While XXII usually distilled normally, there were several occasions on which distillation resulted in extensive decomposition. The cause for this inconsistent behavior could not be determined.

1-Methyl-3-(3-benzoyloxypropyl)-4-phenyl-4-hydroxy-piperidine (XXIII).—A solution of 10.0 g. (0.0364 mole) of XXII in 100 ml. of dry ether was treated dropwise with 56 ml. (0.0364 mole) of a 0.649 *N* solution of phenylmagnesium bromide in ether. A white precipitate formed immediately. The suspension was refluxed for an additional 15 minutes, during which time it underwent no apparent change. The mixture was then treated with 100 ml. of water containing 10 ml. of concentrated hydrochloric acid. The layers were separated; the aqueous layer was extracted once with benzene (discarded), neutralized with an excess of potassium carbonate, and extracted with four 100-ml. portions of benzene. The benzene solution, after drying over potassium carbonate, was distilled to yield: (a) 5.49 g. (55%) of XXII, b.p. 165–170° (0.4 mm.); (b) 3.63 g. (28%) of XXIII, b.p. 210–225° (0.5 mm.). Fraction b cooled to a yellow, glassy material, which could not be obtained in the crystalline state. The hydrochloride, obtained in 57% yield, recrystallized from ethanol–ethyl acetate, melted at 159–160°. The remainder of the hydrochloride could not be made to crystallize.

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.8; H, 7.24; N, 3.59; Cl, 9.10. Found: C, 66.81; H, 7.44; N, 3.56; Cl, 9.05.

The methiodide of XXIII, as obtained from the Grignard reaction, was recrystallized from ethanol–ether and melted at 162.5–163.5°.

Anal. Calcd. for $C_{23}H_{30}INO_3$: C, 55.6; H, 6.10. Found: C, 55.09; H, 6.20.

When phenyllithium was added to the ketone XXII, a white precipitate formed, but there was no indication of the phenylcarbinol XXIII; unchanged XXII was the sole product.

1-Methyl-3-(3-benzoyloxypropyl)-4-phenyl-4-acetoxy-piperidine Hydrochloride (XXIIIa).—A solution of 3.40 g. (0.00871 mole) of the hydrochloride of XXIII and 1.00 g. (0.0098 mole) of freshly distilled acetic anhydride in 75 ml. of dry pyridine was refluxed for 4 hours. The pyridine was removed under diminished pressure on a steam-bath, and on recrystallization of the residue from amyl acetate, 2.74 g. (77%) of XXIIIa, m.p. 174–175°, was obtained as a monohydrate. A second crop of 0.33 g. (9%) was obtained from the mother liquor.

Anal. Calcd. for $C_{24}H_{30}ClNO_4 \cdot H_2O$: C, 64.1; H, 7.17; N, 3.11; Cl, 7.89. Found: C, 64.19; H, 6.95; N, 3.07; Cl, 7.90.

The picrate of this acetate of XXIII, recrystallized from ethanol, melted at 201.5–202°.

Anal. Calcd. for $C_{30}H_{32}N_4O_{11}$: C, 57.8; H, 5.17. Found: C, 57.50; H, 5.18.

1-Methyl-3-(3-hydroxypropyl)-4-phenyl-4-hydroxy-piperidine (XXIV).—A solution of 3.53 g. (0.01 mole) of XXIII and 0.80 g. (0.02 mole) of sodium hydroxide in 50 ml. of 80% ethanol was refluxed for 5 hours, after which the solvent was removed on a steam-bath under diminished pressure. The residue was dissolved in 50 ml. of water, made acid to congo red with hydrochloric acid and extracted with four 50-ml. portions of benzene. The benzene solution was extracted once with 50 ml. of water containing 5 g. of sodium hydroxide which was acidified with hydrochloric acid and cooled to 0°. On filtration, 1.00 g. (82%) of benzoic acid, was obtained. The aqueous solution containing the hydrochloride of XXIV was treated with excess potassium carbonate, and the solid which precipitated, filtered. On recrystallization from ethyl acetate, 1.59 g. (64%) of the glycol XXIV, m.p. 160.5–161°, was obtained as white granules; mol. wt. as determined by titration with acid, 248 (calcd. 249).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.28; N, 5.61. Found: C, 72.08; H, 9.58; N, 5.54.

