosphoryl chloride. The only oxazolopyrimidine prepared by Johnson, 5-ethylmercapto-2-phenyloxazolo(5,4-d)pyrimidine, was found unsatisfactory for the present purposes. When it was heated with alcoholic ammonia solution, it was recovered unchanged at temperatures below 170°,

(1) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(2) G. B. Elion, G. H. Hitchings and H. VanderWerff, *ibid.*, **192**, 505 (1951).

(3) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *ibid.*, **174**, 765 (1948).

(4) P. B. Russell, G. B. Elion and G. H. Hitchings, THIS JOURNAL, **71**, 474 (1949).

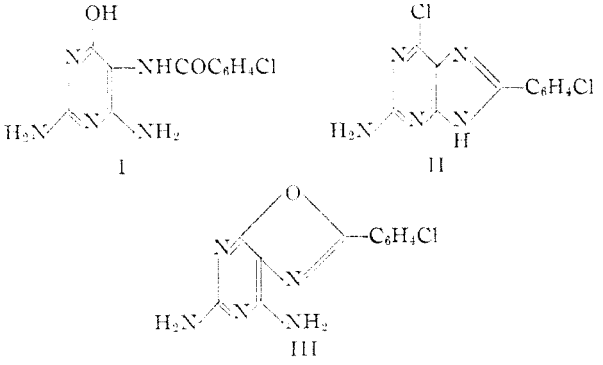
(5) H. Biltz, K. Strufe and J. Karte, *Ann.*, **404**, 180 (1914).

(6) E. Fischer, *Ber.*, **30**, 2226 (1897).

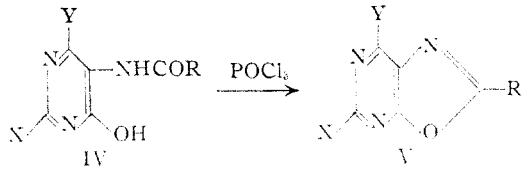
(7) T. B. Johnson, *Am. Chem. J.*, **34**, 191 (1905).

while at higher temperatures a pyrimidine, presumably 5-amino-2-ethylmercapto-4-hydroxypyrimidine, was recovered. However, the cyclization of 5-amido-4-hydroxypyrimidines with phosphoryl chloride proved to be a quite general reaction and a considerable variety of oxazolo(5,4-d)pyrimidines was attained by this method.

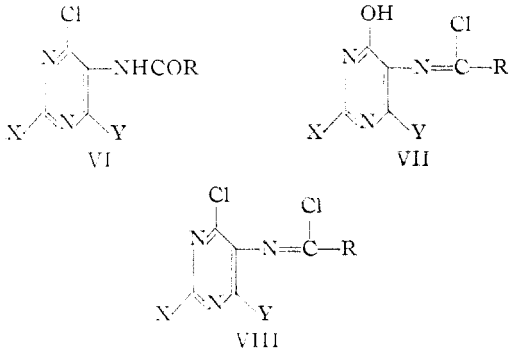
The treatment of 5-(4′-chlorobenzamido)-2,4-diamino-6-hydroxypyrimidine (I) with phosphoryl chloride gave a considerable yield of purine (II) and only a small amount of oxazolopyrimidine (III).



In order to avoid any possible ambiguity with regard to the nature of the products 5-amido-4-hydroxypyrimidine (IV, X = H, Y = H) and its 6-methyl (IV, X = H, Y = CH_3) and 2,6-dimethyl (IV, X = CH_3, Y = CH_3) derivatives were employed in a study of the cyclization. These gave 2-phenyloxazolopyrimidines (V, R = C_6H_5) readily on treatment with phosphoryl chloride. These products, in general, are sparingly soluble in water but are soluble in organic solvents, from which they are easily crystallizable.



In the course of work on the preparation of 8-phenylpurines[8] it was found that treatment of 4-amino-5-benzamido-6-hydroxypyrimidines with phosphoryl chloride gave two products. The fraction soluble in aqueous alkali (purine) was the major product while the alkali-insoluble fraction (oxazolopyrimidine) was present in highly variable (although usually minor) proportion. Investigation showed that with carefully dried amide and freshly distilled phosphoryl chloride, the amount of oxazolopyrimidine was reduced to a trace. When water was added to the phosphoryl chloride, an increased proportion of oxazolopyrimidine was obtained (Table I) reaching a maximum with a reagent containing 0.5 mole of water per mole of phosphoryl chloride (expt. 4, Table I). Chlorination, as an intermediate step in the cyclization, might occur on either the pyrimidine (VI) or amide moiety (VII).



