ethanol and the manganese dioxide was filtered off. The filtrate was acidified and cooled overnight. The crystalline product was collected, washed with water, acetone and ether, and dried; yield 0.7 g. This was dissolved in 15 cc. of warm dilute sodium hydroxide solution, treated with Norite and filtered; 15 cc. of a 10 *N* sodium hydroxide solution was added and the whole solution was cooled well. The crystalline product was collected and recrystallized in the same manner. The product was collected, redissolved in about 60 cc. of water by heating. The hot solution was acidified with hydrochloric acid and cooled to give a white crystalline product; yield 0.4 g.; dried three hours at 140° in a drying pistol over phosphorus pentoxide; m.p., does not melt below 300°.

Anal. Calcd. for $C_7H_4N_4O_4$: C, 40.3; H, 1.92; N, 26.9. Found: C, 40.6; H, 2.64; N, 27.2.

In 0.1 *N* sodium hydroxide this compound showed *E* (1%, 1 cm.) maxima of 935 at 267.5 mμ and 391 at 370 mμ; in 0.1 *N* hydrochloric acid the maxima were 471 at 237.5 mμ, 569 at 265 mμ and 469 at 330 mμ.

Acknowledgment.—The authors are indebted to Dr. B. L. Hutchings for the microbiological assays, to Anne de Grunigen for the ultraviolet determinations and to Mr. Louis Brancone and staff for the microanalyses and chemical assays.

PEARL RIVER, N. Y. RECEIVED APRIL 12, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. IX. The Synthesis of Some 6-Substituted Purines

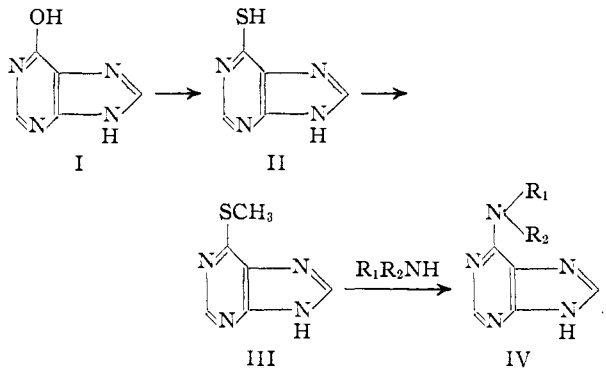
BY GERTRUDE B. ELION, ELIZABETH BURGI AND GEORGE H. HITCHINGS

A variety of 6-aminopurines has been prepared by the reaction of 6-methylmercaptopurine with aliphatic and aromatic amines. The treatment of hypoxanthine with phosphorus pentasulfide under specified conditions leads to the formation of 6-mercaptopurine in satisfactory yields. Some modifications and improvements in the preparation of hypoxanthine from 4-amino-6-hydroxy-2-mercaptopyrimidine are described.

In connection with the program of preparing compounds which might act as antagonists for the purine and pyrimidine portions of nucleic acid[1,2,3] it was decided to synthesize a number of purines in which the amino group of adenine had been substituted by various aliphatic, aromatic and heterocyclic amines. No such purines have been unequivocally synthesized previously, although Bredereck[4] has reported the picrate of an N-methyladenine made *via* the methylation of adenosine with dimethyl sulfate, at *p*H 13–14.

The chlorination of hypoxanthine with phosphoryl chloride either in the presence or absence of dimethylaniline was unsatisfactory. However, it was found that the direct replacement of oxygen by sulfur which had been successful with hydantoins[5] and pyrimidines[6,7] could likewise be applied to purines. The treatment of hypoxanthine (I) with phosphorus pentasulfide led to 6-mercaptopurine (II). Methylation of the latter with methyl iodide or dimethyl sulfate resulted in the formation of III. When dimethyl sulfate was used, spectrophotometric examination of the mother liquors revealed that at least two purines other than 6-mercapto- and 6-methylmercaptopurine were present. These by-products, presumably N-methylpurines, were partially separated from the mother liquor residues by fractional crystallization but were not obtained in a pure state.