The ultraviolet spectrum in ethanol had six maxima, at 241 (log ϵ_{max} 1.88), 247 (log ϵ_{max} 2.07), 251 (log ϵ_{max} 2.22), 257 (log ϵ_{max} 2.31), 264 (log ϵ_{max} 2.18) and 267 mμ (log ϵ_{max} 1.99).

1-Methyl-3-(3-hydroxypropyl)-4-phenyl-1,2,5,6-tetrahydropyridine (XXV) Hydrochloride.—A solution of 0.5 g. (2.0 mmoles) of XXIV in 10 ml. of concentrated hydrochloric acid was refluxed for 1 hour. After cooling to room temperature, the solution was neutralized with an excess of potassium carbonate and extracted with four 50-ml. portions of benzene. The benzene was dried over potassium carbonate, evaporated, the residue dissolved in 50 ml. of dry ether and filtered to remove a trace of insoluble material. The amine was converted to the hydrochloride, and after two recrystallizations from ethanol–ethyl acetate, 0.22 g. (48%) of the hydrochloride of XXV, m.p. 174.5–175.5°, was obtained.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.4; H, 8.28. Found: C, 66.75; H, 8.12.

The infrared spectrum of this hydrochloride, as a mull, had a definite hydroxyl band at 3.0 μ. The free base, recovered from the hydrochloride, had the same band. The ultraviolet spectrum of the hydrochloride in ethanol had a single maximum at 235 mμ (log ϵ_{max} 4.01), typical of styrenes.

The glycol XXIV, when allowed to stand in concentrated hydrochloric acid, 60% sulfuric acid or 85% phosphoric acid at room temperature, was recovered unchanged.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE FRANCIS EARLE LABORATORIES, INC.]

New Syntheses of Purine

BY ALDEN G. BEAMAN

RECEIVED JUNE 9, 1954

Purine has been prepared by the dethiolation of 6-mercaptopurine and 2,6-dimercaptopurine. Although the monomercapto compound can be made directly from hypoxanthine, the analogous treatment of xanthine with phosphorus pentasulfide produced 2-hydroxy-6-mercaptopurine. The dimercapto compound was prepared from 2-mercapto-6-hydroxypurine.

Although substituted purines have been studied extensively, the parent compound, purine, is relatively little known. Unlike the nucleic acid purines and the common alkaloids, caffeine, theobromine and theophylline, purine is quite rare in nature. It was only recently that a natural product, nebularine, obtained from the mushroom *Agarious (Clitocybe) nebularis* Batsch. was shown by Löfgren and Lüning[1] to produce purine and ribose upon hydrolysis. G. B. Brown and Weliky[2] have demonstrated that 9-β-D-ribofuranosylpurine, which they synthesized, is identical with the natural product.

Purine itself was first prepared in extremely small yield by Emil Fischer[3] by the reduction of 2,6,8-trichloropurine which had been synthesized from uric acid.[4,5] A later method by Isay,[6] involved the conversion of 5-nitrouracil to 4,5-diaminopyrimidine, which was then condensed with

(1) N. Löfgren and B. Lüning, *Acta Chem. Scand.*, **7**, 225 (1953).

(2) G. B. Brown and V. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(3) E. Fischer, *Ber.*, **31**, 2550 (1898).

(4) E. Fischer and L. Ach, *ibid.*, **30**, 2208 (1897).

(5) E. Fischer, *ibid.*, **30**, 2220 (1897).

(6) O. Isay, *ibid.*, **39**, 250 (1906).

