700 lb. pressure. After recrystallization from heptane the substance melted at 79–80°.

Nine and two-tenths grams of N-phenyl-*o*-phenylenediamine was refluxed with 12.9 g. of methyl propyl ketone for 18 hours as described in the general procedure. On pyrolysis the initial gas evolution temperature was 230°. A rate study of the decomposition was made at 269° (±0.8°) using 20 ml. of diphenyl ether as a diluent. The results are shown in curve E, Fig. 1. Approximately 400 ml. of an inflammable gas was liberated which was not otherwise investigated. Trituration of the pyrolysis residue with ether and recrystallization from water gave 0.2 g. of 1-phenyl-2-methylbenzimidazole, m.p. 70.5–71.5°, which was identified by mixture m.p.'s with an authentic sample prepared from N-phenyl-*o*-phenylenediamine and acetic acid. Wolff[45] reports m.p. 72–73°.

b. **With Methyl Ethyl Ketone.**—After refluxing 9.2 g. of N-phenyl-*o*-phenylenediamine and 18 g. of methyl ethyl ketone for 8 hours, pyrolysis gave 350 ml. of an inflammable gas which was not investigated further and 0.7 g. of 1-phenyl-2-methylbenzimidazole, m.p. 70–71°.

**Attempted Benzoyl Peroxide Catalysis of the Degradation Reaction.**—To the intermediate obtained from the previously described reaction of I with methyl ethyl ketone, there was added 0.05 of an equivalent of benzoyl peroxide. Heating was carried out at 180–220° (below the previously determined initial evolution temperature of 235°). Other than periodic minor explosive-like evolutions of gas, only a negligible amount was liberated.

**Attempted Reaction of N,N'-Dimethyl-*o*-phenylenediamine with Methyl Isopropyl Ketone.**—Seven grams of the diamine[46] (m.p., 23–25°) and 13 g. of methyl isopropyl ketone were refluxed as described in the general procedure. No water was azeotropically removed. Almost all of the ketone was recovered unchanged.

(45) Wolff, *Ann.*, **394**, 59 (1912).

(46) Fischer and Fussenegger, *Ber.*, **34**, 936 (1901).

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[CONTRIBUTION FROM THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA]

# Synthesis of Potential Purine Antagonists. I. 2,6-Diamino[3',2'-h]-thiazolinopurines

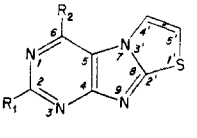
BY MAXWELL GORDON[1]

The synthesis of 2,6-diamino-4'-methyl[3',2'-h]thiazolinopurine is described and a route to 2,6-diamino[3',2'-h]thiazolinopurine is indicated. In addition, the following new derivatives of 2,6-diaminopurine have been prepared: 8-mercapto-, 8-acetonylmercapto-, 8-carboxymethylmercapto- and 8-carbethoxymethylmercapto-2,6-diaminopurine. Ultraviolet spectra of the above compounds have been measured in acid, neutral and alkaline solutions.

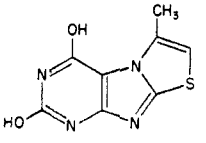
Various investigators have reported[2] that the concentration of nucleic acids in tumor-bearing animals is greater than in normal animals. From these results it has been postulated that adenine and guanine inhibitors could be found which would retard tumor growth. Hitchings[3] has demonstrated adenine inhibition by 2,6-diaminopurine, and Burchenal[4] has reported the activity of this inhibitor against leukemia. Roblin[5] and Kidder[6] have shown purine inhibition by 8-azaguanine, and the latter has extended the investigation of this compound to include demonstration of inhibition of mouse leukemia.[7]

In our work it was thought to be of interest to prepare a series of purine analogs in which riboside formation at the 7- and 9-positions is blocked, and in which riboside formation might take place at other points in the molecule, in order to find compounds of greater cancer-inhibiting action than those described above. An investigation of the literature showed that considerable demethylation of alkyl purines probably occurs in the metabolism of caffeine and other alkyl xanthines,[8] so the use of purines for this study in which the 7- or 9-position was blocked by an alkyl group was ruled out.

