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.

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

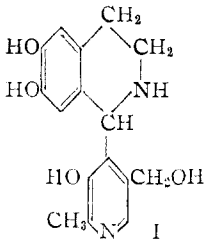
# Chemistry of Vitamin $B_6$. VIII. Additional Pyridoxylideneamines and Pyridoxylamines

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

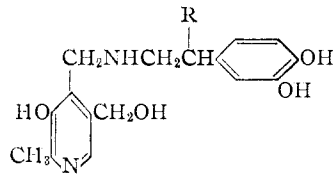
Pyridoxal has been condensed with several amines to form pyridoxylideneamines which have been hydrogenated to yield pyridoxylmethylamine, pyridoxylethylamine, pyridoxyl-3-phenylpropylamine, pyridoxylethanolamine, pyridoxylisopropanolamine, pyridoxylaniline, pyridoxyl-3,4-dihydroxyphenethylamine and pyridoxyl-DL-arterenol. 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.



I



II, R = H
III, R = OH

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 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.

TABLE I

PREPARATION AND PROPERTIES OF PYRIDOXYLIDENEAMINES

| Product, pyridoxylidene- | Reactants: Amine, g. | Pyridoxal, g. | Solvent, ml. | Time of reaction, min. | Yield, % | M.p., °C. | Formula | Analyses, %: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| methylamine | [a] | 8.0 | 100 | [a] | [b] | 150–151 | $C_9H_{12}N_2O_2$ | 59.98 | 60.22 | 6.72 | 6.87 | 15.55 | 15.34 |
| ethylamine | 3.8[c] | 8.0 | 50 | 10 | 88 | 108–109[d] | $C_{10}H_{14}N_2O_2$ | 61.83 | 62.07 | 7.26 | 7.23 | 14.43 | 14.69 |
| 3-phenylpropylamine[e] | 4.00 | 5.00 | 50 | 5 | [f] | 87–89[f] | $C_{17}H_{20}N_2O_2$ | 71.80 | 71.62 | 7.09 | 7.07 | 9.85 | 10.12 |
| ethanolamine | 0.37 | 1.00 | 20 | 5 hr. | 87[g] | 148–149 | $C_{10}H_{14}N_2O_3$ | 57.13 | 57.41 | 6.71 | 6.47 | 13.32 | 13.03 |
| isopropanolamine | 3.15 | 7.00 | 50 | 20 | 70 | 112–114[h] | $C_{11}H_{16}N_2O_3$ | 58.91 | 58.76 | 7.19 | 6.91 | 12.49 | 12.61 |

[a] Generated by dropwise addition of a saturated solution of methylamine hydrochloride into concentrated aqueous potassium hydroxide. The gas was led into the suspension of pyridoxal until the solution was clear. [b] The m.p. and analyses were determined on a small amount of material which crystallized directly from the methyl alcohol solution. No attempt was made to isolate the rest. [c] Excess ethylamine was removed from the solution by a stream of nitrogen. [d] Crystallized once from ether. [e] 3-Phenylpropylamine was made by hydrogenation of phenylpropionitrile according to *Org. Syntheses*, **23**, 72 (1943). [f] Most of the material was not isolated. A small amount which crystallized from the methyl alcohol solution on chilling was collected on a filter and then recrystallized from ether–petroleum ether. [g] Crystallized from methyl alcohol–ether and recrystallized from methyl alcohol. [h] Recrystallized from alcohol–ether–petroleum ether.

