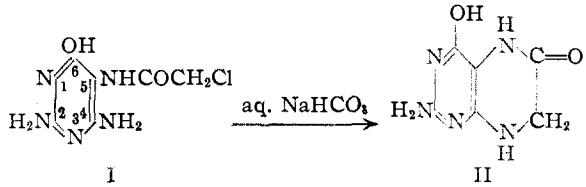
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

A New Condensed Pyrimidine System: Some *p*-Oxazino[2,3-*d*]pyrimidines[1]

BY PETER B. RUSSELL, GERTRUDE B. ELION AND GEORGE H. HITCHINGS

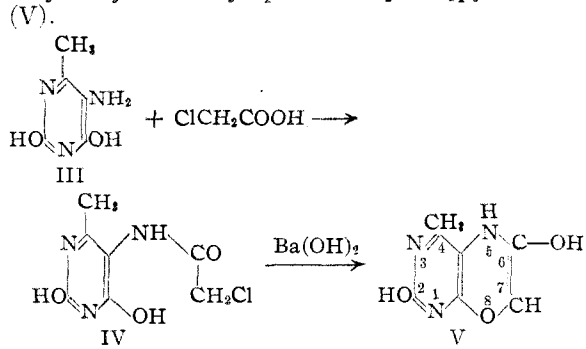
The synthesis of a new isomer of dihydroxanthopterin (II) by the ring closure of 5-chloroacetamido-2,4-diamino-6-hydroxypyrimidine (I) with sodium bicarbonate solution has been reported.[2]



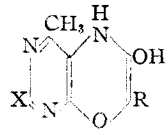
I II

During the investigation of methods for closure of the dihydropyrazine ring other alkaline reagents were studied, and barium hydroxide was found to give a product whose ultraviolet absorption spectrum was different from that of I, II or the α-dihydroxanthopterin of O'Dell and co-workers.[3] Although this new compound was not isolated in pure form, the possibility that ring closure involving the 6-hydroxyl group had taken place was suggested. By analogy with the formation of 3-hydroxy-[benz-*p*-oxazine][4] from *o*-chloroacetamidophenol by treatment with potassium hydroxide solution, it appeared probable that the product obtained by the action of barium hydroxide on I was a member of the hitherto unknown group of substances, the *p*-oxazino[2,3-*d*]pyrimidines.

In order to eliminate the possibility of pteridine formation, 5-chloroacetamido-6-hydroxypyrimidines were prepared which did not carry amino groups at position 4 and these were heated with aqueous barium hydroxide. After failure to isolate any of the desired compounds from 5-chloroacetamidouracil or from 5-chloroacetamido-2-amino-6-hydroxypyrimidine, an experiment with 5-chloroacetamido-2,6-dihydroxy-4-methylpyrimidine, (IV) produced a colorless, crystalline compound, $C_7H_7O_3N_3$, which was believed to be 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (V).



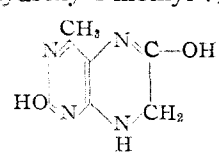
Similar compounds (VI, VII and VIII) were formed from the 2-amino-, 2-methylamino- and 2-dimethylaminopyrimidines corresponding to IV, and two 4,7-dimethyl-*p*-oxazino[2,3-*d*]pyrimidines, IX and X, were prepared from the appropriate 5-α-bromopropionamido derivatives. The reaction failed to occur with the 2-methyl analog of IV or with 5-(α-chlorophenylacetamido)-4-methyl-2,6-dihydroxypyrimidine.

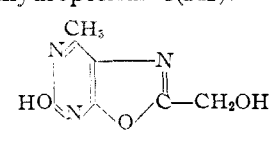


VI	X = NH_2	R = H
VII	X = CH_3NH	R = H
VIII	X = $(CH_3)_2N$	R = H
IX	X = OH	R = CH_3
X	X = NH_2	R = CH_3

In order to prove the structure of these substances, compound V was chosen for more intensive study. The absorption spectrum of V (Fig. 1) was found to have two bands, one of them in the region usually associated with the pyrimidine ring, the second in the higher wave lengths. Hence, the spectrum was consistent with the formulation of the compound as a condensed pyrimidine system. Hydrolysis of V with concentrated hydrochloric acid at 100° resulted in recovery of the pyrimidine (III) showing that there had been no structural changes in the original pyrimidine nucleus during treatment with barium hydroxide. It also ruled out the possibility that one of the nitrogens of the pyrimidine ring may have been alkylated either inter- or intramolecularly by the chloroacetyl group with a subsequent hydrolysis of the amide linkage or linkages. Hydantoin formation would give a product with the observed empirical composition; however, the pyrimidine-N-acetic acids do not hydantoinize.[5] Moreover, such a pyrimidine-N-acetic acid derivative would not be split to the parent pyrimidine III under the rather mild conditions employed.