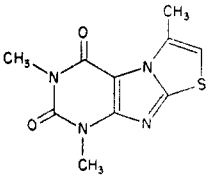
It appeared probable that blocking could be more effectively accomplished by use of a fused ring system, and the [3',2'-h]thiazolinopurines (I) hitherto prepared only by Todd,[9] who synthesized a xanthine homolog (II), and by Ochiai,[10] who prepared a [3',2'-h]thiazolinotheophylline (III), were thought to offer possibilities. Accordingly, a program was undertaken directed toward the synthesis of some thiazolino derivatives of 2,6-diaminopurine (I) ($R_1$, $R_2$ = $NH_2$). The results are recorded in this paper.



I



II



III

The thiazolino derivatives of adenine (I) ($R_1$ = H; $R_2$ = $NH_2$), guanine ($R_1$ = $NH_2$; $R_2$ = OH), and isoguanine ($R_1$ = OH; $R_2$ = $NH_2$) are also being synthesized in this Laboratory and will be made the subject of later communications.

The syntheses recorded in this paper were carried out according to the scheme recorded below. All purines shown are believed to be hitherto unreported in the chemical literature.

(1) Atomic Energy Commission Postdoctorate Research Fellow in the Physical Sciences of the National Research Council 1949–1950. The work described in this paper was sponsored by the Atomic Energy Commission. Present address: Organic Chemistry Department, Imperial College of Science and Technology, London, S. W. 7, England.

(2) Stowell, "Symposia of the Society of Experimental Biology. I. Nucleic Acids," 190 (1947), a review.

(3) Hitchings, *et al.*, *J. Biol. Chem.*, **174**, 765 (1948).

(4) Burchenal, *et al.*, *Cancer*, **2**, 119 (1949).

(5) Roblin, *et al.*, THIS JOURNAL, **67**, 290 (1945).

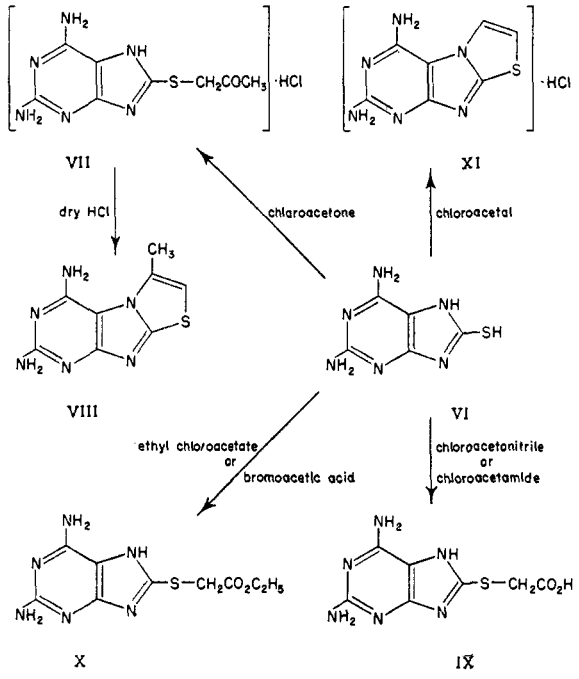
(6) Kidder and Dewey, *J. Biol. Chem.*, **179**, 181 (1949).

(7) Kidder, *et al.*, *Science*, **109**, 511 (1949).

(8) Meyers and Hanzal, *J. Biol. Chem.*, **162**, 309 (1946).

(9) Todd and Bergel, *J. Chem. Soc.*, 1559 (1936).

(10) Ochiai, *Ber.*, **69B**, 1650 (1936).




It is apparent that in the cyclization of VII ring closure may take place to either the 7- or 9-positions of the purine. Todd[9] and Ochiai[10] both reported their thiazolino compounds to 7,8-derivatives, and we have also made this assignment in the absence of any evidence to the contrary.

## Experimental[11]

**2,4,5,6-Tetraaminopyrimidine Sulfate (V).**—This compound was prepared from 2,4,6-triaminopyrimidine (IV) according to published directions,[12] except that only about one-eighth of the amount of sodium hydrosulfite reported was required to reduce the nitroso intermediate.