TABLE II

PREPARATION AND PROPERTIES OF PYRIDOXYLAMINES

| Product, hydrochloride of pyridoxyl- | Pyridoxylidene-amine, g. | Yield, % | M.p., (dec.) °C. | Formula | Analyses, %: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| aniline | 1.5[1,a] | 87[b] | 230–232 | $C_{14}H_{17}N_2O_2Cl$ | 59.89 | 59.95 | 6.11 | 6.05 | 9.98 | 10.40 |
| methylamine | 5.4[a] | 66[b] | 208–209 | $C_9H_{15}N_2O_2Cl$ | 49.43 | 49.70 | 6.91 | 6.87 | 12.81 | 12.86 |
| ethylamine | 6.20[a] | 92 | 184–186 | $C_{10}H_{17}N_2O_2Cl$ | 51.61 | 51.91 | 7.38 | 7.16 | 12.04 | 12.22 |
| 3-phenylpropylamine | 6.93[a] | 76[b] | 180–181 | $C_{17}H_{23}N_2O_2Cl$ | 63.25 | 63.24 | 7.18 | 6.99 | 8.68 | 8.68 |
| ethanolamine[c] | 2.30[d] | 95 | 174–175 | $C_{10}H_{16}N_2O_3$ | 56.58 | 56.64 | 7.60 | 7.66 | 13.20 | 13.42 |
| isopropanolamine[c,e] | 6.24 | 67 | 194–196 | $C_{11}H_{18}N_2O_3$ | 58.39 | 58.21 | 8.02 | 7.78 | 12.38 | 12.46 |

[a] After hydrogenation the filtrate was acidified only to *p*H 6. [b] Ether was added to precipitate the product. [c] This compound was isolated as the free base, which crystallized from the filtrate after hydrogenation. [d] 300 ml. of methyl alcohol was required. [e] The product was separated from the catalyst by extraction with dilute hydrochloric acid; it was reprecipitated with sodium bicarbonate.

in blood pressure was noted when pyridoxyltyramine was given to rats with a lower than normal blood pressure. Tyramine is effective in a dose of 10 μg., phenethylamine in a dose of 20 μg. Substitution of the pyridoxyl group on the nitrogen atom of DL-arterenol also caused loss of most of the pressor activity at a 1 mg. dose level, although the minimum effective dose of arterenol in the rat is 0.15 to 0.3 μg. Dr. Schroeder reported that normal blood pressure was little affected, although a lower than normal pressure rose moderately and a hypertensive one even more. The duration of the rise was usually 1.5 to 5 minutes. It may be possible that members of the vitamin $B_6$ group play a role in the "detoxification" of pressor amines in normal biological systems.

## Experimental[6]

The pyridoxylideneamines are described in Table I; they were all prepared by Procedure A in Paper VII.[1] The pyridoxylamines described in Table II were prepared by Procedure B in Paper VII.[1]

**1-(2-Methyl-3-hydroxy-5-hydroxymethyl-4-pyridyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline** (I).—A solution of 0.93 g. of 3,4-dihydroxyphenethylamine hydrobromide[7] and 0.21 g. of potassium hydroxide in about 25 ml. of methyl alcohol was treated with 0.63 g. of pyridoxal. When most of the pyridoxal had reacted, the solution was filtered. The material which crystallized from the filtrate was collected on a filter and then purified by dissolution in dilute hydrochloric acid and reprecipitation with sodium bicarbonate. The 1-(2-methyl-3-hydroxy-5-hydroxymethyl-4-pyridyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline was collected on a filter and washed thoroughly with water, then with alcohol, and finally with ether; m.p. 242–244° dec.; yield 0.50 g. (44%).

*Anal.* Calcd. for $C_{15}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.16; H, 5.95; N, 9.09.

**Pyridoxyl-3,4-dihydroxyphenethylamine Dihydrochloride** (II).—A suspension of 0.62 g. of pyridoxal and 0.2 g. of Adams platinum catalyst in 70 ml. of methyl alcohol containing 0.92 g. of 3,4-dihydroxyphenethylamine hydrobromide[7] in solution was treated with 0.15 g. of sodium hydroxide pellets, and the mixture was hydrogenated at once. Absorption of hydrogen was complete in less than ten minutes. The catalyst was collected on a filter, and the filtrate, cooled in ice, was made strongly acid with alcoholic hydrogen chloride. After slow crystallization, 0.74 g. (53%) of pyridoxyl-3,4-dihydroxyphenethylamine dihydrochloride was produced. For purification, this material was dissolved in 20 ml. of ice-water, and was then treated with an excess of sodium bicarbonate. The resulting sticky oil was separated, and a solution of it in alcohol was filtered through a sintered glass disc. The clear filtrate, cooled in ice, was acidified with alcoholic hydrogen chloride. The pure crystals of pyridoxyl-3,4-dihydroxyphenethylamine dihydrochloride melted at 241–242° dec.