That halogenation of both positions can occur is indicated by observations on 5-chloroacetamido-2-dimethylamino-4-hydroxy-6-methylpyrimidine on treatment with a mixture of phosphoryl chloride and phosphorus pentachloride. The product of this reaction appears to have the structure VIII (X = $(CH_3)_2N$, Y = CH_3, R = CH_2Cl). Analogous products were obtained during a study of the cyclodehydration of 5-β-hydroxyethyl-4-hydroxypyrimidines with phosphoryl chloride.[9] In the purine series it appears probable that chlorination precedes cyclization,[8] *i.e.*, that a compound of type VIII (Y = NH_2) is a probable intermediate.

Most of the oxazolopyrimidines are reasonably stable to alkali and acid; however, cleavage of the oxazole ring occurs on prolonged treatment with strong acid.[7] When 5,7-diamino-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine was boiled with 6 *N* hydrochloric acid for six hours, ring cleavage and hydrolysis of the 7-amino group occurred. 2-Amino-5-(4′-chlorobenzamido)-4,6-dihydroxypyrimidine (IX) was isolated in good yield. A smaller quantity of 4-chlorobenzoic acid also was identified among the products.

Although attempts to replace an ethylmercapto by an amino group had failed, the desired 5-amino-2-phenyloxazolo(5,4-d)pyrimidine was obtained *via* the 5-chloro derivative. Amination of 5-chloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine took place in good yield when the chloro compound was heated with alcoholic ammonia at 140°, but at 160° cleavage to 2,5-diamino-4-hydroxypyrimidine and conversion to 2-amino-8-phenylpurine both occurred. Similarly 2-(4′-chlorophenyl)-5,7-diamino-1,3-oxazolo(5,4-d)pyrimidine was converted to 2,6-diamino-8-(4′-chlorophenyl)-purine (X) when

TABLE I

PURINE AND OXAZOLOPYRIMIDINE FROM 4-AMINO-5-BENZAMIDO-6-HYDROXYPYRIMIDINES. EFFECT OF PROPORTIONS OF WATER AND PHOSPHORYL CHLORIDE

In each experiment 5 g. of 5-(4′-chlorobenzamido)-2,4-diamino-6-hydroxypyrimidine was heated for two hours at reflux temperature with reagent consisting of the indicated volume of water and sufficient phosphoryl chloride to make 100 ml. Similar results were obtained with 4-amino-5-(4′-chlorobenzamido)-6-hydroxypyrimidine.

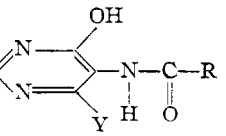
Experiment no.	Water, ml.	Oxazolopyrimidine, g.	Purine, g.
1	1.0	0.29	2.7
2	2.0	0.41	2.9
3	6.5	1.15	2.1
4	9.0	1.34	2.1
5	13.0	0.60	2.7

(8) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **73**, 5235 (1951).

(9) A. Schrage and G. H. Hitchings, *J. Org. Chem.*, **16**, 1153 (1951).

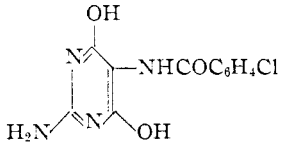
Table II

5-Amido-6-hydroxypyrimidines

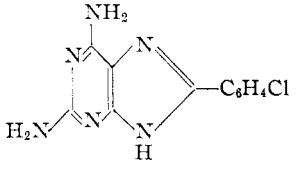


X	Y	R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	C_6H_5	282	$C_{13}H_{13}N_3O_2$	64.2	64.2	5.3	5.1		
CH_3	H	C_6H_5	294	$C_{12}H_{11}N_3O_2$	62.8	63.2	4.8	4.7		
CH_3	CH_3	$C_6H_4CH_3(4)$	278–279	$C_{14}H_{15}N_3O_2$	65.3	65.3	5.8	5.5		
CH_3	CH_3	H	245–248	$C_7H_9N_3O_2$	50.3	50.0	5.4	5.6		
CH_3	CH_3	$C_6H_4Cl(4)$	310–315 dec.	$C_{13}H_{12}ClN_3O_2$					15.2	15.1
CH_3	CH_3	$C_6H_4NO_2(4)$	320 dec.	$C_{13}H_{12}N_4O_4$					19.4	19.1
H	H	C_6H_5	249–250	$C_{11}H_9N_3O_2$	61.3	61.3	4.2	4.0		
$N(CH_3)_2$	CH_3	CH_3	225–227	$C_9H_{14}N_4O_2$	51.5	51.7	6.7	6.1		
H	NH_2	$C_6H_4NO_2(3)$	305 dec.	$C_{11}H_9N_5O_4$					25.4	24.9
H	NH_2	$C_6H_4Cl(4)$	345–350 dec.	$C_{11}H_9ClN_4O_2$					21.2	21.7

heated with alcoholic ammonia at 160° for 96 hours, and the corresponding 7-amino derivative was converted to 6-amino-8-(4′-chlorophenyl)-purine under the same conditions. The last-named oxazolopyrimidine appears to undergo the same type of reaction with methyl and propylamines (to give 9-alkylpurines), but not with benzylamine. However, the 5,7-diamino derivative failed to give isolable products with methyl and benzylamines and aniline.

