Summary

1. α,3,5,3′,4′-Pentahydroxy-4-benzyl-1,2-dihydrocoumarone (the Kostanecki formula for catechin) and α,3,5,3′,4′-pentahydroxy-6-benzyl-1,2-dihydrocoumarone have been prepared and are shown to differ in every respect from catechin.

2. These two 1,2-dihydrocoumarones, also 3,5-dihydroxy-1,2-dihydrocoumarone, show great stability as compared with catechin and there is reason to believe that substances having a coumaran constitution, as suggested by Freudenberg for catechin, will probably show the stability of these 1,2-dihydrocoumarones.

BRISTOL, ENGLAND

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

CONDENSATION REACTIONS OF CYCLIC KETONES. I. THE ACTION OF ISATIN AND ISATIN ALPHA CHLORIDE UPON CERTAIN HYDANTOINS[1]

BY ARTHUR J. HILL AND HENRY R. HENZE[2]

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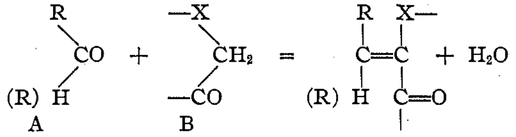
The interaction of aldehydes or ketones with the activated methylene group of substances having the configuration —CO—CH_2—NH— (or S) has frequently been observed. This type of condensation is accompanied by the elimination of water, and is usually effected by glacial acetic acid,[3] or acetic anhydride, with or without sodium acetate.



Among the most important representatives of B are hippuric acid, the hydantoins, rhodanic acid and its derivatives, isothiohydantoins, dioxythiazoles, indoxyl, thio-indoxyl and diketopiperazine.[4]

The ease with which the carbonyl group will combine with these substances is greatly influenced by the molecular configuration of the compound in which it is present. Indeed, in this regard, certain generalizations may be made as follows.

(A) **Aldehydes.**—Nucleus aromatic aldehydes are conspicuously capable of undergoing this reaction and a large number have been investigated.

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[1] This paper is constructed from Part I of the Dissertation presented to the Faculty of the Graduate School of Yale University by Henry R. Henze in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Holder of the National Aniline and Chemical Company Fellowship.

[3] The discussion is therefore restricted to condensations carried out in acid media.

[4] Sasaki, *Ber.*, **54,** 163, 2056 (1921).

Aliphatic aldehydes appear to be rather inactive, the principal exceptions being formaldehyde[5] (an abnormal reaction with hydantoin); *iso*butyraldehyde[6] (with hippuric acid); valeraldehyde[7] (with 3-phenyl-rhodanine); and glyoxal[8] (with indoxyl and thio-indoxyl). The yields with *iso*butyraldehyde and valeraldehyde are poor.

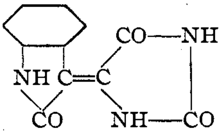
Mention should also be made of cinnamic and α-bromocinnamic aldehydes.[9]

It would appear that activity is associated with the length of chain and also unsaturation.

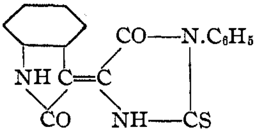
(B) **Ketones.**—Aliphatic and open-chain aromatic ketones and diketones[10] are apparently inactive.

The importance of cyclization is shown in the activity, in particular, of acenaphthenequinone,[11] phenanthraquinone,[12] and isatin[13] (including the α-anil, chloride and ethers) towards certain of the compounds possessing the configuration X—CH_2—CO—.

The object of the present investigation, of which this is the first contribution, is (a) to obtain further information concerning the activity of cyclic ketones (including quinones) towards the grouping, —CO—CH_2—NH—, and (b) to use these condensation products for synthetic purposes. To this end, the writers have been able to effect the condensation of isatin with hydantoin, (I); 3-phenyl-2-thiohydantoin, (II); and 3-phenylhydantoin, (III); and isatin-α-chloride with hydantoin, (IV); and 3-phenyl-2-thiohydantoin, (V). These substances are deeply colored and possess configurations structurally similar to indigo, or indirubin, depending on whether the hydantoin nucleus is linked to the alpha or beta position of isatin. The alpha condensates are somewhat darker in color than the beta isomers. Both types, however, are brown or red and not blue.



I



II

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[5] Behrend and Niemeyer, *Ann.*, **365**, 38 (1909).

[6] Erlenmeyer and Kunlin, *Ann.*, **316**, 151 (1901).

[7] Butscher, *Monatsh.*, **32**, 9 (1911).

[8] Ger. pat. 239,916, **1910.**

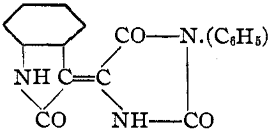
[9] Johnson and Wrenshall, THIS JOURNAL, **37**, 416 (1915).

