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

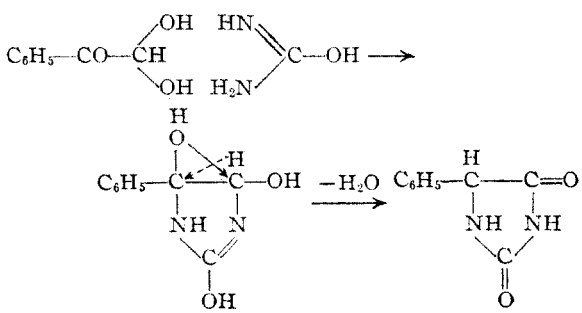
The Glyoxalines. I. Some Hydantoins Resulting from the Reaction between Phenylglyoxal and Urea and Substituted Ureas

BY HOWARD J. FISHER,* JOHN B. EKELEY AND ANTHONY R. RONZIO

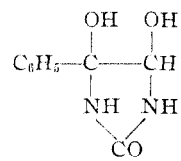
Phenylglyoxal has been shown to react with aminoguanidine to form tautomeric aminotriazines.[1] We are herewith reporting a series of corresponding reactions of phenylglyoxal with ureas, resulting in the formation of hydantoins.

(a) Phenylglyoxal and Urea in Cold Basic Solution.—In basic solution phenylglyoxal and urea condense yielding a compound having the empirical formula $C_9H_8N_2O_2$. A search of the literature revealed that Clark and Francis[2] had obtained a compound which has the identical physical and chemical properties of our compound and which they identified as 4-phenylhydantoin.

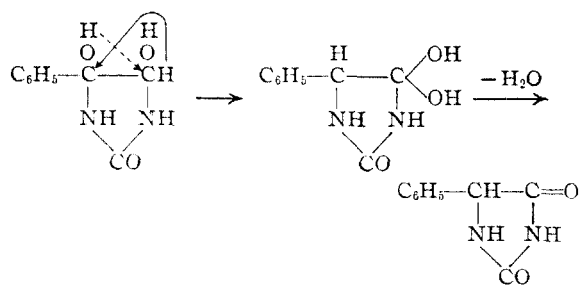
Our compound is therefore 4-phenylhydantoin and the course of the reaction must be:



(b) Refluxing the Reagents in Basic Solution.—Refluxing phenylglyoxal and urea in basic solution for one hour, cooling and acidifying the mixture gave a very small amount of a substance, which on analysis corresponded to a compound having the empirical formula $C_9H_{10}N_2O_3$. The compound on being melted effervesced to give 4-phenylhydantoin. Treatment of the compound in alcohol with hydrochloric acid also gave the 4-phenylhydantoin. Reaction with acetyl chloride or with acetic anhydride gave oils. Evidently the compound is the rather unstable addition product of phenylglyoxal and urea, which readily goes over into 4-phenylhydantoin. The compound cannot, however, be obtained by the hydration of 4-phenylhydantoin no matter how carefully the crystallizing solution is evaporated, nor does the product give a crystallizable reaction product with acetyl chloride or acetic anhydride. The compound undoubtedly has the structure



and passes easily into the hydantoin of known structure as follows



(c) Refluxing 4-Phenylhydantoin in Glacial Acetic Acid or Heating it with 6 *N* Hydrochloric Acid for One Hour.—The product formed in either of the above processes is obtained in a small amount and gives an analysis corresponding to that of 4-phenylhydantoin, but has different physical properties corresponding to a polymer.

(d) Phenylglyoxal and Phenyl Urea.—These two compounds react in hot water solution upon the addition of 50% potassium hydroxide to form 2-keto-3,4-diphenyl-4,5-dihydroxytetrahydroglyoxaline. Heating the compound above its melting point causes the loss of a molecule of water and the formation of 3,4-diphenylhydantoin.

(e) 3-Phenyl-4-methylhydantoin.—The reaction between phenylglyoxal and methyl urea resulted in a compound which, from its properties, was evidently 3-phenyl-4-methylhydantoin.

