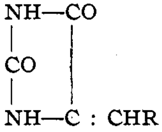
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

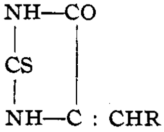
RESEARCHES ON HYDANTOINS. XXVIII. THE SYNTHESIS OF 1,3,4-TRISUBSTITUTED HYDANTOINS FROM DIETHYL ANILINOMALONATE.

BY TREAT B. JOHNSON AND NORMAN A. SHEPARD.

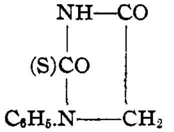
Received May 25, 1914.

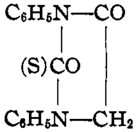
Hydantoin and 2-thiohydantoin interact smoothly with aromatic aldehydes[1] when heated together in acetic acid solution and in the presence of anhydrous sodium acetate, forming characteristic condensation products as represented by formulas (I) and (II), respectively:


(I)


(II)

The reactions are generally very smooth and have been applied successfully in this laboratory with a great variety of aldehydes. The only types of hydantoins which have been recorded as not undergoing condensations in the above manner, are the 3-monosubstituted and 1,3-disubstituted hydantoins. Wheeler and Hoffmann[2] observed, for example, that neither 3-phenyl- nor 1,3-diphenylhydantoins (III and IV)


(III)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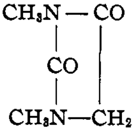
condense with anisic aldehyde in the presence of sodium acetate and acetic anhydride. On the other hand, the corresponding 2-thiohydantoins were later observed to condense smoothly with aldehydes, giving good yields of condensation products.[3] It is also of especial interest to note here, at this time, that Biltz[4] has recorded an observation that 1,3-dimethylhydantoin (V) does not condense with benzaldehyde. Whether this abnormal behavior is to be explained by the fact that such hydan-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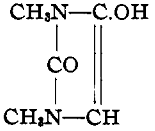
(VI)

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[1] The behavior of aliphatic aldehydes towards hydantoins is now being investigated in this laboratory (T. B. J.).

[2] *Am. Chem. J.*, 45, 368 (1911).

[3] Wheeler and Brautlecht, *Am. Chem. J.*, 45, 446 (1911).

[4] *Ber.*. 45, 1673 (1911).

toins have not a normal constitution (V), but are to be expressed by their pseudo or enol form (VI), must be decided by further investigation.

The study of several of these abnormal cases is now being continued in this laboratory. During the progress of this work, important and unexpected experimental data were obtained,[1] which has made it necessary to develop a new method of preparing trisubstituted hydantoins of the types represented by 1,3-diphenyl-4-benzylhydantoin and its corresponding sulfur analog (Formulas XII and XIV). In other words, it was necessary to have available a practical method of synthesis which does not involve the condensation of an aldehyde with a hydantoin and, furthermore, be applicable for the preparation of any alkylhydantoin desirable, with substituents in the 1,3 and 4 positions of the ring. A description of a method of synthesis, which meets all these requirements, and of its application for the preparation of the hydantoins (XII) and (XIV) is now recorded in this paper.

That diethyl anilinomalonate reacts at ordinary temperature, with alcoholic sodium ethylate, giving a sodium salt, was first observed by Curtiss.[2] No data indicating that he investigated the chemical activity of this substance are recorded, however, in his paper. Later Conrad and Reinbach,[3] who were working with dimethyl anilinomalonate, made the interesting observation that the sodium salt of this ester interacts smoothly with alkyl halides, forming the corresponding substituted anilino malonates. They prepared, in this manner, the following amino esters: dimethyl methylanilinomalonate, $C_6H_5NH(CH_3)C(COOCH_3)_2$, dimethyl benzylanilinomalonate, $C_6H_5NH(C_6H_5CH_2)C(COOCH_3)_2$, dimethyl *o*-nitrobenzylanilinomalonate, $C_6H_5NH(NO_2.C_6H_4CH_2)C(COOCH_3)_2$, and trimethyl anilinoethantricarboxylate, $C_6H_5NH.(CH_2COOCH_3)C(COOCH_3)_2$. Recently, Johnson and Shepard[4] investigated the action of *p*-nitrobenzyl chloride on the sodium salt of diethyl anilinomalonate and obtained the corresponding ester, $C_6H_5NH(NO_2C_6H_4CH_2)C.(COOC_2H_5)_2$. As a by-product of this reaction, they also succeeded in isolating a crystalline substance to which they provisionally assigned the constitution of α-nitrobenzylindoxyl.