[10] Truttwin, "Küpenfarbstoffe," Julius Springer (Berlin), **1920**, p. 198.

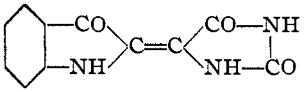
[11] Bezdzik and Friedlaender, *Monatsh.*, **29**, 385 (1905). Ger. pats. 210,905, **1907**; 235,811, **1910**; 258,099, **1908.**

[12] Ref. 7, p. 15. Ref. 10, p. 188.

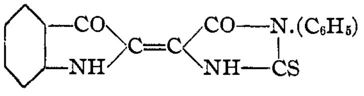
[13] Andreasch, *Monatsh.*, **38**, 121 (1917). Felix and Friedlaender, *Monatsh.*, **31**, 55 (1910), etc.



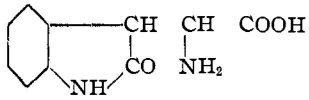
III



IV



V



VI

I and IV offer interesting synthetic possibilities when utilized in the sense of the hydantoin method for the preparation of amino acids. Thus, the reduction and subsequent hydrolysis of I should theoretically lead to the formation of oxindole amino-acetic acid, VI. This phase of the problem is now under active investigation, and is being extended to include brominated and iodated isatin derivatives.

The activating influence of phenyl upon carbonyl is interestingly shown in the comparison of parabanic acid and isatin. The writers were unable to condense the former with hydantoin under the usual conditions. Any explanation of its inactivity should also take into consideration the amidic character of both carbonyls.

Experimental Part

Hydantoin-$[\Delta^{5,3'}]$-oxindole (I).—A mixture of 7.4 g. of isatin, 5 g. of hydantoin, 10 g. of fused sodium acetate and 50 cc. of glacial acetic acid (to which had been added about 2 g. of acetic anhydride) was digested in an oil-bath at 150° for three hours. The solids dissolved completely, and in a short time the reddish-brown condensation product precipitated. The mixture was poured into 500 cc. of water and the indigoid thoroughly triturated. The mixture was then filtered and washed successively with water and alcohol and dried at 100°. It is slightly soluble in boiling glacial acetic acid and nitrobenzene, but insoluble in water and all the common organic solvents. It dissolves in concd. sulfuric acid giving a characteristic, deep red solution.

An attempt to increase the yield by heating the materials in an oil-bath for ten hours at 160–180° was unsuccessful. When the fused sodium acetate was omitted, no condensation took place.

Hydantoin-$[\Delta^{5,2'}]$-pseudo-indoxyl (IV).—This compound was obtained by heating 6.62 g. of isatin-α-chloride,[14] 4 g. of hydantoin and 50 cc. of glacial acetic acid (containing 2 g. of acetic anhydride) in an oil-bath for 7.5 hours at 160°. The condensation product did not separate, even when the solution was cooled; and when it was poured into 400 cc. of water, the dark red, semi-crystalline indigoid was precipitated. This compound is somewhat more soluble in glacial acetic acid and nitrobenzene than the beta analog.

3-Phenyl-2-thiohydantoin-$[\Delta^{5,3'}]$-oxindole (II).—This compound was prepared by digesting 3.85 g. of 3-phenyl-2-thiohydantoin and 2.94 g. of isatin for five hours at 160° in the usual sodium acetate-acetic acid medium. Although this substance is insoluble in water and the ordinary organic solvents, it is somewhat soluble in boiling nitrobenzene.

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[14] For the preparation of this substance, see Friedländer, *Monatsh.*, **29,** 359 (1908).

3-Phenyl-2-thiohydantoin-$[\Delta^{5,2'}]$-pseudo-indoxyl (V).—A solution of 2 g. of 3-phenyl-2-thiohydantoin and 1.65 g. of isatin-α-chloride in 30 cc. of glacial acetic acid was digested for three hours at 125°. The condensation product was isolated in the usual manner. It is insoluble in water and organic solvents.

3-Phenylhydantoin-$[\Delta^{5,3'}]$-oxindole (III).—Two and nine-tenths g. of isatin was condensed with 3.52 g. of 3-phenylhydantoin by means of the sodium acetate-glacial acetic acid solution. The mixture was given a preliminary digestion of one hour upon the steam-bath, followed by two hours at 150° in an oil-bath.

This indigoid is fairly soluble in boiling nitrobenzene and slightly soluble in hot alcohol and glacial acetic acid. It may be purified by crystallization from nitrobenzene.

The properties and analyses of these new indigoids are given in Table I.