Experimental

(a) 4-Phenylhydantoin.—Water solutions of phenylglyoxal hydrate (6.08 g. = 0.04 mole in 80 ml. water) and urea (2.4 = 0.04 mole in 20 ml. of water) were mixed and heated to boiling and then 12 ml. 50% potassium hydroxide added. The solution became pale yellow. A temperature just below boiling was maintained for three minutes. Cooling and neutralizing the solution with concd. hydrochloric acid gave 5.95 g. of a slightly yellow crystalline solid; yield, 85%; recrystallization from water, plates,

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(1) Ekeley, Carlson and Ronzio, *Rec. trav. chim.*, **59**, 496 (1940).

(2) Clark and Francis, *J. Chem. Soc.*, **99**, 319 (1911).

m. p. 179°; soluble in alcohol, dioxane; insoluble in ether and in hydrocarbons.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.3; H, 4.55; N, 15.91. Found: C, 61.2, 61.2; H, 4.50, 4.45; N, 15.95, 15.92.

The compound failed to react with hydroxylamine, phenylhydrazine or semicarbazide. Treatment with nitrous acid in presence of hydrochloric acid or in glacial acetic acid produced no change in the compound. Refluxing the compound with a large excess of acetic anhydride gave crystals of an acetyl derivative. Recrystallization from acetic anhydride gave acetyl-4-phenylhydantoin; m. p. 145°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: N, 12.83. Found: N, 12.78, 12.85.

(b) **2-Keto-4-phenyl-4,5-dihydroxytetrahydroglyoxaline.**—A water solution containing 1.52 g. (0.01 mole) of phenylglyoxal hydrate and 0.6 g. (0.01 mole) of urea to which 1 ml. of 50% potassium hydroxide had been added was refluxed for one hour. A small yield (0.15 g.) of a compound was obtained on neutralizing the cooled solution. Recrystallized from alcohol it melted with vigorous effervescence at 184°.

Anal. Calcd. for $C_9H_{10}N_2O_3$, C, 55.7; H, 5.15; N, 14.42. Found: C, 55.8, 55.8; H, 5.10, 5.20; N, 14.42, 14.33.

Fusion in an oil-bath until effervescence subsided gave 4-phenylhydantoin. Acetylation in pyridine yielded an unrecrystallizable oil. Treatment with phenylhydrazine gave no derivative.

(c) **Polymer of 4-Phenylhydantoin.**—A glacial acetic acid solution containing 1.52 g. (0.01 mole) phenylglyoxal hydrate and 0.6 g. (0.01 mole) urea was refluxed. A white microcrystalline precipitate formed which weighed 1.7 g.; yield, 97%. The compound did not melt below 340°, and was insoluble in the usual solvents. Washed successively with boiling water, alcohol, and ether, the dried compound was analyzed, indicating a polymer.

Anal. Calcd. for $(C_9H_8N_2O_3)_n$: C, 61.3; H, 4.55; N, 15.91. Found: C, 61.3, 61.4; H, 4.88, 4.82; N, 16.0, 16.1.

The compound dissolved in concentrated sulfuric acid, from which it is reprecipitated on dilution with water. Soluble in base, it reprecipitated unchanged upon addition of acid.

(d) **2-Keto-3,4-diphenyl-4,5-dihydroxy-tetrahydroglyoxaline and 3,4-Diphenylhydantoin.**—A water solution containing 1.52 g. (0.01 mole) of phenylglyoxal hydrate and 1.36 g. (0.01 mole) of phenyl urea in 20 ml. was heated to boiling. One ml. of 50% potassium hydroxide was added, producing a milky solution. A white gum separated when the mixture was neutralized with hydrochloric acid. Two ml. 50% potassium hydroxide was then added. The resulting pale yellow solution was boiled for five minutes. Neutralization with dilute hydrochloric acid gave a thick white precipitate; yield quantitative. The compound was insoluble in water, benzene, ligroin and carbon tetrachloride, but readily soluble in alcohol, dioxane and pyridine. Recrystallization from alcohol gave a mass of colorless crystals, melting at 169–170° with vigorous effervescence.