The starting point of this investigation was the diethyl ester of benzylanilinomalonate (VIII). This was obtained easily by the action of benzylchloride on the sodium salt of diethylanilinomalonate. The reaction was very smooth, and, to our surprise, we did not observe the formation of α-benzylindoxyl (X). This ester (VIII) was converted into the corresponding acid (XI) by saponification, and the latter transformed into α-anilino-β-phenylpropionic acid (XIII) by heating above its melting

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[1] The results of this investigation, which is being conducted by Mr. Sidney Hadley, will be discussed in a future paper (T. B. J.).

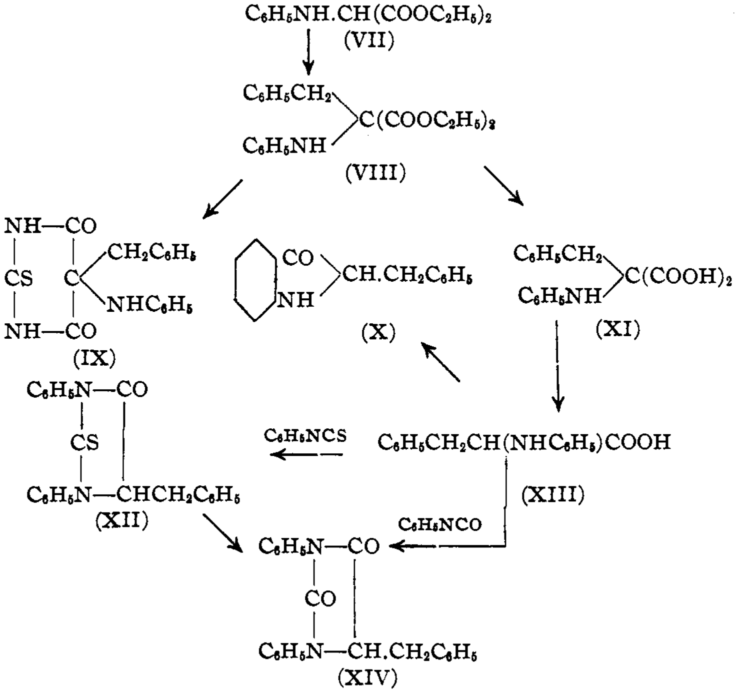
[2] *Am. Chem. J.*, 19, 694 (1885).

[3] *Ber.*, 35, 511 (1903).

[4] THIS JOURNAL, 35, 994 (1913).

point. We found, however, that this change is best effected by boiling an alcoholic solution of the malonic acid, when an almost quantitative yield of the monobasic acid (XIII) is obtained. This observation is of special interest because of the low temperature at which the dissociation of the malonic acid is effected, namely, nearly 100° lower than that temperature at which the acid is decomposed by direct heating.

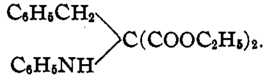
The acid (XIII) interacts with both phenylisothiocyanate and phenylisocyanate, when heated with it at 130–140°, giving hydantoin compounds. In the first case 1,3-diphenyl-4-benzyl-2-thiohydantoin (XII) is formed in good yield. Phenylisocyanate, however, reacts far less smoothly with the anilino acid, forming 1,3-diphenyl-4-benzylhydantoin (XIV). The latter hydantoin is also formed by desulfurization of the thiohydantoin (XII). This is easily accomplished by heating the sulfur hydantoin under pressure with a strong aqueous solution of chloroacetic acid. As a by-product of the above reactions with phenylisothiocyanate and phenylcyanate, we obtained a crystalline substance which gave analytical values agreeing for α-benzylindoxyl (X). 1,3-Diphenyl-4-benzyl-2-thiohydantoin melts at 129–130°. The corresponding oxygen derivative was, however, always obtained as an oil which solidified only after long standing. These various changes are represented by the following formulas:

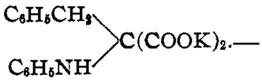


This new method of synthesis will be applied for the preparation of new types of hydantoins which have hitherto received no attention.

Diethyl anilinomalonate, diethylphthalimidomalonate,[1] and diethylaminomalonate,[2] all condense with thiourea, in the presence of sodium ethylate, giving thiouranils. Benzylanilinomalonate (VIII) interacts in an analogous manner, forming 5,5-benzylanilino-2-thiobarbituric acid (IX).