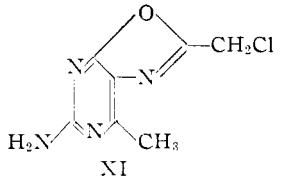


IX

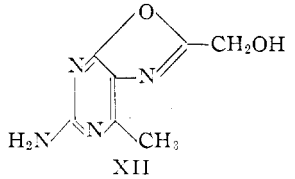


X

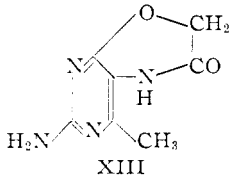
The cyclization of 2-amino-5-chloroacetamido-4-methyl-6-hydroxypyrimidine with phosphoryl chloride was studied. It was expected that the 2-chloromethyloxazolopyrimidine (XI) could be converted to the corresponding 2-hydroxymethyl derivative (XII) which would be isomeric with the oxazinopyrimidines (XIII) reported earlier.[4]



XI



XII



XIII

The first attempts with phosphoryl chloride alone and with added phosphorus pentachloride led to products in which chlorination but not cyclization had occurred. The addition of water to the phosphoryl chloride gave a reagent capable of producing the desired chloromethyloxazolopyrimidine. However, treatment of this compound with acid or alkali or heating in water caused hydrolysis of the oxazole ring under relatively mild conditions. Nevertheless the spectra of compounds of the oxazolopyrimidine type are clearly distinguishable from those of the oxazinopyrimidines (Table IV).

Experimental

5-Benzamidopyrimidines.—These substances (except as described below) were prepared by the treatment of the 5-aminopyrimidines with the acyl halide in alkaline aqueous solution essentially as described by Wilson.[10] The characteristics of the new amides are given in Table II. The known amides were as follows: 5-benzamido-2,4-dihydroxypyrimidine[11] and four 2,4-diamino-6-hydroxypyrimidines: 5-(4′-chlorobenzamido),[12] 5-(2′-bromobenzamido),[8] 5-(3′-nitrobenzamido)[8] and 5-(4′-bromobenzamido).[8]

5-Benzamido-4-hydroxypyrimidine.—This was prepared by the condensation of the crude sodium derivative of 22 g. of ethyl formylhippurate[13] with 5.0 g. of formamidine hydrochloride in 100 ml. of ethanol at room temperature for 72 hours. The yield was 1.9 g. of pyrimidine melting at 249–250° (dec.) after recrystallization from hot ethanol.

5-Benzamido-4-hydroxy-2-methylpyrimidine.—This was prepared by the condensation of ethyl formylhippurate (48 g. of crude sodium derivative) with acetamidine (4.6 g. of the hydrochloride and 2.7 g. of potassium hydroxide) in 150 ml. of water at room temperature for 72 hours (*cf.* 13). After recrystallization from ethanol, the compound (2.45 g.) melted at 294–295° (dec.).

2,4-Dimethyl-5-formamido-6-hydroxypyrimidine.—Two grams of 5-amino-2,4-dimethyl-6-hydroxypyrimidine[14] was heated to boiling with 30 ml. of 98% formic acid for one-half hour and then evaporated to dryness on the steam-bath. The residue was taken up in 20 ml. of water and neutralized with dilute ammonium hydroxide solution. The product thus obtained was recrystallized from 95% ethanol and formed needles melting at 245–248°.

5-Acetamido-2-dimethylamino-4-methyl-6-hydroxypyrimidine.—One gram of 5-amino-2-dimethylamino-4-methyl-6-hydroxypyrimidine[4] was refluxed with 20 ml. of acetic anhydride for one hour. The excess anhydride was removed under reduced pressure and the residue was recrystallized from ethanol. The yield was 800 mg. of compound melting at 225–227°.

1,3-Oxazolo(5,4-d)pyrimidines. General Method.—The 5-amido-4-hydroxypyrimidine was heated at reflux temperature with 10 ml. of phosphoryl chloride per gram of amide. The excess phosphoryl chloride was removed under reduced pressure and the sirupy residue was poured over ice. The mixture was then made alkaline. (Certain modifications for compounds which can form either oxazolopyrimidines or purines are noted below.)

The oxazolopyrimidine was obtained by filtration of the alkaline solution in the case of most of the 2-phenyl deriva-

(10) W. Wilson, *J. Chem. Soc.*, 1157 (1948).