The replacement of mercapto or methylmercapto groups by amino groups is well known in the pyrimidine series[8,9] but has rarely been successful with purines. Such a replacement has been reported, with 2-hydroxy-8-methylmercaptopurine and methylamine[10] but failure has been reported in attempts to replace the 2-methylmercapto group of 2-methylmercaptoadenine.[11]



When 6-mercaptopurine (II) was heated with aqueous ethylamine at 140° for 15 hours in a sealed tube a considerable amount of hydrogen sulfide was formed, and some 6-ethylaminopurine was shown to be present in the reaction mixture by spectrophotometric measurements; with aniline at 180° for seven hours, 90% of II was recovered. On the other hand, the replacement of the 6-methylmercapto group by amines was found to proceed smoothly when III was heated in a sealed tube with primary alkylamines, dimethylamine, morpholine, aniline and *p*-chloroaniline. Diethylamine did not react with III at 130° but when the temperature was raised to 150°, 6-diethylaminopurine (IV, $R_1 = R_2 = C_2H_5$) was obtained. With hydrazine and

(1) G. H. Hitchings, E. A. Falco and M. B. Sherwood, *Science*, **102**, 251 (1945).

(2) G. H. Hitchings, G. B. Elion, E. A. Falco and H. VanderWerff, Abstracts, American Chemical Society, New York, N. Y., 3 C (1947).

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

(4) H. Bredereck, H. Haas and A. Martini, *Ber.*, **81**, 307 (1948).

(5) H. R. Henze and P. E. Smith, THIS JOURNAL, **65**, 1090 (1943).

(6) H. C. Carrington, *J. Chem. Soc.*, 124 (1944).

(7) G. B. Elion and G. H. Hitchings, THIS JOURNAL, **69**, 2138 (1947).

(8) P. B. Russell, G. B. Elion, E. A. Falco and G. H. Hitchings, *ibid.*, **71**, 2279 (1949).

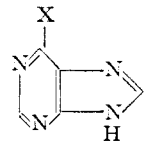
(9) T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **35**, 175 (1905).

(10) C. O. Johns, *J. Biol. Chem.*, **21**, 319 (1915).

(11) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

TABLE I

6-SUBSTITUTED PURINES



Solvents of recrystallization: A, water; B, dissolved in dilute alkali and precipitated with acetic acid; C, 65% aq. ethanol; D, precipitated as the hydrochloride from ethanol by ether; E, 50% aq. ethanol; F, dissolved in concd. hydrochloric acid and precipitated with water.

X	Reaction conditions Temp., °C.	Time, hr.	Yield, %	Solvent of recrystn.	M.p. (dec.), °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3NH	130	17	72	A	312–314	$C_6H_7N_5$	48.3	48.6	4.7	4.5	47.0	48.5[a] 45.8[b]
C_2H_5NH	130	16	73	A	238–239	$C_7H_9N_5$	51.5	52.0	5.5	5.5	42.9	43.5[a] 41.6[b]
n-C_4H_9NH	130	17	50	B	233–234	$C_9H_{13}N_5$	56.5	56.8	6.8	6.9	36.6	36.2[a]
n-$C_{10}H_{21}NH$	140	17	79	C	166–167	$C_{15}H_{25}N_5$	65.5	65.8	9.1	8.8	25.4	25.3[b]
$(CH_3)_2N$	130	15	79	D	251–253	$C_7H_9N_5 \cdot HCl$	42.1	41.8	5.0	5.0	35.1	35.2[a]
$(C_2H_5)_2N$	150	17	70[c]	D	186–187	$C_9H_{13}N_5 \cdot HCl$	47.5	46.8	6.2	6.1		
C_6H_5NH	180	24	80	E	284–285	$C_{11}H_9N_5$	62.6	62.9	4.3	4.2	33.2	32.9[b]
p-ClC_6H_4NH	180	20	35	F	327–328	$C_{11}H_8N_5Cl$	53.8	53.9	3.3	3.1		
$CH_2CH_2OCH_2CH_2N$	130	17	75	E	303–304	$C_9H_{11}ON_5$	52.7	52.9	5.4	5.4	34.1	34.1[a]
$NHNH_2$	110	16	68	A	244–245	$C_5H_6N_6$	40.0	40.2	4.0	4.0	56.0	55.0[b]

[a] Kjeldahl. [b] Dumas. [c] Crude, estimated spectrophotometrically.

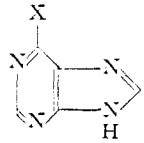
III there was extensive decomposition at 130° but the replacement could be carried out in good yield at 110°. In Table I are given the conditions for the reaction of each of the amines with III.

