

four hours at a temperature of from 37.5 to 40° while the pH of the reaction mixture changed from 3.6 to 2.8.

The pectase activity of Pectinol A, Pectinol 100 D and two samples of sugar-free Pectinol A were found to be as follows: Pectinol A, 4.2; Pectinol 100D, 38.7; sugar-free Pectinol A₁, 47.0, and sugar-free Pectinol A₂, 30.6, all measured at 31° and pH 4.5. These activities were determined by a modification of the method of Kertesz and are expressed as mg. of CH₃O per thirty minutes per gram of enzyme.

The optimal pH range for the pectase activity of these samples of Pectinol A was found to be from 4.3 to 4.6.

It was shown by optical rotation methods that sugar-free Pectinol A will bring about the hydrolysis of sucrose, starch and maltose at 37.5° and pH 3.3. This enzyme showed only slight hydrolysis of inulin and gave no indication of hydrolysis of a suspension of xylan under these conditions.

MORGANTOWN, WEST VIRGINIA

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF COLORADO]

The Glyoxalines. IV. A Study of the Structure of Certain Glyoxalines

BY DAVID LLOYD WILLIAMS,¹ FRED L. SYMONDS,² JOHN B. EKELEY³ AND ANTHONY R. RONZIO⁴

It has been shown that phenylglyoxal reacts with amidines, urea and thiourea to yield glyoxalines,^{5,6} hydantoin⁷ and thiohydantoin⁸ respectively.

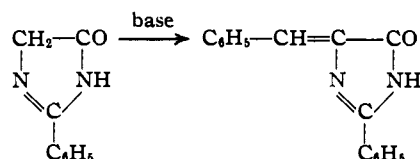
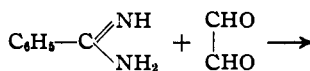
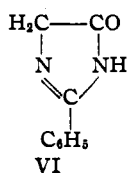
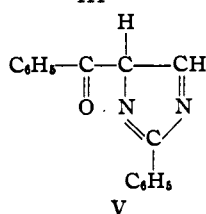
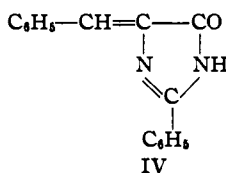
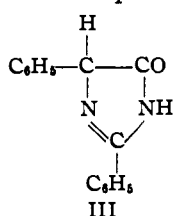
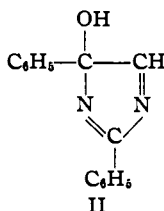
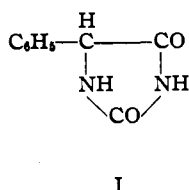
Urea was shown to yield 4-phenyl-hydantoin (I),⁷ a compound which had been prepared previously by a method which left no doubt regarding the structure. Benzamidine was shown to

yield a compound which could be formulated as either a 2,4-diphenyl-4-hydroxyglyoxaline (II), or as a 2,4-diphenyl-5-keto-dihydroglyoxaline (III).

Benzamidine, glyoxal and benzaldehyde react⁹ in basic solution to give a compound which was shown by absorption spectra¹⁰ to be related to benzal-phenyl-glyoxalidone (IV), first synthesized by Ruhemann and Cunningham.¹¹ The structure of a benzoyl-phenyl-glyoxalidone (V) was given to the compound.

The mechanism assumed for the reaction was as follows. The reaction of benzamidine and glyoxal was shown to yield an unstable addition product which easily decomposed in water solution to regenerate benzamidine and glyoxal.⁹ In basic solution, the glyoxal was assumed to react with benzaldehyde to yield C₆H₅COCHOHCHO, which, in turn, was assumed to condense with benzamidine to yield compound (V).

