yield 1.22 g., spec. rot. +1° (24°, D line, *c* 3.5, $CHCl_3$) and −9° (23°, D line, *c* 3.5, dry pyridine).

The product was soluble in acetone, chloroform, glacial acetic acid, pyridine, warm dioxane and benzene. It dissolved somewhat in warm 75% ethanol accompanied by strong swelling. It formed strong, flexible, colorless films from acetone or chloroform solutions.

The saponification equivalents[6] determined in acetone were 99.1 and 99.7 (10.09 cc. and 10.03 cc. 0.1 *N* NaOH per 100 mg.). These values correspond to 0.33 and 0.29 O-pentaacetyl-*d*-gluconyl groups per anhydroglucose unit. Repeated esterification of cellulose acetate under conditions similar to those described above did not raise the substitution above 0.37 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

Summary

1. Crystalline di-(O-pentaacetyl-*d*-gluconates) of ethylene glycol, propanediol-1,3 and bis-(2-hydroxyethyl) ether have been prepared by the reaction of the corresponding glycol with *d*-gluconyl chloride pentaacetate in pyridine.

2. Under similar conditions glycerol, (*dextro*)-sorbitol, *d*-mannitol and α-methyl-*d*-glucoside formed fully esterified O-pentaacetyl-*d*-gluconates in the form of colorless, amorphous powders.

3. Mercerized cotton linters were esterified in the presence of triethylamine and nitrobenzene, forming a fibrous product containing 0.4 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit.

4. A modified cellulose acetate (1.72 acetyl groups per anhydroglucose unit) in pyridine gave a mixed ester containing 0.7 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit and in chloroform and triethylamine, a mixed ester containing 0.3 O-pentaacetyl-*d*-gluconyl group per anhydroglucose unit was formed.

COLUMBUS, OHIO RECEIVED APRIL 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLORADO UNIVERSITY]

The Glyoxalines. II. A Study of the Reaction between Benzamidine and Phenylglyoxal

BY RICHARD C. WAUGH,* JOHN B. EKELEY AND ANTHONY R. RONZIO

A reaction between benzamidine and phenylglyoxal was reported by Kunckell and Bauer[1] in which a compound described as "phenacal benzamidine" (m. p. 224°) was isolated. When repeated by us the reaction proceeded exactly as described by them. The product obtained, recrystallized from ethyl alcohol, melted at 225°. Nitrogen analyses, however, failed to check the value for "phenacal benzamidine." The value obtained (13.65%) was so close to the value for kyanphenin (13.60%) that a melting point of the mixture was taken. The melting point found was 228° (m. p. of pure kyanphenin 230–231°). The solubilities and physical appearance of "phenacal benzamidine" and kyanphenin were also identical. The experiment was repeated many times with the same result. Hence, the work of Kunckell and Bauer was considered to be in error and the reaction between benzamidine and phenylglyoxal was re-investigated.

The products obtained from the reaction between benzamidine and phenylglyoxal under different conditions are shown in Chart I. Compound I was formed when the two reactants were treated with base in cold alcohol solution. Recrystallized from ethyl acetate, the product gave analyses corresponding to the formula $C_{17}H_{18}O_3N_2$. Since the compound formed readily in cold solution, it appeared likely that it was a simple addition product. The compound contains one-half molecule of ethyl acetate of crystallization.

Compound I is converted to Compound II by dissolving in basic solution, heating for a short time, then carefully neutralizing with acid. Recrystallized from dioxane, the analyses correspond to a compound $C_{17}H_{16}O_2N_2$.[2] The compound contains one-half molecule of dioxane of crystallization as proved by a cryoscopic determination.