(11) R. Behrend and R. Grünwald, *Ann.*, **309**, 259 (1899).

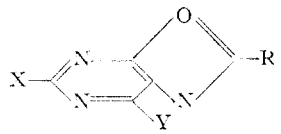
(12) E. A. Falco and G. H. Hitchings, This Journal, **72**, 3203 (1950).

(13) T. B. Johnson and S. H. Clapp, *Am. Chem. J.*, **32**, 130 (1904).

(14) H. Andersag and K. Westphal, *Ber.*, **70**, 2045 (1937).

TABLE III

1,3-OXAZOLO(5,4-d)PYRIMIDINES



X	Y	R	Yield, %	Solvent of recryst.	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	C_6H_5	60	Water	108–109	$C_{13}H_{11}N_3O$	69.3	69.3	4.9	4.6	18.7	18.5
CH_3	H	C_6H_5	68	Water	122	$C_{12}H_9N_3O$	68.2	68.7	4.3	4.4	19.9	19.9
CH_3	CH_3	$C_6H_4OCH_3(4)$	38	Water	176–177	$C_{14}H_{13}N_3O_2$	65.9	66.0	5.1	4.8		
CH_3	CH_3	H	10	Sublimed	118–119	$C_7H_7N_3O$	56.3	56.4	4.7	4.6		
CH_3	CH_3	$C_6H_4Cl(4)$	73	95% Ethanol	196–197	$C_{13}H_{10}ClN_3O$	60.1	59.8	3.9	3.7		
CH_3	CH_3	$C_6H_4NO_2(4)$	10	Methanol	224–225	$C_{13}H_{10}N_4O_3$					20.7	20.3
CH_3	CH_3	$C_6H_4NH_2(4)$	50	95% Ethanol	193 dec.	$C_{13}H_{12}N_4O$	65.0	64.6	5.0	4.8		
H	H	C_6H_5	52	Sublimed	113–116	$C_{11}H_7N_3O$	67.0	66.8	3.6	3.4		
$N(CH_3)_2$	CH_3	CH_3	5	Sublimed	83–84	$C_9H_{12}N_4O$	56.3	56.1	6.3	6.0	29.2	29.1
NH_2	CH_3	CH_2Cl		Benzene	238–239 dec.	$C_7H_7ClN_4O$[a]	42.3	42.3	3.5	3.8		
Cl	H	C_6H_5	62	Sublimed	165–167	$C_{11}H_6ClN_3O$	57.1	57.3	2.6	2.4	18.2	18.6
NH_2	H	C_6H_5		See text	285–287	$C_{11}H_8N_4O$	62.3	62.5	3.8	3.4	26.4	26.4
NH_2	NH_2	$C_6H_4Cl(4)$	[b]	Ethyl acetate	316–318 dec.	$C_{11}H_9ClN_5O$	50.5	50.9	3.1	2.6	26.8	26.5
NH_2	NH_2	$C_6H_4NO_2(3)$	50	Ethyl acetate	291–292 dec.	$C_{11}H_8N_6O_3$	48.5	48.4	2.9	2.9	30.9	30.2
NH_2	NH_2	$C_6H_4Br(4)$	10	Ethyl acetate	320–321 dec.	$C_{11}H_8BrN_5O$	43.1	42.8	2.6	2.5	22.9	22.7
NH_2	NH_2	$C_6H_4Br(2)$	4	Ethyl acetate	247–248 dec.	$C_{11}H_8BrN_5O$	43.1	43.1	2.6	2.7	22.9	23.1
H	NH_2	$C_6H_4NO_2(3)$	11	Ethyl acetate	263–266 dec.	$C_{11}H_7N_5O_3$	51.3	51.1	2.7	2.8	27.2	27.8
H	NH_2	$C_6H_4Cl(4)$	[b]	Ethyl acetate	>320	$C_{11}H_7ClN_4O$	53.5	53.4	2.8	2.9	22.7	22.1

[a] Calcd.: Cl, 17.9 Found: Cl, 17.7. [b] See text.

tives. However, ether extraction from neutral solution was employed for the 2-unsubstituted, the 2-methyl-, the 2-chloromethyl-, the 5-chloro-2-phenyl-, and for the unsubstituted 2-phenyl derivatives.

Purification of the water-insoluble oxazolopyrimidines was effected by solvents indicated in Table III. The ether-soluble compounds were sublimed, except where otherwise indicated in Table III, at 0.03 mm., after evaporation of the solvent. The following sublimation temperatures were found: 2,7-dimethyl-5-dimethylamino-1,3-oxazolo (5,4-d)-pyrimidine, 40°; 5-chloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine, 110–150°; 5,7-dimethyl-1,3-oxazolo(5,4-d)pyrimidine, 80–90°. In the preparation of the last a second substance sublimed at 90–110°, melted at 142–145°. It was found to contain chlorine and was not investigated further.