TABLE I

PROPERTIES AND ANALYSES OF THE INDIGOIDS

						Analyses			
						S		N	
Compound	Yield Wt. G.	Yield %	M. p. °C.	Color	Formulas	Calcd. %	Found %	Calcd. %	Found %
Hydantoin-$[\Delta^{5,3'}]$-oxindole...	7	60	>300	red-brown	$C_{11}H_7O_3N_3$	...	....	18.34	18.36
Hydantoin-$[\Delta^{5,2'}]$-pseudo-indoxyl.....	3.5	40	>300	choc.-brown	$C_{11}H_7O_3N_3$	...	....	18.34	18.46
3-Phenyl-2-thiohydantoin-$[\Delta^{5,3'}]$-oxindole...	5.3	80	±300	red-brown	$C_{17}H_{11}O_2N_3S$	9.98	9.97 10.07	13.08	12.61 12.75
3-Phenyl-2-thiohydantoin-$[\Delta^{5,2'}]$-pseudo-indoxyl.....	3	93	>300	dark red	$C_{17}H_{11}O_2N_3S$	9.98	9.48	13.08	12.96
3-Phenylhydantoin-$[\Delta^{5,3'}]$-oxindole.....	4.5	75	±300	yellow-red	$C_{17}H_{11}O_3N_3$	...	....	13.77	13.38

[a] Calc., C, 57.63; H, 3.08. Found: C, 57.69; H, 2.99. These hydantoin indigoids dissolve readily in caustic alkalies, giving deeply colored solutions, from which they are precipitated unchanged by acids.

Summary

1. Isatin has been condensed with hydantoin, 3-phenyl-2-thiohydantoin and 3-phenylhydantoin. The activity of a cyclic ketone towards the hydantoin nucleus has thus been demonstrated.

2. The α-isatin homologs have been prepared by condensation of the hydantoins with isatin-α-chloride. The alpha compounds are darker than the beta isomers.

3. Hydantoin-$[\Delta^{5,2'}]$-pseudo-indoxyl and hydantoin-$[\Delta^{5,3'}]$-oxindole are important because of their relation to indigo and indirubin, respec-

tively, and because of their possible utilization in the synthesis of other compounds.

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[Contribution from the Laboratory of Organic Chemistry, Tulane University]

THE CHEMISTRY OF FURFURAL. THE PREPARATION OF THE FURAN ANALOG OF BENZOFLAVIN OR DIMETHYL-DIAMINO-FURYL-ACRIDINE HYDROCHLORIDE[1,2]

By S. A. Mahood and C. R. Harris

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Many colored substances have been prepared by the condensation of furfural with aromatic amines[3] but the compounds obtained either are not dyes or give colors which, on the fabric, are fugitive. Condensation has been brought about in three ways. (1) The aldehyde and the unprotected amino groups react to give compounds of the type of Ehrhardt's difuraltolidine. (2) The aldehyde and amine in the presence of free mineral acid give compounds in which the rupture of the furan ring has taken place. The reaction, according to Zincke and Mühlhausen, gives compounds of the general formula $C_6H_5.NH.CH:CH.CH:C(OH)CH:N.C_6H_5.HCl$, which are unstable and readily decompose to give aryl-oxy-pyridonium salts. (3) The aldehyde and the amine, with the basic groups protected, condense to give derivatives of diphenyl-furyl-methane.

Fischer,[4] in connection with his work on malachite green, thought he had prepared the furan analog of that dye by condensing furfural with dimethylaniline. He described it as being lighter in color than malachite green and very unstable toward light. Recently Renshaw and Naylor[5] have repeated Fischer's work and found that the analog is not only darker than malachite green but is also indistinguishable from it in fastness and stability according to standard tests. At the same time they prepared trihydroxyphenyl-furyl ketone, the furan analog of Alizarin Yellow A, and found it to be a stable dye. A. and E. Lederer[6] have patented certain

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[1] Read before the Division of Organic Chemistry at the Milwaukee Meeting of the American Chemical Society, Sept. 10–14, 1923.

[2] Abstract of a thesis presented by C. R. Harris to the Faculty of Graduate Studies of Tulane University in partial fulfilment of the requirements for the Degree of Master of Science.

[3] Stenhouse, *Ann.*, **156**, 199 (1870). H. Schiff, *Ann.*, **201**, 355 (1880); **239**, 349 (1887). De Chalmot, *Ann.*, **271**, 11 (1892). Ehrhardt, *Ber.*, **30**, 2012 (1897). Knoevenagel, *Ber.*, **31**, 2585 (1898). Zincke and Mühlhausen, *Ber.*, **38**, 3825 (1905). Dieckmann and Beck, *Ber.*, **38**, 4122 (1905). König, *J. prakt. Chem.*, [2] **72**, 555 (1905); **88**, 193 (1913). O. Fischer, Balling and Aldinger, *ibid.*, **100**, 86 (1919).

[4] Fischer, *Ber.*, **10**, 1626 (1877).

[5] Renshaw and Naylor, This Journal, **44**, 862 (1922).

[6] A. and E. Lederer, Ger. pat. 264,915, March 15, 1915; Aust. pat. 72,235, Aug. 10, 1916.