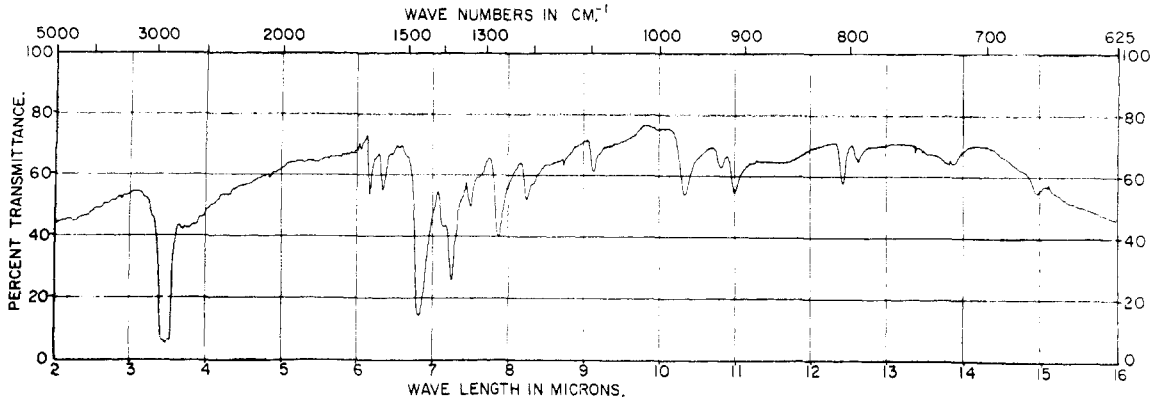


Fig. 1.—Infrared absorption spectrum of purine in Nujol mull.

formic acid to yield purine, following ring closure of the intermediate aminoformylaminopyrimidine. Modification in Isay's synthesis of 4,5-diaminopyrimidine are summarized by Albert[7] and D. J. Brown,[8] and improvements in the techniques for converting various 4,5-diaminopyrimidines to purines have been given by Bendich,[9] Bredereck,[10] and Robins.[11]

It remained of interest, however, to seek a more direct synthesis of purine from available substituted purines.[12] D. J. Brown[13] has shown that Raney nickel may be used to dethiolate mercaptopyrimidines. Elion[14] has described the conversion of hypoxanthine to 6-mercaptopurine (I). In the present work, a solution of 6-mercaptopurine in dilute ammonia was refluxed with Raney nickel to give purine (II) in about 45% yield. The product was purified by sublimation and crystallization. Its infrared and ultraviolet spectra are shown in Figs. 1 and 2.

An attempt was made to prepare purine from the more readily available xanthine. Reaction of xanthine (III) and phosphorus pentasulfide in refluxing pyridine yielded a product $C_5H_4N_4OS$, which was faintly yellow, λ_{max} 340 mμ (log ϵ 4.33) at *p*H 10.4, instead of the anticipated 2,6-dimercaptopurine, $C_5H_4N_4S_2$ (IV). Assuming that no rearrangements have occurred, this product is either 2-mercapto-6-hydroxypurine (V), or 2-hydroxy-6-mercaptopurine (VI). Since the product gave back xanthine, identified by ultraviolet absorption spectrum, upon heating with 25% nitric acid, its substituents are still at positions 2 and 6. 2-Mercapto-6-hydroxypurine, described by Traube,[15] was found to have a different ultraviolet absorption spectrum from the

(7) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(8) D. J. Brown, *J. Appl. Chem.*, **2**, 239 (1952).

(9) A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, **70**, 3109 (1948).

(10) H. Bredereck, H.-G. von Schuh and A. Martini, *Chem. Ber.*, **83**, 201 (1950).

(11) R. Robins, K. Dille, C. Willits and B. Christensen, THIS JOURNAL, **75**, 263 (1953). (Corrected by B. Christensen, *ibid.*, **75**, 6359 (1953).)

(12) Treatment of adenine with nitrous acid in the presence of either ethanol or hypophosphorus acid failed to give purine. (Unpublished observations of the author.)

(13) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

(14) G. Elion, E. Burgi and G. Hitchings, THIS JOURNAL, **74**, 411 (1952).

(15) W. Traube, *Ann.*, **331**, 64 (1904).