Additional evidence in favor of the *p*-oxazinopyrimidine structure was obtained when V was heated with concentrated ammonium hydroxide at 120° in a closed system. The product obtained gave an analysis corresponding to the formula $C_7H_8O_2N_4$ and had an absorption spectrum resembling that of a dihydropteridine (Fig. 2), *cf.* ref. (2). It is therefore considered to be 2,6-dihydroxy-4-methyl-7,8-dihydropteridine(XI).





There remained one further possibility to be

(1) Presented before the Chicago, Ill., meeting of the American Chemical Society, April, 1948.

(2) Hitchings and Elion, THIS JOURNAL, **71**, 467 (1949).

(3) O'Dell, Vandenbelt, Bloom and Pfiffner, *ibid.*, **69**, 250 (1947).

(4) Aschan, *Ber.*, **20**, 1524 (1887).

(5) Wheeler and Liddle, THIS JOURNAL, **30**, 1154 (1908).

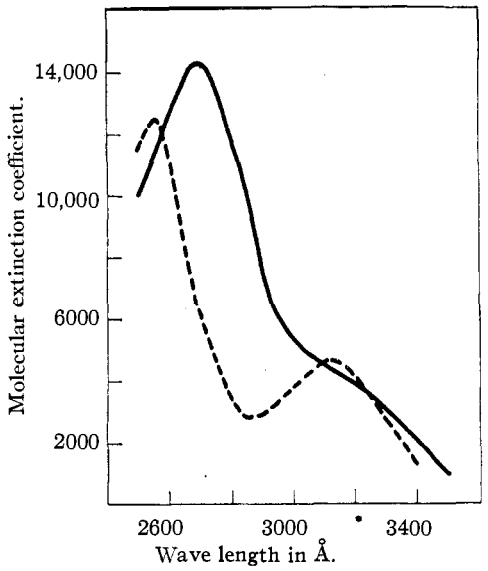


Fig. 1.—Ultraviolet absorption spectra of 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine: ---, at *p*H 1.0; —, at *p*H 11.0.

considered before the structure of V could be regarded as unequivocally established, namely, that a hydroxymethyloxazolo[2,3-*d*]pyrimidine of type XII had been formed. The mode of formation,[6] the structural requirements for ring closure,[7] and the physical properties[7] of the two groups

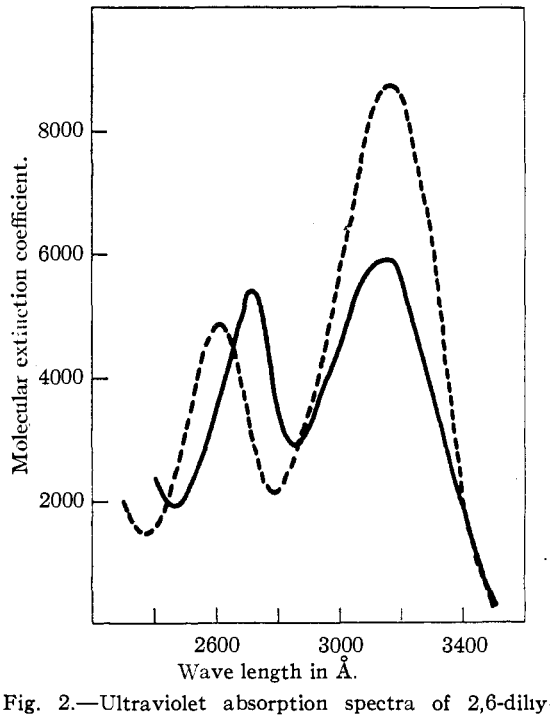
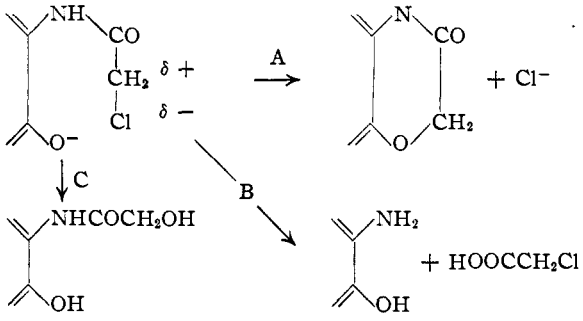