Since hypoxanthine was required in large amounts for the preparation of these 6-N-substituted aminopurines, an improved method for its synthesis was necessary. The preparation of hypoxanthine from 2,6,8-trichloropurine[12] was too laborious, while the treatment of 6-hydroxy-2-mercaptopurine with nitric acid[13] gave considerable amounts of xanthine as a by-product. The action of Raney nickel on 6-hydroxy-2-mercaptopurine likewise proved unsatisfactory, probably due to the insolubility of this purine in water, even in the presence of sodium carbonate. This is in agreement with the poor yields of adenine obtained from the treatment of 6-amino-2-mercaptopurine with Raney nickel.[14] In contrast to the purines, 2-mercaptopyrimidines are easily dethiolated by Raney nickel. Applying the method used by Cavalieri, *et al.*,[15a] for the preparation of 4,5,6-triaminopyrimidine, 4,5-diamino-6-hydroxy-2-mercaptopyrimidine was converted to 4,5-diamino-6-hydroxypyrimidine in good yield.[15b] This was transformed to hypoxanthine by heating with 90% formic acid for two hours.

The ultraviolet absorption spectra of these 6-substituted purines are extremely valuable for determining the extent to which the reactions have proceeded as well as for checking the purities of the compounds. It is particularly useful in following the transformation of hypoxanthine to 6-mercaptopurine, a reaction which does not go to completion under the conditions employed. Since hypoxanthine has an absorption maximum at 250 mμ at *p*H 1[16] while the maximum for 6-mercaptopurine is at 327 mμ at *p*H 1 (Table II), small amounts of hypoxanthine in the product are easily detected. Methylation of the 6-mercapto group shifts the absorption maximum 32 mμ toward the shorter wave lengths. Most of the 6-alkylaminopurines (Table II) have spectra closely resembling that of adenine[17]; the arylaminopurines absorb at slightly longer wave lengths.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 6-SUBSTITUTED PURINES



X	*p*H = 1 $\lambda_{max.}$ mμ	*p*H = 1 ε	*p*H = 11 $\lambda_{max.}$ mμ	*p*H = 11 ε
HS	327	21,300	312	19,600
CH_3S	295	16,200	293	16,600
CH_3NH	267	14,900	272	15,300
C_2H_5NH	270	16,300	273	17,000
n-C_4H_9NH	270	15,400	275	16,800
n-$C_{10}H_{21}NH$			268	18,200[a]
$(CH_3)_2N$	277	15,600	281	17,000
$(C_2H_5)_2N$	276	16,800	282	19,100
C_6H_5NH	285	14,700	295	21,700
p-ClC_6H_4NH			298	33,200[a]
$CH_2CH_2OCH_2CH_2N$	284	18,400	283	19,100
$NHNH_2$	267	13,700	[b]	

[a] In 95% ethanol. [b] See text.

In alkaline solution 6-hydrazinopurine undergoes spontaneous decomposition which is accelerated by

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

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

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

(15) (a) L. F. Cavalieri, J. F. Tinker and A. Bendich, *ibid.*, **71**, 533 (1949); (b) H. Getler, P. Roll, J. Tinker and G. B. Brown, *J. Biol. Chem.*, **178**, 262 (1949).

(16) M. M. Stimson and M. A. Reuter, THIS JOURNAL, **65**, 154 (1943).

(17) L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, *ibid.*, **70**, 3875 (1948).

irradiation with ultraviolet light to such an extent that values for the ultraviolet absorption in alkaline solution were unobtainable. The absorption band diminished in intensity and shifted to shorter wave lengths. Hypoxanthine was identified as a major product of the spontaneous decomposition by treatment of the decomposition products with xanthine oxidase. This resulted in the formation of a considerable quantity of uric acid (determined spectrophotometrically) whereas 6-hydrazinopurine itself is not oxidized under the same conditions and is inhibitory to the enzyme.[18]

The effects of some of the 6-substituted purine on *Lactobacillus casei* have been reported.[19a,b] While 6-mercaptopurine inhibits growth, 6-methylaminopurine can satisfy the purine requirement of this microörganism. The biological activities of these purines on Sarcoma 180 will be reported elsewhere.

Experimental

4,5-Diamino-6-hydroxypyrimidine Sulfate.—The synthesis of this compound from 4-amino-6-hydroxy-2-mercaptopyrimidine is essentially that described by Traube[20] and by Albert[21] with some modifications. The nitrosation mixture is allowed to stand at room temperature for 16 hours before filtration. The crude, moist, orange nitroso derivative is added alternately with sodium hydrosulfite to water at 60–70°. When decolorization is complete, the mixture is cooled and the 4,5-diamino-6-hydroxy-2-mercaptopyrimidine is filtered off. The crude yield from the 4-amino-6-hydroxy-2-mercaptopyrimidines is 80–85%.