**2,6-Diamino-8-mercaptopurine (VI).**—5.0 g. of V (0.0275 mole) and 8.0 g. of thiourea (0.105 mole) were powdered together and heated in an open ignition tube in an oil-bath under a carbon dioxide atmosphere for 25 minutes at a bath temperature of 190–195°. The reaction mixture was stirred occasionally. After 5 minutes of heating the reaction mixture melted to a clear amber fluid and copious evolution of ammonia began. At the end of 20 minutes of heating the mixture resolidified to a brownish-yellow paste. After cooling, the product was boiled with 25 cc. of water to remove unreacted thiourea, then filtered. The yield of crude product was quantitative and it was pure enough to be used for the next step in the synthesis. For analysis the product was dissolved in the minimum amount of dilute ammonia and reprecipitated with acetic acid to give pale yellowish-brown masses which charred without melting when heated on a spatula. The product is insoluble in organic solvents. VI-Hydrochloride was obtained in white microcrystals by dissolving 1.0 g. of free base in 100 cc. of hot 2 *N* HCl and decolorizing with charcoal; the hydrochloride did not melt on a spatula.

*Anal.* Calcd. for $C_5H_6N_6S$: C, 32.96; H, 3.32; N, 46.13; S, 17.59. Found: C, 33.04; H, 3.25; N, 46.35; S, 17.34.

Ultraviolet maxima (hydrochloride) ($c = 2.29 \times 10^{-5}$ mole/l.):

| | *p*H 2.2 | | *p*H 7.1 | | *p*H 9.6 | |
|---|---|---|---|---|---|---|
| mμ | 265 | 326 | 261 | 310 | 218 | 308 |
| ε | 15,900 | 19,700 | 8730 | 20,100 | 17,900 | 17,500 |

At *p*H of 7.1 there are inflections at 227 and 240 mμ.

**2,6-Diamino-8-acetonylmercaptopurine Hydrochloride (VII).**—10.0 g. of VI (0.0556 mole), well powdered, was suspended in 250 cc. of 95% ethanol, 5.2 cc. (0.065 mole) of chloroacetone was added, and the mixture was refluxed for 24 hours. The volume was gradually increased to 700 cc. with ethanol and an additional gram of chloroacetone was added after 24 hours. After a total of 43 hours of refluxing only a few white lumps remained out of solution. The pale brown solution was decolorized with charcoal to give a nearly colorless solution which deposited masses of white ill-defined plates, 8.1 g., m.p. 204–205° (dec.) with frothing. The melting point varies somewhat with the rate of heating, but it is constant in a sealed evacuated capillary. Recrystallization from water or alcohol does not alter the melting point.

Evaporation and prolonged cooling of the mother liquor produced an additional 4.5 g. of VII. The total yield was 84%. The product is quite soluble in water and alcohol, and insoluble in ether, acetone, benzene, ethyl acetate, hexane, carbon tetrachloride, chloroform and dioxane. It formed a dinitrophenylhydrazone, m.p. 235–236° (dec.).

Reaction of chloroacetone with VI-hydrochloride, instead of with the free base, gives a slightly higher yield of product which needs no purification.

*Anal.* Calcd. for $C_8H_{10}ON_6S \cdot HCl$: C, 34.97; H, 4.04; N, 30.59; S, 11.67. Found: C, 34.66; H, 3.86; N, 30.27; S, 11.74.

Ultraviolet maxima ($c = 1.67 \times 10^{-5}$ mole/l.):

| | | *p*H 2.3 | | |
|---|---|---|---|---|
| mμ | 220 | 264 | 302 | |
| ε | 20,500 | 8080 | 18,000 | |
| | *p*H 7.1 | | *p*H 9.6 | |
| mμ | 220 | 257 | 296 | 221 | 297 |
| ε | 26,600 | 8380 | 16,200 | 26,400 | 16,200 |

**2,6-Diamino-4′-methyl[3′,2′-*h*]thiazolinopurine (VIII).**—1.0 g. of VII (0.00365 mole) was refluxed with 100 cc. of absolute ethanol with exclusion of water, then dry hydrogen chloride was passed in for 5 minutes, at the end of which time total solution had been effected. The hydrogen chloride was then turned off and the solution was refluxed for 3.5 hours. A turbidity developed at the end of 0.5 hour and continued to increase on heating. The suspension was filtered hot to give 0.8 g. of white solid (VIII-hydrochloride), m.p. 291–293° (dec.). The product is soluble in ethanol and water, and insoluble in acetone, benzene and dry ether. An additional 100 mg. of product was isolated from the mother liquor; total yield 95%. 100 mg. of the product was recrystallized from 10 cc. of hot water to give, after a few hours of standing, a quantitative recovery of fine needles, m.p. 288–290° (dec.). Analysis shows the hydrochloride to contain between one and two moles of acid. Dissolving VIII-hydrochloride in hot water and making it alkaline with ammonia results in precipitation of the free base VIII in pearly microcrystals, m.p. 288–289° (dec.).