Fig. 2.—Ultraviolet absorption spectra of 2,6-dihydroxy-4-methyl-7,8-dihydropteridine: ---, at *p*H 1.0; —, at *p*H 11.0.

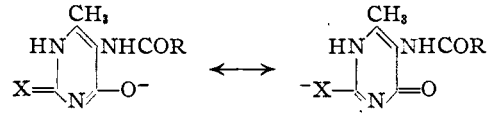
(6) Johnson, *Am. Chem. J.*, **34**, 203 (1905).
(7) Falco and Hitchings, forthcoming publication.

of compounds are so widely different as to leave little doubt that this oxazolo structure can be eliminated from consideration here.

In view of the limitations of this method for the synthesis of *p*-oxazinopyrimidines, it was decided to investigate further the mechanism of the ring closure. The oxazines are formed as a result of reaction A, but the low yields indicate that other reactions, of which B and C are the most probable, are competing with it.



The extent to which reaction A proceeds would be expected to depend on the ease of ionization of the 6-hydroxyl group, and the acid strength of this group would be governed by resonance of the type shown



Thus a greater excess of barium hydroxide is necessary to obtain the maximum yield of (VI), X = NH, than is necessary for (V), X = O (Fig. 3). Where X is a group incapable of taking part in resonance of this type (*e. g.*, methyl), the formation of the oxazine would be expected only at com-

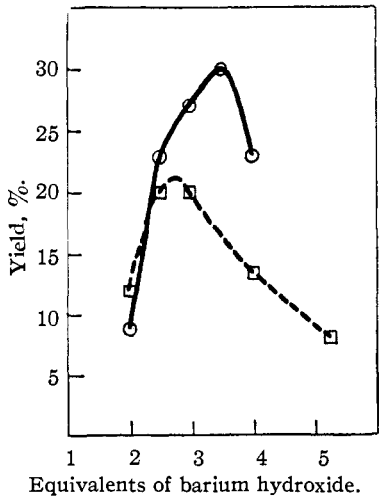


Fig. 3.—Relationship between barium hydroxide concentration and yield of: —⊙—, 2-amino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine; - - -⊡- - -, 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine.

paratively high concentrations of barium hydroxide, conditions which favor reactions B and/or C. This may account for the failure to isolate any *p*-oxazinopyrimidine in the case of 5-chloroacetamido-2,4-dimethyl-6-hydroxypyrimidine. Similar considerations may explain the failure of sodium hydroxide and sodium methoxide to effect ring closure in any of several attempts.

Experimental

5-Chloroacetamido-2,6-dihydroxy-4-methylpyrimidine (IV).—An intimate mixture of 0.5 g. of 5-amino-2,6-dihydroxy-4-methylpyrimidine[8] and 2 g. of chloroacetic acid was heated in a boiling water-bath under vacuum for two hours. The cooled mass was extracted with ether, washed with sodium bicarbonate solution and recrystallized from 50% aqueous ethanol. It formed colorless needles, m. p. 257–258° (dec.), (0.75 g., 98%).

Anal. Calcd. for $C_7H_8O_3N_3Cl$: C, 38.6; H, 3.5. Found: C, 38.9; H, 3.7.

2,6-Dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (V).—5-Chloroacetamido-2,6-dihydroxy-4-methylpyrimidine (0.5 g.) was heated with 30 ml. of a solution containing 1.12 g. of barium hydroxide hydrate (3 equivs. of $Ba(OH)_2 \cdot 8H_2O$). After about one-half hour a crystalline barium salt separated; heating was continued for another hour. The warm solution was treated with an excess of sodium sulfate, the barium sulfate filtered off and the solution made faintly acidic with acetic acid. On standing, the oxazinopyrimidine separated as colorless prisms (0.10 g., 30%). On crystallization from water, it formed elongated prisms, m. p., 348–349° (dec.).