*Anal.* Calcd. for $C_{16}H_{22}N_2O_4Cl_2$: C, 50.93; H, 5.88; N, 7.43. Found: C, 51.09; H, 5.62; N, 7.69.

**Pyridoxyl-DL-arterenol Dihydrochloride** (III).—To a suspension of 0.64 g. of pyridoxal and 0.15 g. of Adams platinum catalyst in 50 ml. of methyl alcohol containing 0.79 g. of DL-arterenol hydrochloride[8] in solution, 0.15 g. of sodium hydroxide pellets was added. The mixture was immediately shaken with hydrogen. After 15 minutes the absorption of hydrogen was complete. A carbon dioxide atmosphere was maintained over the solution until it had been acidified with a solution of hydrogen chloride in methyl alcohol. Addition of ether caused crystallization of 0.93 g. (62%) of pyridoxyl-DL-arterenol dihydrochloride. This ma-

(6) We are indebted to Mr. Richard Boos and his associates for the microanalyses.

(7) Obtained by hydrobromic acid hydrolysis of 3,4-dimethoxyphenethylamine ("Beilstein," Vol. XIII, 2nd supplement, p. 486).

(8) K. Kindler and W. Peschke, *Arch. Pharm.*, **269**, 581 (1931). Another synthesis of arterenol has been published recently by R. Simonoff and W. H. Hartung, *J. Am. Pharm. Assoc.*, **35**, 306 (1946).

terial was purified by neutralization with aqueous sodium bicarbonate solution, dissolution of the free amine in ethyl alcohol, and subsequent reacidification with alcoholic hydrogen chloride. The purified material melted at 177–178° dec.

*Anal.* Calcd. for $C_{16}H_{22}N_2O_5Cl_2$: C, 48.86; H, 5.64; N, 7.13. Found: C, 49.10; H, 5.83; N, 7.08.

RAHWAY, N. J. RECEIVED JUNE 22, 1951

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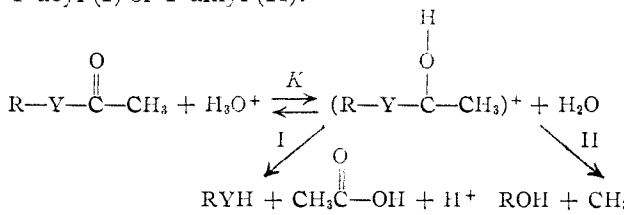
[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# Cleavage of the Carbon–Sulfur Bond. Rates of the Basic and the Acid-catalyzed Hydrolysis of Allyl, Benzyl and Trityl Thioacetates, and the Corresponding Acetates in Aqueous Acetone Solution

BY BETSY K. MORSE AND D. STANLEY TARBELL

The kinetics of the acidic and basic hydrolysis of allyl, benzyl and trityl thiolacetates and the corresponding acetates have been determined in 62% aqueous acetone. The acid-catalyzed hydrolysis of trityl thiolacetate leads to alkyl–sulfur cleavage with the formation of triphenylcarbinol. The reaction is characterized by a large $E$ and a positive $\Delta S^{\ddagger}$. In contrast to the rapid solvolysis of trityl acetate, the alkaline hydrolysis of trityl thiolacetate proceeds at a rate comparable to those of the other esters, and does not appear to involve alkyl–sulfur cleavage. The energy terms for the hydrolysis reactions are compared with those for alkyl acetates and thiolacetates which have been previously studied.