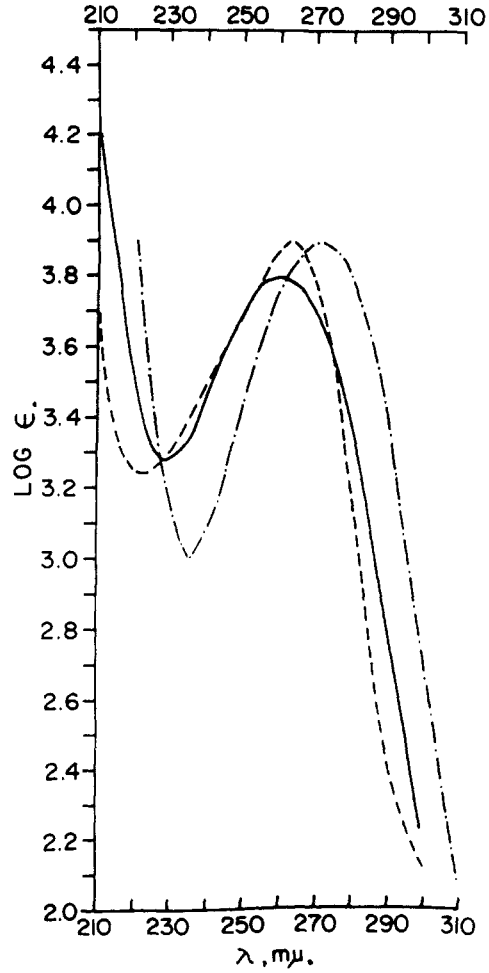


Fig. 2.—Ultraviolet absorption spectra of purine: —, *p*H 1.2; ---, in distilled water; -·-, *p*H 10.4.

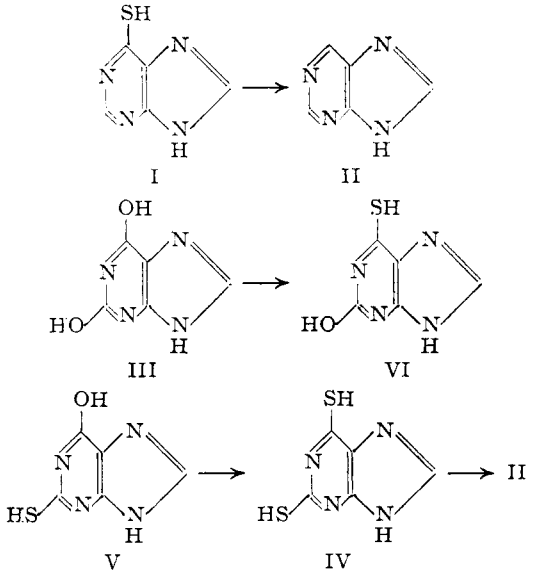
product $C_5H_4N_4OS$ (Fig. 3), which is therefore the isomeric 2-hydroxy-6-mercaptopurine. This conclusion is supported by its faintly yellow color and intense absorption at wave lengths higher than 300 mμ, which appear to be characteristic of 6-mercaptopurines. For example, 6-mercaptopurine itself has been reported[14] to be light yellow and to have an absorption maximum at 312 mμ (log ϵ 4.29) at *p*H 11, and the light yellow 2,6-dimercaptopurine,

the preparation of which is described below, is seen in Fig. 3 to have a maximum at 346 mμ (log ε 4.13) at *p*H 10.4. On the other hand, 2-mercapto-6-hydroxypurine is colorless, with a maximum at 278 mμ (log ε 4.22) at *p*H 10.4.

The results with hypoxanthine and xanthine indicate that a hydroxyl group in the 6-position is quite readily converted to a mercapto group by the action of phosphorus pentasulfide, whereas a hydroxyl group in the 2-position is more resistant to such replacement. This consideration suggests 2-mercapto-6-hydroxypurine[15] as a suitable precursor for 2,6-dimercaptopurine. Robins[11] found that although 2-mercapto-4,5-diamino-6-hydroxypyrimidine[14,15] was not cyclized to 2-mercapto-6-hydroxypurine by refluxing for 20 minutes in formamide, its sulfate was cyclized under these conditions. In the present work, however, it was found that refluxing crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine with formamide, in the ratio of either 5 or 10 milliliters of formamide per gram of the pyrimidine, for 30 minutes gave 2-mercapto-6-hydroxypurine in moderately good yield.