However, should the reaction between benzamidine and glyoxal follow a path analogous to that of phenylglyoxal and urea, the product would then be 2-phenyl-5-keto-dihydroglyoxaline (VI). As is well known, the hydrogen atoms on position 4 in this class of compounds are reactive. Compound (VI) could then condense with benzaldehyde to yield a compound identical with Ruhemann and Cunningham's benzal-phenyl-glyoxalidone (IV), according to the equation



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(4) Now at The Institute of Paper Chemistry, Appleton, Wisconsin.

(5) Waugh, Ekeley and Ronzio, *THIS JOURNAL*, **64**, 2028 (1942).

(6) Third paper of this series, Cole and Ronzio, *ibid.*, **66**, 1584 (1944).

(7) Fisher, Ekeley and Ronzio, *ibid.*, **64**, 1434 (1942).

(8) Unpublished work.

(9) Ekeley and Ronzio, *THIS JOURNAL*, **67**, 1253 (1935). See also Ekeley and Elliott, *ibid.*, **58**, 163 (1936).

(10) Ekeley and Ronzio, *ibid.*, **60**, 1118 (1937).

(11) Ruhemann and Cunningham, *J. Chem. Soc.*, **75**, 954 (1899).

Erlenmeyer, Jr.,¹² described a general reaction for the synthesis of this series of compounds by the action of aromatic aldehydes and hippuric acid, followed by treatment with ammonia. The melting point reported for benzal-phenyl-glyoxalidone by Ruhemann and Cunningham¹¹ was 274°. The melting point reported by Erlenmeyer for the same compound was 270°. The melting point reported by Ekeley and Ronzio for 2-phenyl-4-benzoyl-glyoxaline was 284°. The possibility that, in spite of the variation in melting points, only a single compound is involved was investigated and is here reported.

Erlenmeyer reported that the compound was very difficult to purify and that as the melting point rose, the compound became a deeper yellow.

Samples of the compounds were prepared by the method of Erlenmeyer,¹⁵ by the method of Ekeley and Ronzio⁹ and by the method of Ruhemann and Cunningham¹¹ and carefully purified. The melting points found were 280, 284 and 274°, respectively. The melting points of mixtures of these compounds were always between the melting points of the unmixed compounds. All three exhibited a yellow-green fluorescence in basic alcoholic solution. This fluorescence was enhanced by the addition of ether.

The samples prepared by the method of Erlenmeyer and by the method of Ekeley and Ronzio were reduced with sodium amalgam in acid solution. The reduction products were identical in appearance and melting points. The melting point of a mixture of the two compounds showed no change. The two reduction products also yielded picrates with identical melting points. The identity of the two series of compounds may be considered as established.¹³

An investigation of the two series reveals several compounds prepared by the two methods. These are shown in Table I.

TABLE I

Compound	M. p., °C.	Reference
2-Phenyl-4-benzal-5-glyoxalidone	270	Erlenmeyer ¹²
	284	Ekeley and Ronzio ⁹
	274	Ruhemann and Cunningham ¹¹
2-Phenyl-4-anisal-5-glyoxalidone	283	Erlenmeyer ¹⁴
	307	Ekeley and Ronzio ⁹
2-Phenyl-4-furfural-5-glyoxalidone	241	Erlenmeyer ^{14b}
	293.5	Ekeley and Ronzio ⁹
2-Phenyl-4-cuminal-5-glyoxalidone	245	Erlenmeyer ¹⁶
	246.7	Ekeley and Elliott ¹⁵

As can be seen there is a wide divergence of melting points in almost every instance. The only explanation we can offer for this behavior is that these compounds exist in *cis* and *trans* forms and that the melting point varies with the varying amount of each isomer present in the mixture.

(12) Erlenmeyer, *Ber.*, **33**, 2086 (1900).

(13) The double bond reduced under these conditions is the bond between the two rings. This reduction, which destroys the *cis-trans* isomerism, has been studied by Granacher and Gulbas.¹⁹

(14) (a) Erlenmeyer and Wittenberg, *Ann.*, **337**, 294 (1901);

(b) Erlenmeyer and Stadlin, *ibid.*, **337**, 283 (1904).