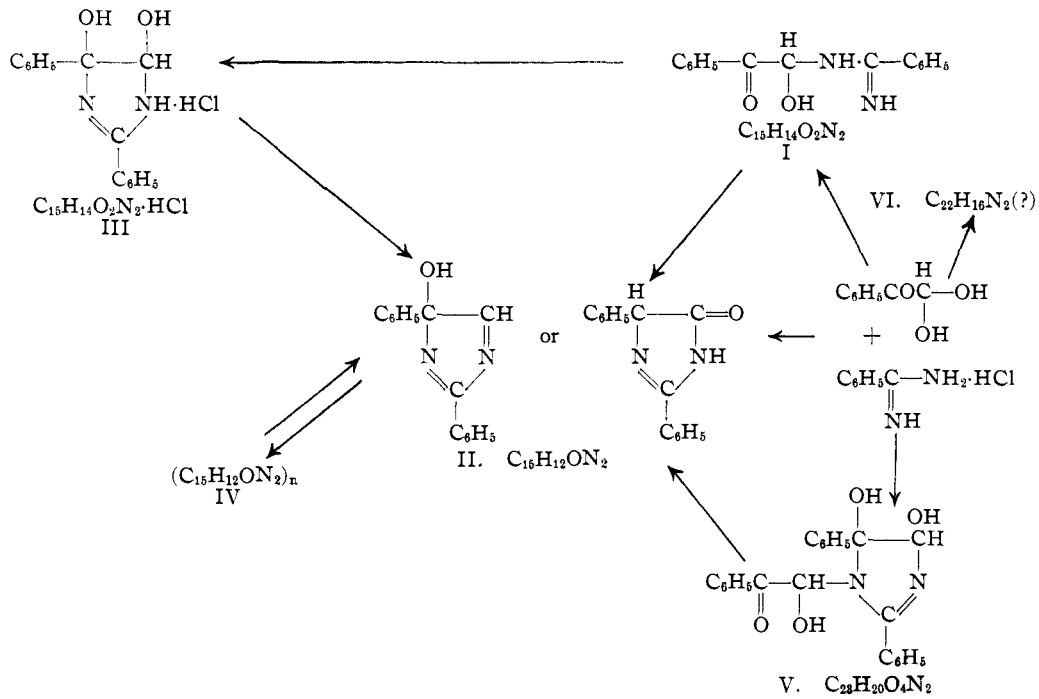
When a basic solution of either Compound I or II is treated with an excess of hydrochloric acid, a voluminous precipitate of the hydrochloride of Compound III is formed. This compound is very unstable in the absence of acids. Analyses gave results corresponding to the formula $C_{15}H_{14}O_2N_2 \cdot HCl$.

* Now with Eastman Kodak Co.

(1) Kunckell and Bauer, *Ber.*, **34**, 3029 (1901).

(2) In the first paper of this series [Fisher, Ekeley and Ronzio, THIS JOURNAL, **64**, 1434 (1942)] it has been shown that phenylglyoxal and urea react to form 4-phenyl-hydantoin. Should a similar reaction take place when benzamidine is used instead of urea, the formula for Compound II would then be the second structure shown on Chart I.

CHART I



Upon standing in solvents containing traces of base, Compound II changes to Compound IV. This compound was insoluble in all the solvents tried. Analyses gave results corresponding to the empirical formula $C_{15}H_{12}ON_2$. It will be seen that this formula is identical to the formula for Compound II without any solvent of crystallization. The analyses and insolubility indicate that Compound IV is a polymer of Compound II.

Phenylglyoxal and benzamidine hydrochloride dissolved in a strong water solution of sodium acetate yields Compound V as an orange powder. When this powder is dissolved in hot alcohol, it almost instantly separates as yellow needles of Compound II. Analyses gave values which could not be formulated into any logical structure. The results were, however, close to those given by a reaction between two molecules of phenylglyoxal and one molecule of benzamidine. It is probable that the orange powder is Compound V mixed with a small amount of Compound II.

A compound of unknown structure (VI) giving analyses for $C_{22}H_{16}N_2$ was obtained by boiling benzamidine hydrochloride together with phenylglyoxal for several hours. Since a strong odor of ammonia was noted, it is probable that the product is formed from fragments of benzamidine and phenylglyoxal.

Experimental

Compound I. Hydroxyphenacylbenzamidine.—Concentrated potassium hydroxide was added to a cooled 95% alcohol solution containing 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride until the solution was distinctly basic. The precipitated potassium chloride was filtered off and the filtrate was cooled in an ice–salt mixture.