The time of heating was in general of the order of two to three hours, but longer heating was required for the 2,7-dimethyl-5-dimethylamino-1,3-oxazolo(5,4-d)pyrimidine (15 hours) and 5-chloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine (36 hours).

Most of the experiments reported here were performed with commercial phosphoryl chloride. Later work indicates that a mixture of phosphoryl chloride and water is a considerably more effective reagent. Phosphoryl bromide was employed for the preparation of 5,7-diamino-2-(3'-nitrophenyl)-1,3-oxazolo(5,4-d)pyrimidine (*cf.*[8]).

The method for compounds which may form either purines or oxazolopyrimidines is illustrated by the preparation of 7-amino-2-(4'-chlorophenyl)-1,3-oxazolo(5,4-d)pyrimidine. Purines formed in the other reactions have been reported previously.[8]

7-Amino-2-(4'-chlorophenyl)-1,3-oxazolo(5,4-d)pyrimidine.—Fourteen grams of 4-amino-5-(4'-chlorobenzamido)-6-hydroxypyrimidine was refluxed for three hours with 140 g. of commercial phosphoryl chloride. The excess phosphoryl chloride was removed under reduced pressure and the residue poured over ice. The mixture was then adjusted to *p*H 10 with 2 *N* sodium hydroxide. The insoluble material (crude oxazole) was then filtered off and the filtrate was neutralized with acetic acid to precipitate the 8-(4'-chlorophenyl)-6-chloropurine. The purine was purified by recrystallization from 95% ethanol.

Anal. Calcd. for $C_{11}H_6Cl_2N_4$: C, 49.8; H, 2.3; N, 21.1. Found: C, 50.1; H, 2.5; N, 21.0.

The absorption spectrum is given in Table IV. The oxazolopyrimidine (1.4 g.) (10% yield) crystallized from a large volume of ethyl acetate in pale yellow plates. When this reaction was carried out with phosphoryl chloride containing 2% of added water the yield of oxazole was 47%.

5-Amino-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine.—5-Chloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine (160 mg.) and ethanolic ammonia saturated at 0° (15 ml.) was heated at 140° for 16 hours. After evaporation of the bomb contents to dryness, the compound was recrystallized from ethanol; m.p. 285–287°.

Acid Hydrolysis of 2-(4'-Chlorophenyl)-5,7-diamino-1,3-oxazolo(5,4-d)pyrimidine.—The diaminoöxazolopyrimidine (175 mg.) was heated at reflux temperature with 60 ml. of 6 *N* hydrochloric acid for six hours. On cooling there formed a few colorless needles, which were soluble in dilute alkali. The substance melted at 240–242° and did not depress the melting point of an authentic sample of 4-chlorobenzoic acid. When the filtrate from the chlorobenzoic acid was neutralized and evaporated to 20 ml. a compound was precipitated which did not melt at 320° and whose ultraviolet absorption spectrum (Table IV) was identical with the pyrimidine described below.

Anal. Found: N, 19.8.

2-Amino-5-(4'-chlorobenzamido)-4,6-dihydroxypyrimidine.—This compound was prepared by the method of Wilson[10] using 150 mg. of 2,5-diamino-4,6-dihydroxypyrimidine hydrochloride[15] and 0.11 ml. of 4-chlorobenzoyl chloride. The product was washed with about 10 ml. of ether and purified by solution in alkali followed by precipitation with dilute acetic acid solution. It did not melt at 320°.

Anal. Calcd. for $C_{11}H_9ClN_4O_3$: N, 20.0. Found: N, 19.7.

2-Amino-8-phenylpurine. (a) From 5-Chloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine.—One gram of the oxazolopyrimidine was heated at 160° in a sealed tube with 50 ml. of alcoholic ammonia (saturated at 0°) for 16 hours. The contents of the tube were cooled and filtered. The precipitate was purified by solution in 3% alcoholic hydrochloric acid followed by precipitation with 100 ml. of ether. The ultraviolet spectrum of this compound (Table IV) was identical with that of an authentic sample of 2,5-diamino-4-hydroxypyrimidine dihydrochloride dihydrate made by the method of Johnson and Johns.[16]

Anal. Calcd. for $C_4H_6N_4O \cdot 2HCl \cdot 2H_2O$: C, 20.4; H, 5.1; N, 23.8; H_2O, 15.3; HCl, 31.1. Found: C, 20.5; H, 5.1; N, 24.3; H_2O, 15.3; HCl, 31.5.

The filtrate, from the original bomb contents, was evaporated to dryness and the residue recrystallized from a small

(15) G. H. Hitchings and G. B. Elion, THIS JOURNAL, **71**, 467 (1949).