*Anal.* Calcd. for $C_8H_8N_6S$: C, 43.62; H, 3.66; N, 38.16; S, 14.56. Found: C, 43.64; H, 3.49; N, 38.06; S, 14.80.

Ultraviolet maxima ($c = 2.72 \times 10^{-5}$ mole/l.):

| | | *p*H 1.7 | | |
|---|---|---|---|---|
| mμ | 253 | 281 | 290 | 318 |
| ε | 28,900 | 12,700 | 12,500 | 9560 |
| | *p*H 6.7 | | *p*H 9.2 | |
| mμ | 240 | 285 | 239 | 285 |
| ε | 23,000 | 15,300 | 23,200 | 15,300 |

Attempts to cyclize VII by means of phosphorus oxychloride or thionyl chloride, or by means of heat alone were unsuccessful, resulting in destruction of the product in the first and third cases and recovery of some unreacted starting material in the second.

**2,6-Diamino-8-carboxymethylmercaptopurine (IX).**— (a) 1.0 g. of VI (0.00556 mole) was suspended in 50 cc. of 95% ethanol and 0.76 cc. of chloroacetonitrile (0.012 mole) was added and the mixture refluxed for 88 hours. The brown product obtained was recrystallized from dilute hydrochloric acid and decolorized with charcoal. 350 mg. of a white powder was obtained which did not melt >300° and was insoluble in water and organic solvents but soluble in alkali.

(11) All melting points are corrected.

(12) Mallette, Taylor and Cain, THIS JOURNAL, **69**, 1814 (1947).

(b) 1.0 g. of VI and 1.22 g. (0.0130 mole) of chloroacetamide were refluxed together for 96 hours in 50 cc. of 95% ethanol. The suspended matter was filtered off to give 0.9 g. of a dirty white product. This was dissolved in dilute ammonia and reprecipitated with acetic acid to give 0.75 g. of IX.

*Anal.* Calcd. for $C_7H_8O_2N_6S$: S, 13.34. Found: S, 13.56.

Ultraviolet maxima ($c = 2.37 \times 10^{-5}$ mole/l.):

| | *p*H 2.0 | | | | |
|---|---|---|---|---|---|
| mμ | 220 | | | 301 | |
| ε | 19,000 | | | 17,100 | |
| | *p*H 6.9 | | | *p*H 9.3 | |
| mμ | 218 | 257 | 297 | 220 | 298 |
| ε | 26,400 | 9280 | 16,200 | 24,100 | 16,000 |

At *p*H of 2.0 there is an inflection at 241–264 mμ.

Attempts to cyclize IX by means of refluxing with phosphorus oxychloride or with dry hydrogen chloride in ethanol resulted in isolation of unreacted starting material.

**2,6-Diamino-8-carbethoxymethylmercaptopurine (X).**—(a) 1.0 g. of VI (0.00556 mole) was refluxed with 2.4 g. of ethyl chloroacetate (0.195 mole) for 85 hours in 50 cc. of 95% ethanol. Solution was effected and the color was a clear amber at the end of that time, so the solution was decolorized and allowed to cool. 0.85 g. of pearly white masses with a slight mercaptan odor was filtered off, X-hydrochloride, m.p. 222–224° (dec.) with rapid heating. The mother liquor gave an additional 150 mg. of product, giving a total yield of about 60%.

(b) 1.0 g. of VI was refluxed with 0.9 g. (0.0065 mole) of bromoacetic acid in 80 cc. of 95% ethanol for 43 hours and then filtered hot. The filtrate was reduced in volume to 40 cc. and on standing several hours 0.5 g. of pearly white masses deposited, X-hydrobromide, m.p. 222–224° (dec.). Esterification had obviously taken place in the course of the coupling reaction. The product is soluble in alcohol and water and insoluble in benzene.

*Anal.* Calcd. for $C_9H_{12}O_2N_6S \cdot HBr$; C, 30.95; H, 3.75; N, 24.07; S, 9.18. Found: C, 31.17; H, 3.85; N, 24.45; S, 9.28.

Calcd. for $C_9H_{12}O_2N_6S \cdot HCl$: C, 35.48; H, 4.27; Cl, 11.64. Found: C, 35.15; H, 4.13; Cl, 11.78.