Dropwise addition of water precipitated a colorless compound which was filtered off, dried and recrystallized from ethyl acetate containing just enough absolute ethyl alcohol to dissolve the compound. The compound must be dried *in air*. Either heat or a drying agent cause decomposition. The compound is soluble in acids, bases, alcohol, acetone and dioxane; insoluble in ether, hydrocarbons and chloroform; m. p. 112–115° with decomp., yield, 2.4 g. (40%).

Anal. Calcd. for $2(C_{15}H_{14}O_2N_2)\cdot CH_3\text{-}COO\text{-}C_2H_5$: C, 68.60; H, 6.05; N, 9.30. Found: C, 68.83; H, 5.99; N, 9.40.

Compound II. 2,4-Diphenyl-4-hydroxyglyoxaline (or 2,4-Diphenyl-5-ketodihydroglyoxaline).—Three grams of phenylglyoxal hydrate (0.02 mole) and 3.8 g. of benzamidine hydrochloride (0.02 mole) were dissolved in 200 ml. of warm water. The addition of 1 ml. of 50% potassium hydroxide and boiling caused a deep brown color to form. After fifteen minutes the solution was cooled and carefully neutralized, whereupon a flocculent yellow solid formed. Recrystallized from dioxane, the sparkling yellow needles melted at 251–252°; the yield was 64%.

Anal. Calcd. for $2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$: C, 72.90; H, 5.72; N, 10.00. Found: C, 72.80; H, 5.80; N, 10.03.

A molecular weight determination by the method of Smith and Young[3] gave a value of 189. Calcd. for $2(C_{15}$-

(3) J. Smith and W. Young, *J. Biol. Chem.*, **75**, 289 (1927).

$H_{12}ON_2)\cdot C_4H_8O_2$: mol. wt., 189. The compound is soluble in base, alcohol, dioxane and ethyl acetate; insoluble in ether, acetone and the hydrocarbons; soluble in acids but reprecipitates in a short time. A basic alcohol solution of the compound shows a blue fluorescence upon the addition of ether.

The same compound may be prepared by dissolving Compound I in hot base, followed by neutralization of the solution with acid.

A portion of this compound boiled with acetic anhydride yielded a gummy solid, which, recrystallized from a mixture of dioxane and water, yielded colorless plates of the monoacetyl derivative melting at 174°.

Anal. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.40; H, 5.05; N, 10.07. Found: C, 73.50; H, 5.00; N, 9.95.

Compound III. 2,4-Diphenyl-4,5-dihydroxydihydroglyoxaline.—A solution of 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride in 50 ml. of glacial acetic acid was refluxed. Within ten minutes a white precipitate began to form. After being heated for an hour the mixture was cooled and filtered. The solid gave a positive chloride test. The product was recrystallized from glacial acetic acid containing enough concentrated hydrochloric acid to prevent the formation of a yellow color. The colorless needles obtained in this manner melted at 282° after darkening at 260°; the yield was 62%.

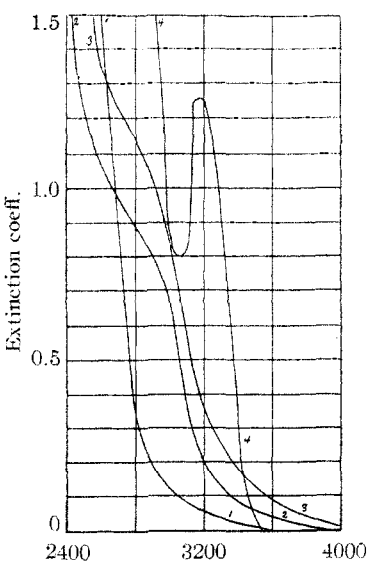


Fig. 1.

The compound was also prepared by adding a large excess of concentrated hydrochloric acid to a basic solution of either Compound I or Compound II. This method of preparation is less convenient.

In the absence of acid the compound quickly forms Compound II.

Anal. Calcd. for $C_{15}H_{14}O_2N_2\cdot HCl$: C, 62.00; H, 5.17; N, 9.65. Found: C, 61.90; H, 5.20; N, 9.50.