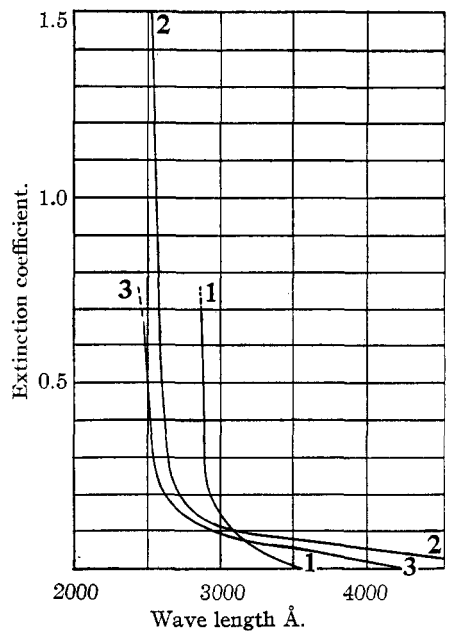

Fig. 1.—Curve 1, 4-phenylhydantoin, 0.00338 g./50 ml. distilled H_2O, 1-cm. cell; curve 2, 2-keto-3,4-diphenyl-4,5-dihydroxy-tetrahydroglyoxaline. 0.00155 g./50 ml. absolute EtOH, 1-cm. cell; curve 3, 3,4-diphenylhydantoin, 0.00339 g./50 ml. absolute EtOH, 1-cm. cell.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.7; H, 5.17; N, 10.35. Found: C, 66.8, 66.8; H, 5.25, 5.16; N, 10.27, 10.22.

The compound resulting from melting the above at 169–170°, or one obtained by refluxing a solution in alcohol acidified with hydrochloric acid for one hour, gave colorless crystals which melted at 189–190°. Analysis for nitrogen indicated that one molecule of water had been given off from the original compound. The product showed all the properties of an hydantoin.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: N, 11.11. Found: N, 11.20, 11.16.

Acetylation procedures yielded only oils. The compound formed no semicarbazone nor oxime.

(e) **3-Methyl-4-phenylhydantoin.**—Addition of 3 ml. 50% potassium hydroxide to a boiling water solution of 1.52 g. (0.01 mole) of phenylglyoxal hydrate and 0.74 g. (0.01 mole) of methyl urea yielded a yellow solution. When neutralized with hydrochloric acid and cooled with ice, a yellow oil separated parts of which solidified on being scratched. Boiling it with 10% hydrochloric acid gave more of the solid when cold; yield, 26%. The compound was soluble in water, dioxane, alcohol, pyridine and in the cellosolves, only slightly soluble in hydrocarbons. Recrystallization from diluted alcohol gave long colorless needles; m. p. 174°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.27; N, 14.72. Found: C, 63.3, 63.3; H, 5.38, 5.33; N, 14.77, 14.72.

No semicarbazone, phenylhydrazone, acetyl nor benzoyl derivative could be prepared. The compound forms a monopotassium salt which hydrolyzes readily with water.

Absorption spectra data were taken for all of the com-

pounds prepared. These data were obtained using a Hilger E3 spectrograph, Hilger sector photometer and Eastman Kodak Co. panchromatic plates. An underwater spark served as light source.

Summary

1. Phenylglyoxal reacts with urea in cold basic solution to form 4-phenylhydantoin, and, when refluxed in basic solution to form on cooling and acidifying 2-keto-4-phenyl-4,5-dihydroxytetrahydroglyoxaline which on melting loses water to become 4-phenylhydantoin.

2. Phenylglyoxal and urea refluxed in glacial acetic give a polymer of 4-phenylhydantoin. The same polymer is obtained by heating 4-phenylhydantoin with 6 *N* hydrochloric acid.