The ultraviolet spectrum of X-hydrochloride is identical with that of IX. The spectrum of the X-hydrobromide is qualitatively also identical; the extinction coefficients of the maxima of the hydrobromide are slightly higher than those of the hydrochloride.

Attempts to cyclize these esters by the methods described under IX above were likewise unsuccessful.

**2,6-Diamino[3',2'-*h*]thiazolinopurine (XI).**—Reaction of chloroacetal with VI results in a yellow product whose ultraviolet spectrum is different from that of VI. Its spectrum has the double peak noted in the case of VIII, and the peak in the neighborhood of 260 mμ is much higher than that at about 325 mμ. This compound could not be purified sufficiently to give a satisfactory analysis, despite repeated attempts. No intermediate thioglycolaldehyde could be isolated.

Attempts to form thiazolinopurines by the reaction of VI with 1,2-dibromomethylene or with phenacyl chloride were unsuccessful.

**Acknowledgment.**—The author is grateful to Prof. Melvin Calvin for his kind encouragement and interest in this work, as well as for providing the facilities for this project. Elemental analyses were performed by the microanalytical laboratory of the Chemistry Department, University of California.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MAY & BAKER LIMITED]

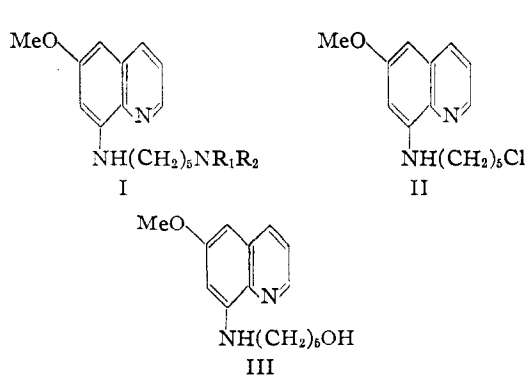
# The Synthesis of 8-(5-Hydroxyamylamino)-6-methoxyquinoline: a New Method of Preparation of Pentaquin and its Analogs

BY MAURICE BERKELEY GREEN

8-Amino-6-methoxyquinoline and 5-chloroamyl acetate react readily on heating, yielding 8-(5-hydroxyamylamino)-6-methoxyquinoline which is converted by treatment with thionyl chloride to 8-(5-chloroamylamino)-6-methoxyquinoline. Reaction of this latter compound with isopropylamine, *n*-butylamine and diethylamine gives the corresponding 8-(5-alkylaminoamylamino)-6-methoxyquinolines. Reduction of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline with hydrogen and Raney Ni gives the tetrahydro derivative.

The report by Loeb[1] of radical cure of *P. vivax* infections with pentaquin (8-(5-isopropylaminoamylamino)-6-methoxyquinoline, I, $R_1 = i\text{-Pr}$, $R_2 = H$) led us to undertake the preparation for biological assessment of a number of analogous 8-(5-alkylaminoamylamino)-6-methoxyquinolines (I) and, in continuation of previous work on tetrahydropamaquin,[2] also of the tetrahydro derivatives of some of these compounds.

Hitherto 8-(5-alkylaminoamylamino)-6-methoxyquinolines (I) have been prepared by condensation of a 1-chloro-5-alkylaminopentane hydrochloride with 8-amino-6-methoxyquinoline,[3,4,5] by condensation of 1-bromo-5-phthalimidopentane with the same aminoquinoline and subsequent alkylation,[6] or by reductive alkylation of the appropriate




8-aminoamylaminoquinoline with the requisite aldehyde or ketone.[5]

We have now found that condensation of 8-(5-chloroamylamino)-6-methoxyquinoline (II) with a mono- or dialkylamine yields an 8-(5-alkylaminoamylamino)-6-methoxyquinoline (I). This reaction should be a worthwhile addition to previously described methods since it makes possible the prep-

(1) Loeb, *J. Am. Med. Assoc.*, **132**, 321 (1946).
(2) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).
(3) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933); **273**, 320 (1935); *J. Gen. Chem. (U. S. S. R.)*, **8**, 899 (1938)
(4) Drake, *et al.*, THIS JOURNAL, **68**, 1529 (1946)
(5) Drake, *et al.*, *ibid.*, **71**, 455 (1949).
(6) Baldwin, *J. Chem. Soc.*, 2959 (1929).