Compound III refluxed with acetic anhydride yielded a gummy product which, when recrystallized from dioxane-water mixture, yielded colorless plates of the diacetyl derivative which melted at 181° after three recrystallizations.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.85; H, 5.95; N, 8.70. Found: C, 70.90; H, 5.65; N, 8.85.

Compound IV $(C_{15}H_{12}ON_2)_x$.—When an alcohol or dioxane solution of Compound II containing a trace of base was allowed to stand, it gradually lost its yellow color and a white powder was deposited. Insoluble in the solvents tried, the powder was washed successively with boiling alcohol, ethyl acetate, methyl alcohol, dioxane and acetone. After this treatment the compound darkened at 250° and melted at 262°.

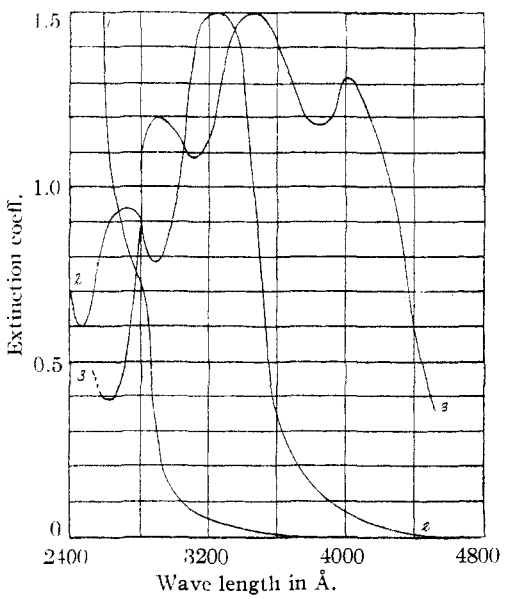


Fig. 2.

Attempts at acetylation produced an unrecrystallizable gum. Solution in hot base regenerated Compound II which was precipitated upon neutralization.

Anal. Calcd. for $(C_{15}H_{12}ON_2)_x$: C, 76.30; H, 5.08; N, 11.80. Found: C, 76.20; H, 4.73; N, 11.85.

Compound V. 2,4-Diphenyl-4,6-dihydroxy-3-(β-hydroxyphenacyl)-dihydroglyoxaline.—A water solution made by dissolving 3.8 g. (0.02 mole) of benzamidine hydrochloride, 3 g. (0.02 mole) of phenylglyoxal hydrate and 10 g. of sodium acetate in 200 ml. of water was allowed to stand for three days at room temperature. A brilliant orange powder was formed which defied all attempts at recrystallization; weight 3.3 g. (87%). The compound dissolved easily in alcohol, then, upon standing about one minute, yellow needles of Compound II precipitated out. The only purification that could be carried out was solution in benzene followed by precipitation of the compound by adding petroleum ether. The melting point of the product thus purified was 73–80°.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: C, 71.10; H, 5.16; N, 7.23. Found: C, 72.80; H, 5.14; N, 7.50.

Partial decomposition to Compound II is the only explanation which can, at present, be offered for these anomalous results.

Compound VI, $C_{22}H_{16}N_2$.—When 3 g. (0.02 mole) of phenylglyoxal hydrate and 3.8 g. (0.02 mole) of benzamidine hydrochloride in 300 ml. of water were boiled for three hours, a gummy substance formed which was filtered from the hot solution and recrystallized three times from ethyl alcohol. The colorless needles obtained melted at 170–172°. The yield was less than 1%.

Anal. Calcd. for $C_{22}H_{16}N_2$: C, 85.70; H, 5.19; N, 9.09. Found: C, 85.83; H, 5.38; N, 9.18.

No structure could be assigned to fit the formula and which would explain its formation. It would appear that the compound is the result of reaction between decomposition fragments.