(16) T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **34**, 554 (1905).

Table IV

Ultraviolet Absorption Spectra

Compound	pH 1 $\lambda_{max.}$, mμ	pH 1 ε	pH 1 $\lambda_{min.}$, mμ	pH 1 ε	pH 11 $\lambda_{max.}$, mμ	pH 11 ε	pH 11 $\lambda_{min.}$, mμ	pH 11 ε
2,7-Dimethyl-5-dimethylamino-1,3-oxazolo(5,4-d)pyrimidine	255	18,300	230	5,950	260	16,800	285	1430
	325	3,280	285	1,340	320	5,560		
2-Chloromethyl-5-amino-7-methyl-1,3-oxazolo-(5,4-d)pyrimidine	245	25,800	275	3,180	250	14,900	275	4480
	310	8,410			300	11,200		
2-(4′-Chlorophenyl)-7-amino-1,3-oxazolo(5,4-d)-pyrimidine	295	[a]	250	[a]	242		270	[a]
					295			
2-(4′-Chlorophenyl)-5,7-diamino-1,3-oxazolo-(5,4-d)pyrimidine	310	[a]	255	[a]	242		265	[a]
					315	[a]		
2-Amino-5-(4′-chlorobenzamido)-4,6-dihydroxy-pyrimidine	255	20,800			240	16,000		
					253[b]	13,750		
2,5-Diamino-4-hydroxypyrimidine	255	6,150	233	4,250	242	7,270	270	3350
					295	4,920		
6-Amino-8-phenylpurine	238	15,500	255	7,350	243	20,800	270	9300
	297	23,100			313	20,400		
2-Amino-8-phenylpurine	260	23,200	235	13,800	240	17,200	275	6550
	335	12,400	285	7,900	330	18,800		
6-Amino-8-(4′-chlorophenyl)-9-methylpurine	238	15,500	255	7,350	243	20,800	270	9300
	297	23,100			313	20,400		
6-Chloro-8-(4′-chlorophenyl)-purine	242	12,700	255	6,150	240	19,900	260	3850
	305	30,000			312	30,000		
2-Amino-6-hydroxy-4-methyl-*p*-oxazino(2,3-d)-pyrimidine	255	8,650	240	4,500	243	5,950	262	4500
	310	3,060	290	2,520	285	5,200		
2-Dimethylamino-6-hydroxy-4-methyl-*p*-oxazino(2,3-d)pyrimidine	235	10,900	250	8,500	280	11,300	245	3560
	265	11,500	295	2,180				
	325	3,170						

[a] Compounds are very insoluble, run in saturated solution. [b] Inflection.

amount of water. There was obtained 120 mg. of 2-amino-8-phenylpurine in faintly pink needles which melted at 265–268°.

Anal. Calcd. for $C_{11}H_9N_5$: C, 62.6; H, 4.3; N, 33.2. Found: C, 62.1; H, 4.2; N, 32.8.

The ultraviolet absorption data are given in Table IV.

(b) **From 5-Benzamido-2,4-diaminopyrimidine.**[12]—The amide (750 mg.) was heated at 205–210° for one-half hour. The solid was then dissolved in 0.1 *N* sodium hydroxide, filtered, and precipitated by neutralization with glacial acetic acid. The compound melted at 265–268°. Its analysis and ultraviolet absorption spectra showed it to be 2-amino-8-phenylpurine identical with the compound described above.

6-Amino-8-(4′-chlorophenyl)-9-methylpurine.—A mixture of 7-amino-2-(4′-chlorophenyl)-1,3-oxazolo(5,4-d)pyrimidine and 75 ml. of 10% alcoholic methylamine solution was heated in a sealed tube at 160° for 16 hours. The reaction mixture was evaporated to dryness, taken up in hot 2 *N* hydrochloric acid and allowed to stand overnight. The precipitated pale pink needles were dried at 120°.

Anal. Calcd. for $C_{12}H_{10}ClN_5 \cdot HCl \cdot 2H_2O$: C, 43.3; H, 4.5; N, 21.0; HCl, 10.9; H_2O, 10.8. Found: C, 43.7; H, 4.0; N, 20.4; HCl, 10.4; H_2O, 10.5.

Its ultraviolet spectrum resembled that of the 9-unsubstituted purine (below) except for a shift in the longer wave length band (Table IV).

6-Amino-8-(4′-chlorophenyl)-purine. (a) From the Oxazolopyrimidine.—A mixture of 60 mg. of 7-amino-2-(4′-chlorophenyl)-1,3-oxazolo(5,4-d)pyrimidine and 100 ml. of alcoholic ammonia (saturated at 0°) was heated in a sealed tube at 160° for 70 hours. The pale pink solid, obtained on evaporation to dryness, was dissolved in 0.1 *N* sodium hydroxide and precipitated by neutralization with glacial acetic acid.