Anal. Calcd. for $C_7H_7O_3N_3$: C, 46.4; H, 3.9; N, 23.2. Found: C, 46.5; H, 3.7; N, 23.5.

Hydrolysis of V with Hydrochloric Acid.—One hundred mg. of V was dissolved in 5 ml. of concentrated hydrochloric acid and the solution was heated on the steam-bath for twenty hours. The hydrochloric acid and water were removed by evaporation to dryness several times in an open dish. The residue was dissolved in 2 ml. of water and saturated sodium acetate solution was added until the *p*H was about 7. Slightly yellow plates separated (80 mg.) with a m. p. of 257° (dec.). Mixed with an authentic sample of 5-amino-2,6-dihydroxy-4-methylpyrimidine (m. p., 256–259°), the m. p. was 258–260°. Its absorption spectrum in acid and in alkaline solution was identical with that of 5-amino-2,6-dihydroxy-4-methylpyrimidine.

Treatment of V with Ammonium Hydroxide.—One hundred mg. of V was heated in a sealed tube with 10 ml. of concentrated ammonium hydroxide solution at 120° for six hours. The contents were filtered and evaporated to dryness on the steam-bath. The residue was treated with 5 ml. of water and acidified with acetic acid; the solution had a blue fluorescence. The brownish material was filtered off, dissolved in water, treated with carbon and the filtrate was evaporated to dryness. It decomposed at 305–310° without melting.

Anal. Calcd. for $C_7H_8O_2N_4$: C, 46.6; H, 4.5; N, 31.1. Found: C, 47.0; H, 4.4; N, 31.2.

5-α-Bromopropionamido-2,6-dihydroxy-4-methylpyrimidine.—This was prepared by heating 0.5 g. of 5-amino-2,6-dihydroxy-4-methylpyrimidine with 2.5 g. of α-bromopropionic acid. The product was obtained in almost quantitative yield. It was almost insoluble in hot alcohol. Recrystallized from water it formed colorless needles, m. p. 275–276° (dec.).

Anal. Calcd. for $C_8H_{10}O_3N_3Br$: C, 34.9; H, 3.3. Found: C, 35.0; H, 3.3.

2,6-Dihydroxy-4,7-dimethyl-*p*-oxazino[2,3-*d*]pyrimidine (IX).—The α-bromopropionamido derivative (0.3 g.) described above was heated with 30 ml. of an aqueous solution of barium hydroxide containing 0.57 g. (3 equiv.) of the hydrate in a boiling water-bath for one and one-half hours. After precipitation of the barium as sulfate, the solution was filtered and acidified with acetic acid. The oxazinopyrimidine crystallized slowly (0.08 g.). When recrystallized from water it formed stout colorless needles, m. p. 338–340° (dec.).

Anal. Calcd. for $C_8H_9O_3N_3$: C, 49.2; H, 4.6; N, 21.4. Found: C, 49.3; H, 4.6; N, 21.4.

5-Benzeneazo-2-amino-6-hydroxy-4-methylpyrimidine.—Guanidine hydrochloride (19.2 g.) was added to a solution of 44 g. of ethyl benzeneazoacetoacetate[9] in 250 ml. of absolute alcohol. The mixture was stirred while a sodium ethoxide solution (9.2 g. of sodium in 200 ml. of absolute alcohol) was added over three and one-half hours. After the mixture had stood two days at room temperature, the orange solid was filtered off and dissolved in 1 liter of water. The solution was acidified with acetic acid and the precipitate collected. After washing with 1 liter of 5% sodium bicarbonate solution and then with water, it was dried at 100° (30 g.). On recrystallization from pyridine, it formed orange-red prisms, m. p. 274° (dec.).

Anal. Calcd. for $C_{11}H_{11}ON_5$: C, 57.6; H, 4.8. Found: C, 57.9; H, 4.8.