TABLE I

ABSORPTION SPECTRA CURVES (1-CM. CELL)

Plate	Compound	Formula	Wt. used, g.	Solvent, ml.	Curve
I	IV	$(C_{15}H_{12}ON_2)_x$	0.00277	50 1% KOH	1
I	II	$2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$	.00250	50 1% KOH	2
I	III	$C_{15}H_{14}O_2N_2\cdot HCl$	.00266	50 1% KOH	3
I	VI	$C_{22}H_{16}N_2$	.00338	50 abs. EtOH	4
II	I	$2(C_{15}H_{14}O_2N_2)\cdot C_4H_8O_2$	.00250	50 abs. EtOH	1
II	III	$C_{15}H_{14}O_2N_2\cdot HCl$	.00112	50 EtOH contg. 5 ml. concd. HCl	2
II	II	$2(C_{15}H_{12}ON_2)\cdot C_4H_8O_2$	.00198	50 abs. EtOH	3

Absorption spectra data were obtained using a Hilger E3 spectrograph, Hilger Sector photometer and Eastman Wrattan and Wainwright Panchromatic plates. An under-water spark served as a light source.

It may be seen that Curves II and III, Plate I, and Curve I, Plate II are identical. This clearly demonstrates the formation of Compound II when base is added to a solution of either Compound I or Compound III.

Summary

1. The reaction between benzamidine and phenylglyoxal has been studied and found to yield a 2,4-diphenyl-4-hydroxyglyoxaline (or 2,4-diphenyl-5-keto-dihydroglyoxaline).

2. Intermediate, unstable compounds have been isolated and studied, and formulas proposed for them.

3. Absorption spectra curves in the ultraviolet and visible have been obtained for the compound studied.

BOULDER, COLORADO RECEIVED JUNE 16, 1942

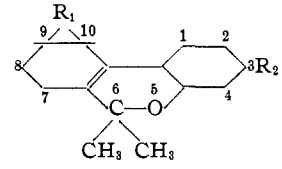
[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Some Analogs of Synthetic Tetrahydrocannabinol

BY GORDON A. ALLES, ROLAND N. ICKE AND GEORGE A. FEIGEN

The recent elucidation of the structure of cannabinol by Adams and co-workers,[1] and the discovery of marihuana activity in synthetic tetrahydrocannabinol[2a] and hexahydrocannabinol[2b] has opened the field for study of relationships between chemical constitution and this type of physiological action. The optically active tetrahydrocannabinols and hexahydrocannabinols derived by isomerization of cannabidiol[3] are of considerable interest in this connection, though their exact structure is in some doubt. Similarly, pulegone-5-*n*-alkylresorcinol products studied by Todd and co-workers,[4] and by Adams and co-workers[5] are of much interest, though the composition of such products is not yet certain.

Several series of compounds of known structure that are analogs or homologs of synthetic tetrahydrocannabinol and hexahydrocannabinol have been prepared by Adams and co-workers,[5,6] by Todd and co-workers[4,7] and by Bembry and Powell.[8] The object of the present work was to prepare and study the physiological activity of a series of analogs of synthetic tetrahydro*nor*-cannabinol[5,7,8] (Series I) and of tetrahydrocannabinol (Series II) that lack a hydroxyl group in the 1-position.



Series I, $R_1 = H$
Series II, $R_1 = CH_3$

The series of compounds were prepared in which the R_2 group in the 3-position was amyl, methyl, hydroxy, butyloxy, butyroxy, ethoxy and acetoxy. Of these, the hydroxy and acetoxy com-

(1) (a) Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940); (b) Adams and Baker, *ibid.*, **62**, 2401 (1940).

(2) (a) Adams and Baker, *ibid.*, **62**, 2405 (1940); (b) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, *ibid.*, **62**, 2566 (1940).

(3) (a) Adams, Pease, Cain and Clark, *ibid.*, **62**, 2402 (1940); (b) Adams, Cain, McPhee and Wearn, *ibid.*, **63**, 2209 (1941).

(4) Ghosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).

(5) (a) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941); (b) Adams, Loewe, Smith and McPhee, *ibid.*, **64**, 694 (1942).

(6) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941).

(7) (a) Ghosh, Todd and Wilkinson, *J. Chem. Soc.*, 1121 (1940); (b) Russell, Todd, Wilkinson, MacDonald and Woolfe, *ibid.*, 826 (1941).

(8) (a) Bembry and Powell, THIS JOURNAL, **63**, 2766 (1941); (b) Bembry, Columbia Univ. Dissertation (1941).