In the acid-catalyzed hydrolysis of ester and thiol esters, two types of fission are possible, either Y-acyl (I) or Y-alkyl (II).[1]



The formation of the transition state intermediate for path I is visualized as a weakening of the acyl–Y bond upon the attack of water on the conjugate acid of the ester, accompanied by solvation of RY. By path II, solvation of the departing group, $R^+$, is required with the weakening of the alkyl–Y bond. The cleavage step (either I or II) is the rate-determining step; the reversible addition of the proton, defined by the equilibrium constant $K$, is rapid.[2]

It has been suggested[3] that *t*-butyl acetate hydrolyzes by alkyl–oxygen cleavage (path II), and this idea was supported by kinetic data given in the preceding paper of this series.[4] It was further shown[4] that *t*-butyl thiolacetate hydrolyzed by path I, a result which is not unexpected in view of the very numerous observations indicating that alkyl–sulfur cleavage occurs much more slowly than alkyl–oxygen cleavage.[5] However, esters of trityl mercaptan have been shown to undergo alkyl–sulfur cleavage[6] under strongly acidic conditions. The object of the present work was to measure rates of the acid-catalyzed and basic hydrolyses of some esters and thiolesters which might be expected to hydrolyze by path II.

**Acid-catalyzed Hydrolysis.**—It was found on qualitative experiments that trityl acetate, $(C_6H_5)_3COCOCH_3$, was hydrolyzed instantly even in neutral solution.[7] The sulfur analog, trityl thiolacetate, hydrolyzed at a measurable rate, with the formation of triphenylcarbinol, which was isolated and identified; thus alkyl–sulfur cleavage was indicated. Trityl mercaptan was stable under the conditions of the hydrolysis and therefore could not be a precursor of the triphenylcarbinol, according to the scheme

$$(C_6H_5)_3CSCOCH_3 + H_2O^+ \longrightarrow (C_6H_5)_3SH + CH_3COOH \xrightarrow{H_2O} (C_6H_5)_3COH + H_2S$$

The acid hydrolysis of benzyl thiolacetate was shown to proceed by path I, with the formation of benzyl mercaptan, by the isolation of the crystalline benzyl 3,5-dinitrothiolbenzoate, $(O_2N)_2C_6H_3COSCH_2C_6H_5$, from the hydrolysis product. A similar investigation of the hydrolysis product from allyl thiolacetate yielded insufficient low-boiling material for the conclusive identification of allyl mercaptan, but it appeared that oxidation or polymerization products of allyl mercaptan, were present, and hence that this hydrolysis likewise had proceeded by path I.

The details of the acid-catalyzed hydrolyses are given in Table I, where the pseudo first-order constants are given. In Table II are given the Arrhenius activation energies, $E$, and the other energy terms, obtained in the usual way.[8] The corresponding terms for the alkyl acetates and thiolacetates have been calculated from the data of Rylander and Tarbell[4] and are tabulated for comparison with the results of the present study. All of the quantities in this table are subject to the ambiguity previously mentioned.[2]

The most striking thing in Table II is that the

(1) Day and Ingold, *Trans. Faraday Soc.*, **376**, 686 (1941).

(2) The pseudounimolecular rate-constants, in which rates of acid-catalyzed hydrolysis of esters are usually expressed, are composite constants, as is clear from the exact rate equation, $-d(\text{ester})/dt = kK(H_3O^+)(\text{ester})$, where $k$ is the specific rate constant for path I or II, and $K$ is the equilibrium constant defined above. The temperature coefficient of the observed rate constant thus includes an unknown contribution whose amount depends on the heat of reactions for the rapid reversible addition of the proton to the ester (*cf.* Carlin, Nelb and Odioso, THIS JOURNAL, **73**, 1006 (1951)).

(3) Cohen and Schneider, *ibid.*, **63**, 3382 (1941).

(4) Rylander and Tarbell, *ibid.*, **72**, 3021 (1950).

(5) Tarbell and Harnish, *Chem. Revs.*, **49**, 1 (1951).

(6) Iskander, *Nature*, **155**, 141 (1945).

(7) Gomberg and Davis (*Ber.*, **36**, 3926 (1903)) reported that trityl acetate is converted rapidly by water or alcohol to triphenylcarbinol or its ethyl ether. Hammond and Rudesill, THIS JOURNAL, **72**, 2769 (1950), have recently shown that trityl benzoate, in methyl ethyl ketone–alcohol solution, is converted to trityl ethyl ether by a first-order solvolysis, with alkyl–oxygen fission (path II).

(8) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.