Anal. Calcd. for $C_{11}H_8ClN_5$: N, 28.5. Found: N, 28.5.

The ultraviolet absorption data (Table IV) showed the compound to be identical with the purine described below.

(b) **From 5-(4′-Chlorobenzamido)-4,6-diaminopyrimidine.**—Five grams of the crude amide, prepared in the usual way, was heated at 200° for one hour and the product was purified by solution in dilute sodium hydroxide solution followed by precipitation with glacial acetic acid. The purine was then recrystallized from 2 *N* hydrochloric acid.

Anal. Calcd. for $C_{11}H_8ClN_5 \cdot HCl$: C, 46.6; H, 3.2; N, 24.7. Found: C, 47.1; H, 3.5; N, 24.9.

8-(4′-Chlorophenyl)-2,6-diaminopurine from 2-(4′-Chlorophenyl)-5,7-diamino-1,3-oxazolo(5,4-d)pyrimidine.—The oxazolopyrimidine (550 mg.) was heated at 160° for 96 hours with 150 ml. of alcoholic ammonia (saturated at 0°). The reaction mixture was evaporated, taken up in dilute sodium hydroxide solution and filtered. After neutralization with acetic acid the precipitate (250 mg.) was collected. The alkali-insoluble material was identified as the starting material and the alkali-soluble compound was found identical in all respects with an authentic specimen of 8-(4′-chlorophenyl)-2,6-diaminopurine.[8]

5-Amino-2-chloromethyl-7-methyl-1,3-oxazolo(5,4-d)pyrimidine.—Two grams of 2-amino-5-chloroacetamido-4-hydroxy-6-methylpyrimidine[9] was refluxed for 90 minutes with 20 ml. of phosphoryl chloride to which had been added 1.3 ml. of water. The phosphoryl chloride was removed under reduced pressure and the residual sirup was poured over ice. The cold mixture was neutralized with ammonium hydroxide (to *p*H 8.5), then extracted three times with 100-ml. portions of ether and three times with 100-ml. portions of benzene. The extracts were combined and dried over sodium sulfate and evaporated to dryness. The residue, recrystallized from benzene, formed colorless microprisms, melting at 237–239° (dec.).

Anal. Calcd. for $C_7H_7ClN_4O$; C, 42.3; H, 3.5; N, 28.2; Cl, 17.9. Found: C, 42.3; H, 3.8; N, 28.0; Cl, 17.7.

On standing for three hours in 2.5 *N* sulfuric acid at room temperature hydrolytic cleavage of the oxazole ring apparently occurred, as evidenced by the absorption spectrum of the product which was essentially that of the chloroacetamidopyrimidine. On boiling with 2 *N* sodium hydroxide, the compound dissolved in about 15 minutes, being converted to a substance with the absorption spectrum of 2,5-diamino-4-hydroxy-6-methylpyrimidine.

Attempted Preparation of 2-Chloromethyl-5-dimethylamino-7-methyl-1,3-oxazolo(5,4-d)pyrimidine from 5-Chloroacetamido-2-dimethylamino-4-methyl-6-hydroxypyrimidine.[4] **(a) With Commercial Phosphoryl Chloride.**—When

750 mg. of the pyrimidine (m.p. 258°) was heated for 15 hours with 50 ml. of phosphoryl chloride and worked up by the general method described above (using ether extraction), there was obtained by sublimation at 120° and 0.03 mm. a compound with a proportion of chlorine higher than that of the starting amide. The colorless needles melted at 168–170°.

Anal. Calcd. for $C_9H_{12}Cl_2N_4O$: C, 41.1; H, 4.6; Cl, 27.0. Found: C, 40.9; H, 4.5; Cl, 26.0.

(b) **With Phosphoryl Chloride Containing Phosphorus Pentachloride.**—Treatment of the starting material (750 mg.) with 50 ml. of phosphoryl chloride containing 10 g. of phosphorus pentachloride under the same conditions again failed to give the desired oxazolopyrimidine but gave a small quantity of product with an even lower carbon analysis, giving a strong qualitative test for chlorine.

Anal. Calcd. for $C_9H_{11}Cl_3N_4$: C, 38.4; H, 3.9. Found: C, 37.4; H, 3.4.

(c) **With Phosphoryl Chloride Containing Water.**—When 350 mg. of starting material was heated for 90 minutes with 4 ml. of phosphoryl chloride to which had been added 0.65 ml. of water and worked up as above, there was obtained 150 mg. of a product which sublimed in needles at 90–130° (0.03 mm.), m.p. 107–108°. The oxazolopyrimidine was not obtained in a completely pure state, being accompanied by a substance richer in chlorine from which complete separation was not achieved. Nevertheless the ultraviolet absorption spectrum and analysis indicated the probability of its presence as the major component of the mixture.