2,5-Diamino-6-hydroxy-4-methylpyrimidine.—The above azo compound (3.5 g.) was suspended in 100 ml. of 50% aqueous ethanol and reduced catalytically at 60° using a platinum catalyst and two to three atmospheres of hydrogen. Reduction was complete after three hours. The solution was filtered and evaporated to dyness on a steam-bath under diminished pressure. The residue was washed with acetone to remove aniline, and the almost colorless residue recrystallized from water (1.0 g.). The m. p. was 280°. This compound had previously been prepared by Jaeger[10] in poor yield from the corresponding 5-bromo compound and ammonia and reported to have a m. p. of 275°.

Anal. Calcd. for $C_5H_8ON_4$: C, 42.9; H, 5.7. Found: C, 43.0; H, 5.8.

5-Chloroacetamido-2-amino-6-hydroxy-4-methylpyrimidine.—The above diaminopyrimidine (0.5 g.) was heated with 2 g. of chloroacetic acid in a boiling water-bath under vacuum. After two hours, the mixture was cooled and the excess chloroacetic acid dissolved in ether. The residue was recrystallized from 30% aqueous ethanol and formed colorless needles, m. p. 285–290° (dec.). Yield was 0.73 g., 95%.

Anal. Calcd. for $C_7H_9O_2N_4Cl$: C, 38.8; H, 4.2; N, 23.9. Found: C, 38.6; H, 4.6; N, 23.5.

2-Amino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (VI).—The above chloroacetamide (0.4 g.) was dissolved in 10 ml. of water and treated with 20 ml. of an aqueous solution of barium hydroxide (1.04 g. of hydrate). The solution was heated in a boiling water-bath for three hours, the barium removed in the usual manner and the filtrate acidified with acetic acid. The small colorless needles (0.15 g.) after recrystallization from water darkened at about 290° but did not melt below 350°.

Anal. Calcd. for $C_7H_8O_2N_4 \cdot 2H_2O$: C, 38.9; H, 5.6; N, 25.9; H_2O, 16.7. Found: C, 38.5; H, 5.3; N, 26.1; H_2O, 17.2 (dried at 120° *in vacuo*).

Hydrolysis of VI with Hydrochloric Acid.—The oxazinopyrimidine, V, (150 mg.) was heated with 5 ml. of concentrated hydrochloric acid on the steam-bath for three hours. The mixture was evaporated to dryness in an open dish. The residue was dissolved in 3 ml. of water and neutralized to *p*H about 6.5 by adding a saturated sodium acetate solution dropwise. The precipitate of fine needles was recrystallized from water and dried at 120°. The melting point was 283° (dec.) and was not depressed on admixture with an authentic sample of 2,5-diamino-6-hydroxy-4-methylpyrimidine.

5-α-Bromopropionamido-2-amino-6-hydroxy-4-methylpyrimidine.—This was prepared in a similar manner to the 5-chloroacetamido compound. It was very difficult to

(8) Lythgoe, Todd and Topham, *J. Chem. Soc.*, 315 (1944).

(9) Bülow and Neber, *Ber.*, **45**, 3736 (1912).

(10) Jaeger, *Ann.*, **262**, 365 (1891).

crystallize, solutions tending to form gels on cooling. However, a small sample was obtained as needles from 60% aqueous ethanol. It decomposed at about 300°.

Anal. Calcd. for $C_8H_{11}O_2N_4Br$: C, 35.1; H, 4.0. Found: C, 34.8; H, 4.2.

2-Amino-6-hydroxy-4,7-dimethyl-*p*-oxazino[2,3-*d*]-pyrimidine (X).—One gram of the crude 5-α-bromopropionamido derivative was heated with 50 ml. of barium hydroxide solution (2 g. of hydrate, 3.5 equivs.). The product was isolated in the usual manner. The fine colorless needles (0.35 g.) melt at 299° (dec.).

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.5; H, 5.2; N, 28.9. Found: C, 49.3; H, 5.4; N, 28.9.

5-*p*-Chlorobenzeneazo-2-methylamino-6-hydroxy-4-methylpyrimidine.—*p*-Chloroaniline (3.2 g.) was dissolved in 60 ml. of *N* hydrochloric acid, diazotized with sodium nitrite solution (2 g. in 10 ml. of water) and 5 g. of sodium bicarbonate was added. The neutralized diazonium solution was added to a solution of 3.5 g. of 2-methylamino-6-hydroxy-4-methylpyrimidine[11] in 500 ml. of water. The solution was allowed to stand for four to five hours, the orange precipitate filtered off, washed well with water and then alcohol and dried at 100° (5.5 g., 80%). After recrystallization from pyridine, the orange prisms melted at 244° (dec.).