Brief refluxing of a solution of 2-mercapto-6-hydroxypurine and phosphorus pentasulfide in pyridine gave 2,6-dimercaptopurine in 55–60% yield. Refluxing a solution of 2,6-dimercaptopurine in dilute ammonia with Raney nickel gave purine, but in somewhat lower yield than was obtained in the analogous preparation from 6-mercaptopurine.

Acknowledgment.—We are indebted to Dr. S. M. Nagy, Massachusetts Institute of Technology, and his associates for taking the infrared spectrum and for the microanalyses reported here.



Experimental[16]

Purine (II) from 6-Mercaptopurine.—To a warm solution of 30.0 g. of 6-mercaptopurine monohydrate[14] in 700 ml. of distilled water plus 70 ml. of concd. ammonia was added 125 g. of ethanol-wet Raney nickel[13] and the mixture refluxed for 2 hours. The catalyst was filtered hot and washed with a little water. The filtrate plus water wash was returned to the flask, 60 g. of ethanol-wet Raney nickel and 40 ml. of concd. ammonia added, and the mixture refluxed for 1 hour. The nickel was filtered hot and rinsed as before. The filtrate was colorless initially, but soon turned brownish-pink. The filtrate was evaporated to dryness at reduced pressure, the residue warmed several minutes with about 250 ml. of ethanol, and the solution filtered from about 1 g. of dark insoluble material. The ethanol solution was evaporated to dryness at reduced pressure to give about 11 to 12 g. of crude purine which upon sublimation at water aspirator vacuum (bath temperature 200–210°) gave 8.7 to 10.2 g. (41 to 48%) of nearly pure material. The slight color possessed by this material could be removed by crystallization from ethanol–toluene using charcoal. The m.p. of purine, 215–216°; its picrate, 208–210°; and its nitrate, 203–204°, dec., are in agreement with those reported by Fischer.[3] The ultraviolet absorption spectrum shows a minimum at 235 mμ (log ε = 3.00) and a maximum at 271 mμ (log ε = 3.90) at *p*H 10.4.

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 49.91, 49.96; H, 3.44, 3.55; N, 46.68, 46.89.

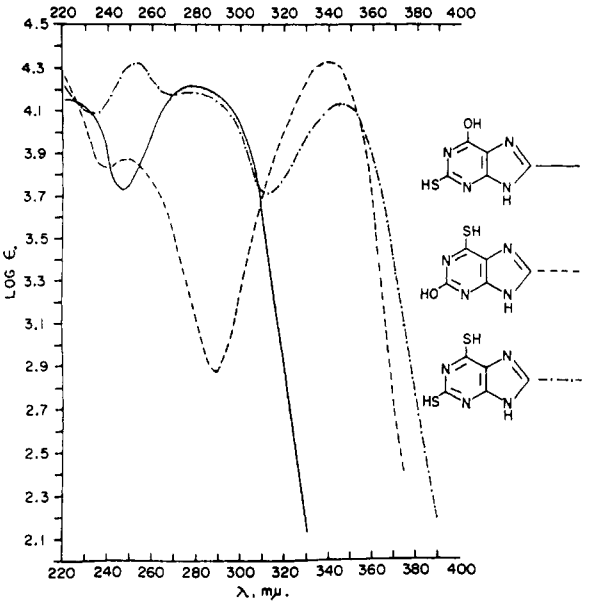


Fig. 3.—Ultraviolet absorption spectra, *p*H 10.4.

2-Hydroxy-6-mercaptopurine (VI).—Xanthine (15.1 g.) and 81 g. of phosphorus pentasulfide were added to 1350 ml. of stirred, dry reagent pyridine in a 2-l., three-necked flask fitted with a sealed stirrer and reflux condenser with drying tube. The mixture was stirred and refluxed for 3.5 hours during which time virtually all the solid dissolved. The hot solution was decanted from 0.55 g. of solid into 8 l. of water plus ice. The solid which formed remained insoluble upon addition of dilute sodium hydroxide solution and was discarded. The filtrate from this solid (made acid with acetic acid) was boiled down at atmospheric pressure (temperature slightly above 100°) to about 4.5 l. and cooled. There formed 11.2 g. of orange-brown solid. Trituration with acetone removed much of the dark color. The remaining solid was dissolved in a solution of 7.5 g. of sodium hydroxide in about 650 ml. of water, the solution treated with charcoal and filtered, and the filtrate heated to boiling and made acid with acetic acid. The light yellow solid which formed weighed 8.06 g. (50%), based on the weight of xanthine which dissolved. 2-Hydroxy-6-mercaptopurine does not change upon heating to 325°. It may be recrystallized from about 800–900 parts of boiling water to give faintly yellow microscopic needles.