A mixture of 80 g. of crude 4,5-diamino-6-hydroxy-2-mercaptopyrimidine, 68 g. of sodium carbonate and 120 g. of wet W-6 Raney nickel catalyst[22] in 1200 ml. of water was boiled, under reflux, for two hours. After a short settling period, the hot mixture was filtered and enough 10 *N* sulfuric acid added immediately to bring the *p*H to 5. The nickel was washed with 200 ml. of hot water, the washings added to the main filtrate, and the *p*H again adjusted to 5. The sulfate of 4,5-diamino-6-hydroxypyrimidine began to precipitate from the hot solution. After chilling, the precipitate was collected, washed with water and dried at 110°.

The crude product (61.1 g.) could be used directly for conversion to hypoxanthine or recrystallized from 70 volumes of hot water to give an 88% recovery of the purified sulfate. After two recrystallizations from water the colorless, crystalline sulfate showed an ultraviolet absorption spectrum corresponding to that reported for the hydrochloride.[17]

Anal. Calcd. for $C_4H_6N_4O \cdot {}^1/_2H_2SO_4$: N, 32.0. Found: N, 32.3.

Hypoxanthine (I).—A suspension of 24.5 g. of 4,5-diamino-6-hydroxypyrimidine sulfate in 300 ml. of 90% formic acid was refluxed for two hours. The solid went rapidly into solution. The solution was evaporated to dryness under reduced pressure and the residue dissolved in 600 ml. of water by the addition of 6 *N* sodium hydroxide solution. After acidification with acetic acid, the precipitate of hypoxanthine was collected, washed with water and dried at 100° (17.75 g., 93%). The ultraviolet absorption spectrum indicated that this product was about 95% pure, and it was therefore used directly for the next step. In order to obtain pure hypoxanthine, its precipitation as the silver nitrate complex from nitric acid was most satisfactory.[23,24]

6-Mercaptopurine (II).—A mixture of 18.5 g. of crude hypoxanthine and 100 g. of phosphorus pentasulfide in 500 ml. of tetralin was heated at 190–200°, with mechanical stirring, for 12 hours. The mixture was cooled and filtered and the solid residue washed with petroleum ether. The crude product was boiled with 2 liters of water, filtered hot and the *p*H value of the filtrate adjusted to 4 with concentrated ammonium hydroxide. On standing, dark-yellow crystals of 6-mercaptopurine hydrate (12 g., 54%) precipitated. This compound has a pronounced tendency to remain supersaturated, especially in the presence of hypoxanthine, even after crystallization has started. Precipitation can be hastened by blowing air through the solution and by persistent rubbing. Concentration of the mother liquors on the steam-bath led to the recovery of 5 g. of crude hypoxanthine, mixed with a small amount of 6-mercaptopurine. The hypoxanthine recovered in this manner was used in subsequent runs. The 6-mercaptopurine was purified by two recrystallizations from 100 parts of hot water, using Darco for decolorizing. The yellow prisms, m.p. 313–314° (dec.), contain a molecule of water of crystallization which is lost at 140°, but not at 110°.

In a series of eleven experiments, the average yield of purified 6-mercaptopurine was 40% and the average recovery of crude hypoxanthine 37%.

Anal. Calcd. for $C_5H_4N_4S.H_2O$: C, 35.3; H, 3.5; N, 32.9; H_2O, 10.6. Found: C, 35.6; H, 3.6; N, 32.8; H_2O, 10.8.

6-Methylmercaptopurine. A. Methyl Iodide.—To a solution of 11.55 g. (0.076 mole) of 6-mercaptopurine in 40 ml. of 2 *N* sodium hydroxide and 75 ml. of water was added slowly, with shaking, 11 g. (0.078 mole) of methyl iodide. After two hours at room temperature, the mixture was chilled, the *p*H adjusted to 5 with acetic acid and the colorless needles of 6-methylmercaptopurine trihydrate were filtered off. After recrystallization from water, the compound was dried at 120° (8.9 g., 79%), m.p. 218–220° (dec.).

Anal. Calcd. for $C_6H_6N_4S$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.9; H, 3.6; N, 34.1.