Anal. Calcd. for $C_{12}H_{12}ON_5Cl$: C, 51.9; H, 4.3. Found: C, 52.2; H, 4.5.

5-Amino-2-methylamino-6-hydroxy-4-methylpyrimidine.—The above azo compound (4.5 g.) was suspended in 20 ml. of ethanol and reduced with hydrogen in the presence of platinum catalyst. The solution was filtered from the catalyst and some insoluble yellow material. The residue was washed with alcohol and the combined filtrate and washings were evaporated to dryness. The residue was washed with a mixture of 60 parts ether and 40 parts acetone. Recrystallized from alcohol it formed almost colorless needles (0.94 g.), m. p. 208–210°.

Anal. Calcd. for $C_6H_{10}ON_4$: C, 46.8; H, 6.5. Found: C, 46.5; H. 6.2.

With benzoyl chloride in alkaline solution it gave a benzoyl derivative which separated as colorless needles from water, m. p. 289–290° (dec.).

Anal. Calcd. for $C_{13}H_{14}O_2N_4 \cdot H_2O$: C, 56.5; H, 5.8. Found: C, 56.3; H, 5.6.

5-Chloroacetamido-2-methylamino-6-hydroxy-4-methylpyrimidine.—The above aminopyrimidine (0.75 g.) was heated with 3 g. of chloroacetic acid in a boiling water bath in vacuum for four hours. The product was worked up as usual and recrystallized from water. The colorless needles melt at 227–228° (dec.) (1.05 g.).

Anal. Calcd. for $C_8H_{11}O_2N_4Cl$: C, 41.7; H, 4.8. Found: C, 41.8; H, 4.7.

2-Methylamino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]-pyrimidine (VII).—Five hundred mg. of the above chloroacetamide was treated in the usual manner with 1.3 g. of barium hydroxide hydrate in 40 ml. of water. The oxazinopyrimidine was isolated as needles (0.145 g., 35%) decomposing at 340–350° without melting. The crystals contained one-half mole of water of crystallization which was lost at 120° *in vacuo*.

Anal. Calcd. for $C_8H_{10}O_2N_4 \cdot {}^1/_2H_2O$: C, 46.3; H, 5.4; N, 27.6. Found: C, 46.3; H, 5.2; N, 27.6. Calcd. for $C_8H_{10}O_2N_4$: C, 49.5; H, 5.2. Found: C, 49.1; H, 5.2.

2-Dimethylamino-6-hydroxy-4-methylpyrimidine.—2-Ethylmercapto-4-methyl-6-hydroxypyrimidine[12] (10 g.) was heated with 30 g. of a 33% ethanolic solution of dimethylamine in a sealed tube at 100° overnight. The mixture was evaporated to dryness in an open dish and the residue extracted with ether containing sufficient acetic acid to render the solution faintly acidic. The ethereal solution was filtered, concentrated to about 50 ml., and an equal volume of petroleum ether (b. p. 30–60°) was added. The first crop of needles which separated was slightly purple but successive crops were white, m. p. 106°, yield 9.4 g.

Anal. Calcd. for $C_7H_{11}ON_3$: C, 55.0; H, 7.2. Found: C, 55.4; H, 7.2.

5-Benzeneazo-2-dimethylamino-6-hydroxy-4-methylpyrimidine.—A solution of 2.6 g. of *p*-chloroaniline in 50 ml. of *N* hydrochloric acid was diazotized with 1.4 g. of sodium nitrite and neutralized with 4.5 g. of sodium bicarbonate. This diazonium solution was added to a solution of 7 g. of the above pyrimidine in 300 ml. of water and the *p*H adjusted to 7 with sodium carbonate. The orange precipitate which separated was filtered off after two hours, washed well with water and dried at 100° (2.3 g.). Recrystallized from pyridine, it formed orange-red prisms, m. p. 217°.