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.71; H, 2.40; N, 33.32; S, 19.06. Found: C, 35.48; H, 2.45; N, 32.75; S, 19.06.

Xanthine (III) from 2-Hydroxy-6-mercaptopurine.—To 43 ml. of 25% HNO_3 heated in a water-bath at 89–94° was added 3.00 g. of 2-hydroxy-6-mercaptopurine in small por-

(16) All melting points are corrected. The ultraviolet absorption spectra were taken in aqueous solution using a Model DU Beckman quartz spectrophotometer. A carbonate–bicarbonate buffer was used for *p*H 10.4; 0.1 *N* HCl, for *p*H 1. The infrared spectrum was taken in a Nujol mull using a Baird infrared spectrophotometer.

tions over a period of 5 to 10 min. After each addition dark fumes were evolved. The mixture was heated for about 5 min. more in this temp. range and then filtered hot from 0.07 g. of dark yellow material which was discarded. From this filtrate upon cooling came 2.97 g. of yellow solid. A portion of this solid was purified by dissolving in dilute NaOH solution and precipitating with acetic acid followed by crystallization from water. The ultraviolet absorption spectrum of the purified material in an aqueous carbonate–bicarbonate buffer of *p*H 10.5 showed maxima at 241 mμ and 277–278 mμ (log ε values 3.92 and 3.95, respectively) and was identical with the spectrum of an authentic sample of xanthine.

2-Mercapto-4,5-diamino-6-hydroxypyrimidine.—This compound was prepared by the method of Traube[15] using certain modifications including those of Elion.[14] The condensation of thiourea and ethyl cyanoacetate was carried out on a 5-mole scale using sodium in absolute methanol in place of absolute ethanol. A reflux period of 2.5 hours was employed, and the resulting reaction mixture was poured into enough water to dissolve the solid. Acidification with acetic acid gave 641 g. (80%) of 2-mercapto-4-amino-6-hydroxypyrimidine. Using the modifications of Elion[14] 640 g. of this compound gave 546 g. (87%) of crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine.

2-Mercapto-6-hydroxypurine (V).—Crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine (40.0 g.) and 400 ml. of C.P. formamide were added to a 1-l., three-necked flask fitted with a sealed stirrer and reflux condenser with drying tube. The mixture was stirred and heated, and just after reflux began, the solid completely dissolved. After 30 minutes reflux, the reaction mixture was allowed to cool. The solid which formed weighed 24.3 g. after washing with water and acetone and drying. Evaporation of the formamide to dryness at reduced pressure gave a further 18.1 g. making the crude yield 99%. Purification by dissolving in a warm dilute solution containing an equivalent amount of sodium hydroxide, treating with charcoal, and acidifying the boiling filtrate from the charcoal with acetic acid gave 28.0 g. (66%) of material having the same ultraviolet absorption spectrum as the 2-mercapto-6-hydroxypurine prepared by the method of Traube.[15] In another run refluxing 100 g. of crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine with 500 ml. of formamide for 30 minutes gave 61.9 g. (58%) of purified 2-mercapto-6-hydroxypurine.