B. Dimethyl Sulfate.—To a solution of 12.95 g. (0.076 mole) of crude 6-mercaptopurine hydrate in 43 ml. of 2 *N* sodium hydroxide and 100 ml. of water was added 7.3 ml. (0.078 mole) of dimethyl sulfate in 0.5-ml. portions with shaking. The mixture was chilled and the *p*H adjusted to 5 with acetic acid. The precipitate of 6-methylmercaptopurine was collected, washed with water and dried at 100° (5.85 g., 47%).

The filtrate from the reaction mixture was taken to dryness on the steam-bath and the residue taken up in 800 ml. of an alcohol–ether (1:1) mixture. The insoluble salts were filtered off and the alcohol–ether mixture taken to dryness. The ultraviolet absorption spectrum of the sticky yellow residue showed four maxima at *p*H 11.

On fractional crystallization of an aqueous solution of this material several fractions were obtained differing in their spectra from each other and from 6-mercapto- and 6-methylmercaptopurine. These products, presumably methylated on the ring nitrogens, were not further identified.

In another run, where 8 g. of 6-mercaptopurine hydrate was methylated in a similar manner, except that the addition of dimethyl sulfate was somewhat slower, 6.3 g. (81%) of crude 6-methylmercaptopurine was obtained.

Reaction of 6-Methylmercaptopurine with Amines.—In general, the 6-methylmercaptopurine was heated with 2 to 3 molecular equivalents of the amine in aqueous solution in a sealed tube at the temperature and for the period given in Table I; with aniline and *p*-chloroaniline no solvent was used. After the reaction, the excess of amine was removed by evaporation to dryness in the case of the volatile amines and by leaching with an appropriate solvent for the high-boiling amines: water for morpholine, petroleum ether for *n*-decylamine, ether for aniline and *p*-chloroaniline. The yields, solvents of recrystallization and analyses are given in Table I.

Considerable difficulty was encountered in obtaining correct nitrogen analyses for some of these compounds. With the 6-anilino derivatives satisfactory results were obtained by the Dumas method, but not by the Kjeldahl. On the other hand, with 6-methylamino- and 6-ethylaminopurine high nitrogen values were obtained by the Kjeldahl but

(18) We are indebted to D. Lorz for the experiments with xanthine oxidase.

(19) (a) G. B. Elion and G. H. Hitchings, *J. Biol. Chem.*, **185**, 651 (1950); (b) G. B. Elion, G. H. Hitchings and H. VanderWerff, *ibid.*, **192**, 505 (1951).

(20) W. Traube, *Ann.*, **331**, 71 (1904).

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

(22) H. R. Billica and H. Adkins, *Org. Syntheses*, **29**, 24 (1949).

(23) G. Bruhns, *Z. physiol. Chem.*, **14**, 531 (1890).

(24) G. H. Hitchings, *J. Biol. Chem.*, **143**, 43 (1942).

low values by the Dumas method. In common with other compounds containing vicinal nitrogen atoms, 6-hydrazinopurine cannot be expected to give correct nitrogen analyses by the Kjeldahl method. The nitrogen found was somewhat high for four of the six nitrogen atoms present (calcd.: N, 37.4. Found: N, 38.7).

The 6-dimethylaminopurine, after preliminary recrystallization from a small volume of water, was best purified for analysis by conversion to its hydrochloride in absolute ethanol and precipitation with ether. Only a small amount of 6-diethylaminopurine could be isolated and purified in the same manner; the yield of crude compound was therefore, estimated spectrophotometrically. Two examples are given below as illustrations of the general procedure employed.

6-Methylaminopurine.—A mixture of 1.87 g. of 6-methylmercaptopurine and 4 ml. of a 25% aqueous methylamine solution was heated in a sealed tube at 130° for 17 hours. A considerable pressure due to methylmercaptan developed in the tube. After cooling, the reaction mixture was evaporated to dryness and the residue recrystallized from 50 ml. of water, employing Darco for decolorizing (1.2 g., 72%).

6-Anilinopurine.—A mixture of 3.4 g. of 6-methylmercaptopurine and 15 ml. of aniline was heated in a sealed tube at 180° for 24 hours. The reaction mixture, after cooling, was leached with 200 ml. of ether and the residue recrystallized from 250 ml. of 50% aqueous ethanol (3.4 g., 80%).

Ultraviolet Absorption Spectra.—The spectra were measured with a model DU Beckman spectrophotometer, at a concentration of 10 mg. per liter. For solutions of *p*H 1, 0.1 *N* hydrochloric acid was used and for *p*H 11, a Sørensen glycine–sodium hydroxide buffer.