(15) Erlenmeyer and Matter, *ibid.*, **337**, 271 (1904).

All attempts to isolate either of the two isomers or convert all to one form met with failure.

The original sample of the compound first synthesized by the method of Ekeley and Ronzio (1934) and which had been preserved in a well closed sample vial showed a melting point of 278°. Recrystallization from glacial acetic acid did not materially raise the melting point. The original melting point of this sample was 284°. The only deduction we can make is that the two forms are in equilibrium with each other.

Based on this evidence and from the reaction of phenylglyoxal and urea, we may conclude that the reaction of amidines with glyoxal and phenylglyoxal yields 5-keto-glyoxalines.¹⁶

The possibility that hydroxy-ketone may be the reacting form of glyoxal was investigated in the following manner.

It has been shown by de Fourcrand¹⁷ that the heat given up by the reaction glyoxal + water → glycolic acid is 4.93 kcal.

The heats of formation of the following molecules calculated from the bond energy values given by Pauling, were as follows:

Glyoxal.....	531.2 kcal.
Hydroxyketene.....	516.5 kcal.
Water.....	220.4 kcal.
Glyoxal + water.....	751.6 kcal.
Hydroxyketene + water.....	736.9 kcal.
Glycolic acid.....	742.6 kcal.

It may be assumed that the glyoxal used by de Fourcrand was an equilibrium mixture of glyoxal and its tautomeric form, hydroxyketene. The heat of formation of the glyoxal equilibrium mixture is 4.93 kcal. greater than that of glycolic acid or 747.5 kcal.

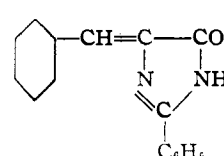
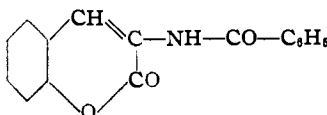
Using these values, the percentage of enol in the mixture may be calculated.

$$751.6a + 736.9(1 - a) = 747.5$$

The percentage of enol is thus found to be 27.8%. This value may be checked using bond distances. Assuming the distance between carbon atoms to be the normal spacing in glyoxal (1.54 Å.) and that the carbon-to-carbon distance in hydroxyketene is the normal ethylene type of spacing (1.34 Å.) the average carbon-to-carbon distance is calculated to be 1.48 Å.

$$\text{Distance} = 0.722(1.54) + 0.278(1.34) = 1.48 \text{ \AA.}$$

(16) It is interesting to note that salicylaldehyde gives benzoylaminocoumarin (I) by the method of Erlenmeyer,^{14a} whereas the normal 4-salicylidene-2-phenyl-5-glyoxalidone (II) is obtained by the method of Ekeley and Ronzio.⁹



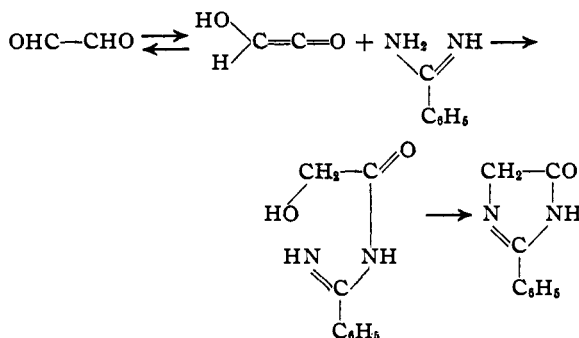
I, Colorless, m. p. 172-173°

II, Yellow, m. p. 338°

(17) de Fourcrand, *Compt. rend.*, **98**, 295 (1884).

This is in fair agreement with the electron diffraction measurements of LuValle and Schomaker,¹⁸ who found a value of 1.47 Å.

The following equation is a suggested mechanism for the reaction of benzamidine and glyoxal.