2,6-Dimercaptopurine (IV).—2-Mercapto-6-hydroxypurine (50.0 g.) and 200 g. of phosphorus pentasulfide were added to 1750 ml. of stirred, dry reagent pyridine in a 3-l., three-necked flask fitted with a sealed stirrer and reflux condenser with drying tube. The mixture was refluxed for 1.5 hours and the resulting red-black solution allowed to cool about 10 minutes with stirring. It was then poured with stirring into a solution of 663 g. of sodium hydroxide in 5 l. of water plus ice. The two layers which formed were thoroughly shaken in a separatory funnel and separated. The pyridine layer was washed with a cold solution of 70 g. of sodium hydroxide in 500 ml. of water, and this wash combined with the main aqueous layer which was then acidified with 1200 ml. of glacial acetic acid. The mixture was cooled in ice, and the brown solid which formed was collected and washed with water. After air drying it weighed 44.0 g. (80% crude yield). For purification the crude material was dissolved in a solution of 22 g. of sodium hydroxide in about 4 l. of water and the solution filtered from a little insoluble solid. The filtrate was treated with charcoal, filtered, and the boiling filtrate acidified with acetic acid. The solid which formed on cooling was purified again in the same way to give 30.7 g. (56%) of pure light yellow crystalline material. 2,6-Dimercaptopurine is unchanged upon heating to 330°. It may be recrystallized from about 2000–3000 parts of boiling water.

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.60; H, 2.19; N, 30.41; S, 34.80. Found: C, 32.63; H, 2.19; N, 30.02; S, 34.50.

Purine (II) from 2,6-Dimercaptopurine.—2,6-Dimercaptopurine (15.0 g.) was dissolved in a mixture of 250 ml. of distilled water plus 50 ml. of concd. ammonia by warming. Then 100 g. of ethanol-wet Raney nickel was rinsed in with about 100 ml. of water, and the mixture refluxed 1.5 hours. The catalyst was filtered hot, washed with a little water, and the filtrate plus water wash returned to the reaction flask and refluxed one hour with a second 100 g. of ethanol-wet Raney nickel plus 30 ml. of additional concd. ammonia. The catalyst was filtered as before and the initially colorless filtrate evaporated to dryness at reduced pressure to give 3.42 g. (35%) of crude purine. It is possible that the low yield is a result of the very large quantities of Raney nickel employed. However, a single treatment with 125 g. of Raney nickel (2 hours reflux) gave a crude product containing a considerable quantity of unreacted starting material. The optimum quantity of Raney nickel (and the number of treatments therewith) have not been determined. The crude product could be purified as described above to give purine m.p. 216–216.5° which was not depressed upon admixture with a sample prepared from 6-mercaptopurine. The ultraviolet absorption spectrum of the purine obtained from 2,6-dimercaptopurine was the same as that of the purine from 6-mercaptopurine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Study of the Bromination of 5-Alkylhydantoins; Conversion of 5-Propylhydantoin into 5-Propylidenehydantoin and 5-(α-Bromopropylidene)-hydantoin[1]

BY EUGENE J. McMULLEN,[2] HENRY R. HENZE AND B. WOODROW WYATT[3]

RECEIVED APRIL 19, 1954

Bromination of a 5-alkylhydantoin leads to the formation of a 5-alkylidenehydantoin which then is converted into a 5-(α-bromoalkylidene)-hydantoin. 5,5-Dialkylhydantoins are not thus attacked by bromine.

An attempt in this Laboratory to synthesize 5-alkyl-5-aminohydantoins, as intermediates in the formation of some sulfanilamidohydantoins, involved the preparation of 5-alkyl-5-bromohydantoins which, subsequently, were to be converted by treatment with ammonia into the corresponding amino derivatives. This sequence seemed plausible for Gabriel[4] had shown that bromination of 5-phenylhydantoin yielded 5-bromo-5-phenylhydantoin, and that the latter reacted with ammonia to form 5-amino-5-phenylhydantoin. However, in the present investigation, several 5-alkylhydantoins upon treatment with bromine yielded products which could be shown to be unsaturated as well as to contain bromine. Thus, for example, 5-propylhydantoin (I) was converted into a compound II of molecular formula $C_6H_7BrN_2O_2$. Under identical conditions, of exposure to bromine, several repre-

(1) From the Ph.D. dissertations at The University of Texas, respectively, of B. Woodrow Wyatt (1943) and Eugene J. McMullen (1947).

(2) Parke, Davis and Company Fellow, 1945–1946; Reseach Assistant, Project 175, The University of Texas Research Institute, 1946–1947.

(3) Cotton Research Foundation Fellow, 1938–1940; Parke, Davis and Company Fellow, 1942–1943.

(4) S. Gabriel, *Ann.*, **350**, 118 (1906).