Experimental Part.

Diethylbenzylanilinomalonate,  $\left.\begin{matrix}C_6H_5CH_2\\C_6H_5NH\end{matrix}\right\rangle C(COOC_2H_5)_2$.—This ester was prepared by the action of benzylchloride on the sodium salt of diethyl anilinomalonate. Three and six-tenths grams of sodium were dissolved in 200 cc. of absolute alcohol and 40 grams of the diethyl ester added to the solution. On warming gently, the ester dissolved, and finally its sodium salt began to deposit. Twenty and four-tenths grams of freshly distilled benzylchloride were then added and the mixture heated on the steam bath. There was an immediate reaction with separation of sodium chloride and within a few minutes the reaction was complete. The alcohol was then removed by distillation under diminished pressure, when the aniline ester was obtained as a heavy yellow oil. This was washed with water to remove sodium chloride, extracted with ether and dried over potassium carbonate. We obtained 50 g. of the crude, dry ester, corresponding to a yield of 93% of the theoretical. It was found that this ester can be distilled under diminished pressure, but not without considerable decomposition. It boiled at 257–260° at 50 mm. For our investigation, however, it was used without further purification.

Potassium Salt of Benzylanilinomalonic Acid,  $\left.\begin{matrix}C_6H_5CH_2\\C_6H_5NH\end{matrix}\right\rangle C(COOK)_2$.—Fifty grams of the crude diethyl ester (above) were saponified by heating with 24.6 g. of potassium hydroxide in 56 cc. of 50% alcohol. The potassium salt soon began to separate. After heating for 2 hrs. the solution was cooled to 0° and the salt separated by filtration. It was purified by crystallization from 50% alcohol and deposited in beautiful, colorless, hexagonal plates. When heated at 295–300° for a long time it finally melted to a clear yellow oil. The yield of purified salt was 28 g.

Calc. for $C_{16}H_{13}O_4NK_2$: N, 3.88; found: N, 3.84, 4.1.

From the alcohol filtrates left after purification of this salt, we isolated 4.5 g. of α-anilino-β-phenylpropionic acid (see below). This corresponds to 6.7 g. of the dipotassium salt of benzylanilinomalonate.

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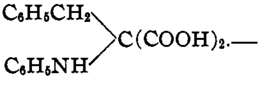
[1] Johnson and Shepard, *Loc. cit.*

[2] Johnson and Nicolet, THIS JOURNAL, 36 (1914).

Benzylanilinomalonic Acid,  $\begin{matrix}C_6H_5CH_2\\C_6H_5NH\end{matrix}\!\!>\!C(COOH)_2$.—A quantitative yield of this acid was obtained by treatment of the above potassium salt in aqueous solution with hydrochloric acid. All attempts to purify the acid by crystallization from alcohol were unsuccessful, as carbon dioxide was evolved immediately on warming the solutions. It was purified for analysis by precipitation with hydrochloric acid from an ice-cold solution of its potassium salt. Under these conditions it separated in clusters of radiating needles, which melted at 170–173° to a clear oil. Carbon dioxide was evolved when the acid was heated to 190–200°.

Calc. for $C_{16}H_{15}O_4N$: N, 4.91; found: N, 4.87, 5.07.

Disilver Salt.—This was obtained by dissolving the potassium salt in water and then adding the required amount of silver nitrate. It separated as a colorless, amorphous precipitate, which was unstable on heating. Analysis of the salt after drying in a desiccator over concentrated sulfuric acid:

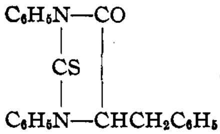
Calc. for $C_{16}H_{13}O_4NAg_2$: N, 2.8; found: N, 2.78.

α-Anilino-β-phenylpropionic Acid, $C_6H_5CH_2CH(NHC_6H_5)COOH$.—Benzylanilinomalonic acid readily loses carbon dioxide when heated above its melting point and is converted into this amino acid. Much decomposition, however, takes place by this treatment and the yield is not good. It is best prepared by heating an alcoholic solution (absolute or dilute) of the malonic acid at the boiling temperature for a few minutes. On cooling, the propionic acid separates in glistening plates showing distinct, rhombic forms. This compound begins to yield at 165°, when heated in a capillary tube, and then melts at 170–3° to a clear oil without any apparent decomposition. It is easily soluble in alcohol, moderately soluble in benzene, and cold ether, and difficultly soluble in hot water. It is best purified by recrystallization from 50% alcohol.