Anal. Calcd. for $C_{13}H_{14}ON_5Cl$: C, 53.6; H, 4.0. Found: C, 53.9; H, 4.4.

5-Amino-2-dimethylamino-6-hydroxy-4-methylpyrimidine.—The above azo compound (10 g.) in 30 ml. of ethanol was reduced catalytically in two hours using a platinum catalyst at 60°. The catalyst and a small amount of insoluble yellow material was removed by filtration. The mother liquors were concentrated to about 20 ml. and 40 ml. of ether added. The product separated in glistening prisms (4.5 g.) and was reprecipitated from 10 ml. of ethanol by the addition of 30 ml. of ether, m. p. 204–205°.

Anal. Calcd. for $C_7H_{12}ON_4$: C, 50.0; H, 7.2. Found: C, 50.2; H, 7.0.

5-Chloroacetamido-2-dimethylamino-6-hydroxy-4-methylpyrimidine.—The above aminopyrimidine (0.5 g.) was heated with 2 g. of chloroacetic acid in a boiling water-bath under vacuum. The product was isolated in the usual manner (0.6 g.) and recrystallized from water. The needles melt at 258°.

Anal. Calcd. for $C_9H_{13}O_2N_4Cl$: C, 44.3; H, 5.3. Found: C, 44.7; H, 5.7.

2-Dimethylamino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine.—The above chloroacetamide (0.3 g.) was heated with 30 ml. of a solution of barium hydroxide (0.63 g. of hydrate, 3.5 equivs.) for two and one-half hours in a boiling water-bath. The product was isolated in the usual manner: white needles, m. p. 311–312° (dec.), yield 0.15 g. On heating in the melting point tube it sublimed at 220–250°, forming fine colorless needles.

Anal. Calcd. for $C_9H_{12}O_2N_4$: C, 52.0; H, 5.8. Found: C, 52.0; H, 5.5.

5-*p*-Chlorobenzeneazo-2,6-dihydroxy-4-phenylpyrimidine.—One gram of 4-phenyluracil[13] in 2 liters of water was treated with a diazonium solution prepared from 0.6 g. of *p*-chloroaniline in 12 ml. of *N* hydrochloric acid diazotized with 0.4 g. of sodium nitrite and neutralized with 1 g. of sodium bicarbonate. After standing one hour the yellow precipitate was filtered off and washed with water and methanol (0.65 g.). Several recrystallizations from pyridine produced orange-red prisms, m. p. 240° (dec.). Because of the low solubility of 4-phenyluracil and the resultant poor yield of this coupling reaction, the reduction of the azo compound to the corresponding 5-amino compound was abandoned.

Anal. Calcd. for $C_{16}H_{11}O_2N_4Cl$: C, 59.1; H, 3.4. Found: C, 59.4; H, 3.5.

Effect of Concentration of Alkali on the Yield of *p*-Oxazinopyrimidines.—The chloroacetamidopyrimidines (0.5 g.) were heated with a solution of the required amount of barium hydroxide hydrate in 25 ml. of water in a boiling-water-bath for one and one-half hours. The mixture was then treated with a 10% excess of sodium sulfate, warmed to coagulate the barium sulfate and filtered. The solution was adjusted to *p*H 5–6 with acetic acid and allowed to stand sixteen hours. The crystalline material was collected, washed well with water, then with ethanol and air dried. The dry material was weighed, allowance being

(11) Johnson and Mackenzie, *Am. Chem. J.*, **42**, 363 (1909).

(12) List, *Ann.*, **236**, 14 (1886).

(13) Johnson and Hemmingway, THIS JOURNAL, **37**, 380 (1915.)

made for any combined water of crystallization in calculations of yield. Results are reported in Fig. 3.

Acknowledgment.—We are indebted to Samuel W. Blackman for the microanalyses which are reported here.

Summary

The formation of *p*-oxazino[2,3-*d*]pyrimidine derivatives from 6-hydroxy-5-α-chloroacylamidopyrimidines by treatment with aqueous barium hydroxide solution is described. This ring closure has been found to be dependent on the nature of the substituent in the 2-position of the pyrimidine ring.