Anal. Calcd. for $C_9H_{11}ClN_4O$: C, 47.7; H, 4.9; Cl, 15.7. Found: C, 46.5; H, 4.9; Cl, 16.2.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined using the Beckman model DU spectrophotometer, in aqueous solutions at a concentration of 10 mg. per l. (unless otherwise indicated) in 0.1 *N* hydrochloric acid and in a Sørensen glycine–sodium hydroxide buffer at *p*H 11.

Acknowledgments.—The authors are indebted to S. W. Blackman and N. Martinez, Jr., for the microanalyses reported here.

TUCKAHOE, NEW YORK

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

Constituents of Pyrethrum Flowers. XXIV. Synthetic *dl-cis*-Cinerolone and Other Cyclopentenolones[1,2]

BY MILTON S. SCHECHTER, NATHAN GREEN AND F. B. LAFORGE

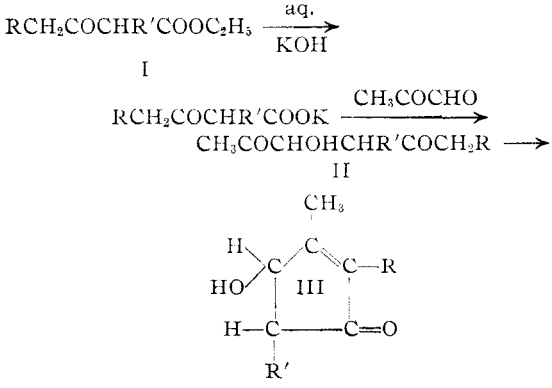
RECEIVED NOVEMBER 10, 1950

A general synthesis of cyclopentenolones previously described has been extended to the preparation of some new ones with chlorine-containing side chains. A synthesis of *dl-cis*-cinerolone identical with the product from the natural source is also presented.

The general procedure originated by Schechter, *et al.*,[2] for the synthesis of cyclopentenolones analogous to cinerolone and pyrethrolone has made possible the preparation of completely synthetic, highly potent insecticidal esters of the pyrethrin type.[3] The ester considered to be most practical from the standpoint of both technical production and entomological results, *dl*-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one esterified with a mixture of *cis*- and *trans-dl*-chrysanthemum monocarboxylic acids, for which the name allethrin has been adopted, is now being produced commercially.[4] It seems to be relatively safe on the basis of pharmacological results,[5] its properties in this respect being in marked contrast to the toxic chlorine- or phosphorus-containing insecticides, such as DDT, chlordane, parathion, etc.

As with most biologically active compounds, it is of interest to effect changes in the structure of an active compound with the hope of producing a more potent one or to learn something about the effect of structure on activity. Since the pyrethrin-like compounds are esters, it is possible to make changes in either the acid or the cyclopentenolone moieties.

This article describes a number of new cyclopentenolones which are analogs of cinerolone. They were prepared by the same general procedure as described previously,[2] which consists in the condensation of pyruvaldehyde with a salt of a β-keto acid obtained by saponification of a β-keto ester (I) and cyclization of the resulting hydroxydiketone (II) to a cyclopentenolone (III) in the presence of alkali.



R′ = H except in e; c, R = —$CH_2CH{=}CClCH_3$
a, R = —$CH_2CH{=}CHCl$; d, R = —$CH_2C{\equiv}CCH_3$
b, R = —$CH_2CCl{=}CH_2$; e, R and R′ = —$CH_2CH{=}CH_2$

In our previous article,[2] the synthesis of 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one was described and it was stated that this synthetic product was probably the *trans* isomer because of the *trans* configuration of the crotyl bromide used as a starting material. Furthermore, a comparison of derivatives with those of natural

(1) Presented before the Division of Organic Chemistry at the A.C.S. Meeting in Chicago, Illinois, on September 5, 1950.

(2) For XXIII see M. S. Schechter, N. Green and F. B. LaForge, THIS JOURNAL, **71**, 3165 (1949).

(3) Anon., *Chem. Eng. News*, **27**, 1942 (1949); M. S. Schechter, N. Green and F. B. La Forge, *Agr. Chemicals*, [6] **4**, 57 (1949).

(4) Anon., *ibid.*, [4] **5**, 75 (1950).

(5) D. F. Starr, P. Ferguson and T. N. Salmon, *Soap and Sanit. Chem.*, [3] **26**, 139 (1950); C. P. Carpenter, C. S. Weil, U. C. Pozzani and H. F. Smyth, *Arch. Ind. Hyg. Occupational Med.*, **2**, 420 (1950).