3. Phenylglyoxal reacts in hot alkaline solution with phenyl urea to form 2-keto-3,4-diphenyl-4,5-dihydroxytetrahydroglyoxaline which on being melted loses water to become 3,4-diphenylhydantoin.

4. Phenylglyoxal reacts with methyl urea in hot alkaline solution to form 3-methyl-4-phenylhydantoin.

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Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses. I. Iodinated Aracyl Esters[1a]

BY WILLIAM H. STRAIN, JOHN T. PLATI[1b] AND STAFFORD L. WARREN

With the object of developing absorbable insoluble liquid contrast media for use in radiographic diagnoses, three classes of iodinated organic compounds have been studied: (1) esters of iodinated *o*-acyl derivatives of glycolic acids; (2) esters of iodinated phenoxy fatty acids; and (3) esters of iodinated phenyl fatty acids. Most of the work was confined to ethyl esters, since these are relatively fluid and easily purified.

Esters of Iodinated O-Acylglycolic Acids.—The iodinated O-acylglycolic acids were obtained by heating the sodium salt of the several iodinated acids with an ester of chloroacetic acid. The method is described by the equation $R—CO_2Na + Cl—CH_2CO_2R' \rightarrow R—CO_2—CH_2CO_2R'$, and has previously been employed for the synthesis of ethyl O-benzoyl-glycolate.[1c] Compounds prepared in this way were ethyl O-(*o*-iodobenzoyl)-glycolate, ethyl O-[β-(*p*-iodophenyl)-propionyl]-glycolate, and the ethylene glycol ester of O-(*o*-iodobenzoyl)-glycolic acid. All were obtained in yields of 50–70%.

An attempt was made to prepare ethyl O-(κ-iodoundecylyl)-glycolate by the interaction of sodium κ-iodoundecylate and ethyl chloroacetate, but widespread decomposition occurred when the two were heated together. The analogous reaction between sodium undecylenate and ethyl chloroacetate proceeded satisfactorily, however.

Ethyl Esters of Iodophenoxy Fatty Acids.—From *o*-iodophenol the two iodinated phenoxy fatty acid esters, ethyl γ-(*o*-iodophenoxy)-*n*-butyrate and ethyl κ-(*o*-iodophenoxy)-undecylate, were prepared. The former was obtained from the corresponding acid, which in turn was synthesized from sodium *o*-iodophenoxide and trimethylene bromide by a series of reactions modelled after those employed by Marvel and Tannenbaum[2] in the preparation of γ-phenoxy-*n*-butyric acid. A similar reaction with ethylene bromide in place of trimethylene bromide was carried through the stage of α-bromo-β-(*o*-iodophenoxy)-ethane; with this a small amount of α,β-di-(*o*-iodophenoxy)-ethane was obtained. Ethyl κ-(*o*-iodophenoxy)-undecylate was obtained by the interaction of sodium *o*-iodophenoxide and ethyl κ-bromoundecylate.

Ethyl Esters of Iodinated Phenyl Fatty Acids.—By the addition of iodobenzene to ethyl undecylenate and to ethyl oleate, respectively, in the presence of aluminum chloride at *ca.* 5°, reaction products were isolated, which are doubtless mixtures of isomers. With ethyl undecylenate and iodobenzene, a 40% yield of a product boiling at 205–213° (1.5 mm.) was obtained. It is probably a mixture of the ι- and κ-(iodophenyl)-esters,[3] in analogy with the reaction prod-

(1a) Aided by a grant from the Research Laboratory of the Eastman Kodak Company.

(1b) This work is taken from part of the Ph.D. dissertation of John T. Plati, 1940. Present address: The Massachusetts Institute of Technology, Cambridge, Massachusetts.

(1c) Wislicenus and Andrieff, *Ann.*, **133**, 284 (1865).

(2) Marvel and Tannenbaum, THIS JOURNAL, **44**, 2647 (1922).

(3) The composition of this mixture will be the subject of a future communication.