Acknowledgment.—The authors wish to thank Samuel W. Blackman, Nick Martinez, Jr., and Pauline Kulka for the microanalyses reported here. This work was supported by a grant from the Charles F. Kettering Foundation.

TUCKAHOE 7, N. Y. RECEIVED JULY 5, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Chemistry of Vitamin B_6. VIII. Additional Pyridoxylideneamines and Pyridoxylamines

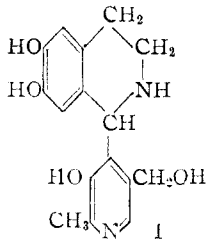
BY DOROTHEA HEYL, EILEEN LUZ, STANTON A. HARRIS AND KARL FOLKERS

Pyridoxal has been condensed with several amines to form pyridoxylideneamines which have been hydrogenated to yield pyridoxylmethylamine, pyridoxylethylamine, pyridoxyl-3-phenylpropylamine, pyridoxylethanolamine, pyridoxylisopropanolamine, pyridoxylaniline, pyridoxyl-3,4-dihydroxyphenethylamine and pyridoxyl-DL-arterenol. All these compounds have 50–100% of the activity of pyridoxine in rats, with the exception of the last two which are only 10–20% as active under the test conditions. Pyridoxyl-DL-arterenol has been tested for pressor activity in rats and shows almost no activity, although it is derived from a highly pressor amine.

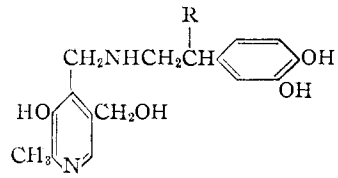
Pyridoxylidene and pyridoxyl derivatives of several amines, including pressor amines, have been described.[1] The pyridoxylamines showed remarkable biological activity in that they retained high vitamin B_6 activity (50–100% of the activity of pyridoxine) in rats, although the corresponding pyridoxylamino acids[2] showed low activity. Additional pyridoxylideneamines and pyridoxylamines which have now been synthesized by the method previously described[1] include derivatives of methylamine, ethylamine, 3-phenylpropylamine, ethanolamine, isopropanolamine and aniline.

Condensation of pyridoxal and 3,4-dihydroxyphenethylamine yielded, instead of the Schiff base, a product of further condensation, 1-(2-methyl-3-hydroxy-5-hydroxymethyl-4-pyridyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (I).[3] Pyridoxyl-3,4-dihydroxyphenethylamine (II) and pyridoxyl-DL-arterenol (III) were made by immediate hydrogenation of a mixture of the reactants, before the initially formed Schiff base could undergo further condensation.

Tests[4] for vitamin B_6 activity in rats showed that all of the pyridoxylamines, with the exception of those represented by structures IV and V, were 50–100% as active as pyridoxine. It seems remarkable that the chemical structure of pyridoxine can



I



II, R = H
III, R = OH

be changed in such gross and varied manner, as represented by these pyridoxylamines, with maintenance of essentially full vitamin B_6 activity. Such high activity suggests that compounds of this type may occur in living systems as members of the vitamin B_6 group or as intermediates in their function. Comparable chemical structural changes of other water soluble vitamins with similar maintenance of activity is unknown.

Pyridoxyl-DL-arterenol (III) and pyridoxyl-3,4-dihydroxyphenethylamine (II) were 10–20% as active as pyridoxine. The lower activity of these two compounds may be due to partial oxidative destruction, because of the presence of the two ortho hydroxyl groups, before the compounds enter vitamin enzyme systems. The tetrahydroisoquinoline derivative I had almost no activity.

In contrast to retention of high vitamin B_6 activity, the pyridoxyl derivatives of such pressor amines as tyramine[1] and phenethylamine[1] showed very little pressor activity[5] in rats when given intravenously in doses as high as 1 mg. A slight rise

(1) Paper VII of this series: D. Heyl, E. Luz, S. A. Harris and K. Folkers, THIS JOURNAL, **70**, 3669 (1948).

(2) D. Heyl, S. A. Harris and K. Folkers, *ibid.*, **70**, 3429 (1948).

(3) Similar condensations of phenethylamines and aldehydes have been described by C. Schöpf and collaborators, *Ann.*, **544**, 1 (1940), and previous publications.

(4) We are indebted to Dr. Gladys Emerson of the Merck Institute for Therapeutic Research for these tests.

(5) We are indebted to Dr. Henry A. Schroeder of the Washington University School of Medicine for these tests.