Calc. for $C_{15}H_{15}O_2N$: N, 5.8; found: N, 5.88, 5.99, 6.06.

Ethyl Ester, $C_{17}H_{19}O_2N$.—This is easily obtained, in the usual manner, by esterification of the acid with ethyl alcohol in the presence of sulfuric acid. After removing the excess of alcohol, by heating under diminished pressure, the ester was extracted with ether, washed with water, and finally dried over anhydrous sodium sulfate. It was purified by distillation under diminished pressure and boiled at 206–9° at 12 mm. A second sample boiled at 218–221° at 19 mm. pressure. Under these conditions the ester was obtained as a thick, yellow oil, which solidified on standing. It crystallized from alcohol in stout, hexagonal prisms or blocks which melted at 48–49° to a clear oil without decomposition. The weight of purified material was 5.0 g. or 68% of a theoretical yield.

Calc. for $C_{17}H_{19}O_2N$: N, 5.20; found: N, 5.18, 5.15.

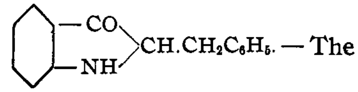
1,3-Diphenyl-2-thio-4-benzylhydantoin, 

$$\begin{array}{ll}C_6H_5N & -CO\\ \quad | & \quad | \\ \quad CS & \quad | \\ \quad | & \quad | \\ C_6H_5N & -CHCH_2C_6H_5\end{array}$$

.—Three and four-tenths grams of α-anilino-β-phenylpropionic acid and 1.9 g. of phenyl mustard oil were heated together at 130–135°. Water was evolved immediately, and a small amount of the unchanged propionic acid sublimed during the operation. After heating for 5 hrs. we obtained a brown oil, which was diluted with alcohol. A crystalline substance separated at once. This was separated and then triturated with cold benzene, when the above hydantoin dissolved, immediately leaving behind an insoluble crystalline product (see below).

The benzene solution was evaporated, whereupon we obtained a yellow gum which immediately solidified after trituration with 95% alcohol. This was purified by crystallization from alcohol and separated in clusters of needle-like prisms which melted at 129–130° to a clear oil without decomposition. The hydantoin gave a strong test for sulfur. The compound is very soluble in cold benzene and ether; easily soluble in glacial acetic acid, and very difficultly soluble in hot water. It is insoluble in dilute sodium hydroxide solution even on warming. The yield of purified material was 56% of the theoretical.

Calc. for $C_{22}H_{18}ON_2S$: N, 7.82; found: N, 7.96, 7.94.

α-Benzylindoxyl,  .—The substance obtained in the preceding experiment, which was insoluble in cold benzene, was purified by crystallization from glacial acetic acid. It separated in well-defined, prismatic crystals (cubical) which melted at 271–272° to a clear oil. They did not contain sulfur. The compound was difficultly soluble in water and very soluble in alcohol and acetic acid. The yield was very small.

Calc. for $C_{15}H_{13}ON$: N, 6.28; found: N, 6.21.

Several attempts were made to obtain this compound in larger quantities. The corresponding p-nitrobenzyl derivative[1] was obtained as a secondary product in the preparation of diethyl nitrobenzylanilinomalonate, and it seemed probable that this corresponding benzyl compound would be formed under similar conditions. A careful examination, however, of the secondary products formed in the reaction between benzyl chloride and the sodium salt of diethyl anilinomalonate failed to reveal a trace of the indoxyl compound.

Benzylanilinomalonic acid was also heated with phenylisothiocyanate, but, here again, the yield of indoxyl was not increased. This malonic

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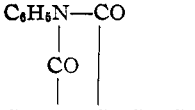
[1] Johnson and Shepard, *Loc. cit.*

acid was also heated alone at its melting point, but no formation of the indoxyl compound was observed. We finally heated α-anilino-β-phenylpropionic acid with potassium hydroxide at 200°, but the result was negative, nothing but benzoic acid being identified.