Experimental

The compound obtained from benzamidine, glyoxal and benzaldehyde was prepared by the method described by Ekeley and Ronzio.⁹ The product, recrystallized several times from *s*-amyl alcohol, melted at 284° (capillary tube melting point).

One gram of the finely powdered product was suspended in 100 ml. of alcohol in a two-necked flask fitted with a reflux condenser and mechanical stirrer. The solvent was heated to boiling and 2% sodium amalgam was added, in small portions, through the reflux condenser. Glacial acetic acid was then added periodically in quantities sufficient to keep the mixture acidic throughout the reaction. After about one hour the yellow color disappeared and the

(18) LuValle and Schomaker, *THIS JOURNAL*, **61**, 3520 (1939).

solution became clear. The solution was separated from the mercury and evaporated to dryness in a vacuum. The solid residue was washed first with water, then with a little ether. The yield of crude product was 85%. Recrystallized twice from xylene (using carbon), and washed with petroleum ether and dried, the colorless crystals melted at 150–151°.

Anal. Calcd. for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.10, 76.28; H, 6.46, 6.65; N, 10.88, 10.92.

The compound easily formed a picrate melting at 238°.

A like amount of compound prepared from benzaldehyde, hippuric acid, and ammonia (m. p. 280°), according to the directions of Erlenmeyer,¹⁶ was reduced in exactly the same manner. The colorless crystals melted at 150–151°.¹⁹

Anal. Calcd. for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.29, 76.28; H, 6.40, 6.20; N, 11.03, 10.92.

A picrate of the compound melted at 238°.

A melting point determination of a mixture of the two reduction products showed no change in melting point.

Summary

The series of products prepared by Erlenmeyer from aromatic aldehydes, hippuric acid, and ammonia and by Ekeley and Ronzio from aromatic aldehydes, benzamidine, and glyoxal have been shown to be identical—namely, 2-phenyl-4-arylidine-5-glyoxalidones.

Thermodynamic calculations indicate the existence of the tautomer of glyoxal, hydroxyketene, to the extent of about 28%.

(19) Granacher and Gulbas (*Helv. Chim. Acta*, **10**, 819 (1927)) obtained 145–146° for the melting point of this reduction product after recrystallization from methanol.

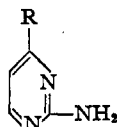
APPLETON, WISCONSIN RECEIVED SEPTEMBER 25, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. V. 2-Amino-4-basically-substituted-pyrimidines¹

BY ROBERT R. ADAMS² AND FRANK C. WHITMORE

As an extension of our previous investigations on pyrimidine compounds,³ we have prepared a number of basically-substituted pyrimidines which correspond to the formula



where R is an aminoalkylamino or a di-(ω -aminoalkyl)-amino group of three to eight carbon atoms which may be interrupted by an oxygen atom or an amino group and in addition may have either

(1) This paper is taken from a portion of the doctoral dissertation of Robert R. Adams, the Pennsylvania State College, 1944.

(2) Parke, Davis and Company, Research fellow, 1942–1944; present address, Parke, Davis and Company.

(3) Adams and Whitmore, *THIS JOURNAL*, **67**, 745 (1945).

a straight or branched carbon chain. The ω -amino group may be either diethylamino, di-*n*-propylamino, di-*n*-amylamino, piperidino or morpholino. The properties of these compounds and their derivatives are shown in Table I.

These compounds were prepared by treatment of 2-amino-4-chloropyrimidine⁴ with two moles of the basically-substituted aliphatic amine⁵ or with about one and two-tenths moles of the amine in pyridine. When triethylamine was used as solvent instead of pyridine in the reaction of 2-amino-4-chloropyrimidine with δ -diethylamino-butylamine, the yield dropped from 79 to 27%. This is perhaps because the chloropyrimidine is soluble in the excess diamine or in pyridine but

(4) Kindly furnished by the Calco Chemical Division of American Cyanamid Company.

(5) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, *THIS JOURNAL*, **66**, 725 (1944).