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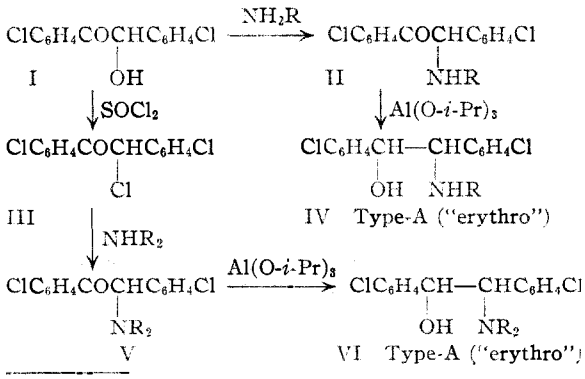
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Substituted-Amino Ketones and Alcohols Related to 4,4′-Dichlorobenzoin[1]

BY ROBERT E. LUTZ AND ROBERT S. MURPHEY[2]

In the light of evidence for the necrotizing action against mammalian tumors of several substituted-amino ketones and alcohols derived from benzoin,[3] it seemed worth while to investigate analogous compounds carrying in one or both phenyl nuclei substituents which might have the effect of enhancing the pharmacological activity. The present paper is the first of a series dealing with this phase of the problem. The 4,4′-dichloro series was chosen for study because of the well-known influence of halogen in increasing other types of pharmacological activity such as antimalarial and insecticidal.

The starting material, 4,4′-dichlorobenzoin (I),[4] has to date been obtainable only in poor yields by the benzoin condensation with *p*-chlorobenzaldehyde. By modification of the procedure developed by Willgerodt and Ucke[5] for the preparation of 4,4′-diiodobenzoin, the dichloro analog has been obtained consistently in yields of 80–88%. It is noteworthy that this product is exceptionally easily oxidized to 4,4′-dichlorobenzil upon manipulation involving contact with air.



The secondary amino ketones (II, see table) were made by the action of primary amines on 4,4′-dichlorobenzoin (the Voigt reaction[3,6]). In most runs phosphorus pentoxide was used as a catalyst; however, in one test using ethanolamine, an equally successful preparation resulted when the catalyst was omitted. All of the products were stable as the salts; however, in the form of the bases they underwent ready hydrolysis and oxidation to 4,4′-dichlorobenzil. Only one arylamino ketone, but none of the alkylamino ketones, was obtainable as a crystalline free base.

The amino ketones were reduced by means of aluminum isopropoxide to the amino alcohols (IV). Since only one of the two theoretically possible stereoisomers was isolated in each case, it is to be presumed that the configurations are of the same type (Type-A "erythro") and are analogous to those of the majority of the compounds prepared correspondingly in the parent benzoin series.[3] This presumption is supported by the synthesis of one of these (REL 691) through the *trans-p,p′*-dichlorostilbene oxide (see below).

4,4′-Dichlorodesyl chloride[4d] (III) was readily made by the action of thionyl chloride on 4,4′-dichlorobenzoin, but in poor yields (*ca.* 33%). It proved to be unstable and exceptionally easily converted into 4,4′-dichlorobenzil under various manipulations in contact with air.

Representative tertiary-amino ketones (V) were made by condensation of 4,4′-dichlorodesyl chloride (III) with the appropriate amine. These were reduced to the amino alcohols (VI) by means of aluminum isopropoxide. Since here also only one of the two possible diastereoisomers was obtained in each case, these compounds are presumed to be of the type-A ("erythro") configuration.

Two ethanolamino ketones were made. The monoethanolamino compound itself (II, R = CH_2CH_2OH) was made by the Voigt reaction from 4,4′-dichlorobenzoin and was readily re-

(1) Agents Causing Necrosis in Tumors, II. This work was carried out under a grant-in-aid from the National Institute of Health, recommended by the National Cancer Institute. The larger part of this work was included in a dissertation for the M.S. degree, University of Virginia, June, 1947.

(2) Holder of National Cancer Institute Junior Research Fellowship, 1947–1948.

(3) Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2015 (1948).

(4) (a) Hantzsch and Glover, *Ber.*, **40**, 1519 (1907); (b) Kenner and Witham, *J. Chem. Soc.*, **97**, 1967 (1910); (c) Gomberg and Van Natta, THIS JOURNAL, **51**, 2241 (1929); (d) Karrer and Forster,