1,3-Diphenyl-4-benzylhydantoin,



.—This hydantoin is formed by the action of phenylisocyanate on α-anilino-β-phenylpropionic acid. The reaction, however, is not smooth and the yield of hydantoin is poor. One and three-tenths grams of the propionic acid were heated with 0.8 g. of the isocyanate for 3 hrs. at 140–150°, when a brown colored product was obtained. On triturating with alcohol, the latter completely dissolved with the exception of a very small amount of crystalline material, which melted at 270–272°. This was α-benzylindoxyl. The alcohol filtrate was concentrated to remove the alcohol, when an oil was obtained which dissolved in ether. A small amount of diphenylurea was obtained by this treatment. After drying the ether and then allowing to evaporate the diphenylhydantoin was obtained as an oil which finally solidified after long standing. This hydantoin is extremely soluble in the common organic solvents and was not obtained in a crystalline condition. The crude dry product melted from 58 to 62°

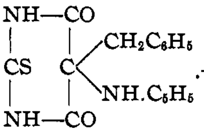
Calc. for $C_{22}H_{18}O_2N$: N, 8.1; found (Kjeldahl): N, 7.75.

This same hydantoin is also formed by heating phenylisocyanate with the ethyl ester of α-anilino-β-phenylpropionic acid.

Formation of 1,3-Diphenyl-4-benzylhydantoin by Desulfurization of 1,3-Diphenyl-2-thio-4-benzylhydantoin.—Three grams of the thiohydantoin were heated with 8.0 g. of chloroacetic acid and 15 cc. of water for 6 hours at 150°. The desulfurized product was obtained as an oil. This was finally digested with hydrochloric acid to destroy any addition product formed with the halogen acid and then dissolved in ether and dried over calcium chloride. After evaporating the ether the hydantoin was then dried over concentrated sulfuric acid and finally by heating at 105–110°.

Calc. for $C_{22}H_{18}O_2N_2$: N, 8.1; found: N, 7.72.

2-Thio-5-benzyl-7-phenyluramil,



.—This uramil was obtained in the form of its sodium salt by digesting thiourea in alcoholic solution with sodium ethylate (2 molecular proportions) and diethyl benzylanilinomalonate. After heating on the steam bath for 9 hrs. the yellow sodium salt, which had deposited, was separated by filtration and dissolved in water. After washing with ether to remove a trace of oil, the uramil was precipitated by addition of hydrochloric acid. It separated as an oil, which finally solidified on standing. The yield was 2.1 g. or 35% of theory. It was purified by crystallization from alcohol and separated in stout, prismatic blocks. They melted at 219–220° to a clear oil, which soon began to decompose with effervescence. This pyrimidine is very soluble in glacial acetic acid, moderately soluble in hot benzene and cold ether, and very difficultly soluble in hot water. The condensation was repeated with four molecular proportions of sodium, but the yield of pyrimidine was not increased. A portion of the malonic ester undergoes decomposition during the reaction and α-anilino-β-phenylpropionic acid is fomed.

Calc. for $C_{17}H_{15}O_2N_3S$: N, 12.92; found: N, 12.75, 12.69, 13.03.

NEW HAVEN, CONN.
May 20, 1914.

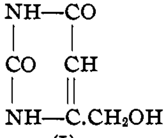
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES: LXXI. SYNTHESIS OF THE PYRIMIDINE NUCLEOSIDE, 4-HYDROXYMETHYLURACIL.

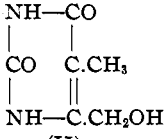
BY TREAT B. JOHNSON AND LEWIS H. CHERNOFF.

Received June 6, 1914.

This paper is our third contribution to the chemistry of pyrimidine nucleosides.[1] It includes a description of the synthesis and properties of the simple nucleoside of uracil, namely, *2,6-dioxy-4-hydroxymethylpyrimidine* represented by Formula (I).



(I)



(II)

The method of synthesis, which has been applied successfully for the preparation of this interesting pyrimidine, is perfectly analogous to that employed for the preparation of the corresponding simple nucleoside of thymine, namely, 2,6-dioxy-4-hydroxymethyl-5-methylpyrimidine[2] represented by Formula (II). The starting point, in this case, was the ethyl ester of ethoxyacetic acid (III), which was prepared in quantity by interaction of sodium ethylate with ethyl chloroacetate, and also from the nitrile $C_2H_5O.CH_2CN$[3] by direct esterification with ethyl alcohol in the presence of hydrochloric acid (imidoester method). The ester undergoes condensation with ethyl bromoacetate, in the presence of amalgamated

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[1] Johnson and Chernoff, *J. Biol. Chem.*, **14**, 307; THIS JOURNAL, **35**, 585 (1913).

[2] Johnson and Chernoff, *Loc cit.*

[3] Sommelet, *Compt. rend.*, **143**, 827.