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Azolone Studies

I. On the Reaction between Phenylglyoxal and Urea or Substituted Ureas in Alkaline Solution

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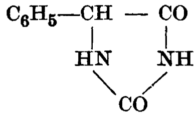
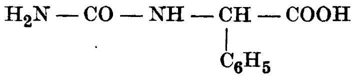
Some years ago Fisher, Ekeley and Ronzio[1] published a paper in which they reported on the reaction between phenylglyoxal and urea or substituted ureas in alkaline solution. Their experiments have been repeated in this laboratory and the structures of the reaction products re-examined and changed so as to be more in accord with the experimental findings.

The condensation between phenylglyoxal and urea "in cold basic solution"* was claimed[1] to give an 85 % yield of 5-phenylhydantoin (I), a compound which was first described in the literature by Pinner[2].



I.



$H_2N—CO—NH—CH(C_6H_5)—COOH$

II.

In our hands, however, the condensation, which was performed under identical conditions, gave consistently lower yields (30-40 %) of (I). In addition there was isolated an 8-10 % yield of α-phenylhydantoic acid (II), identified by comparison with an authentic specimen prepared according to Pinner (*l. c.*). The reaction in question merely constitutes an extension of the classical Biltz synthesis[3, 12] of 5,5-diphenylhydantoin from benzil and urea.

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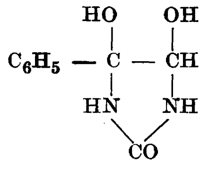
* Quoted from ref. 1. From the experimental section, however, it appears that the reaction was performed by heating the solution for three minutes at a temperature just below boiling.

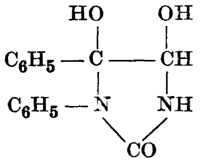
When the reaction was carried out by refluxing the reactants in alkaline solution, Fisher *et al.* (*l. c.*) obtained a low yield of a compound, $C_9H_{10}N_2O_3$, to which they ascribed the structure (III).



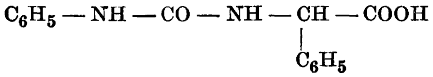
III.

This formula has now proved to be incorrect, the condensation product being in fact α-phenylhydantoic acid (II), presumably formed in a secondary reaction by ring-opening of (I). In keeping with this view is the readiness with which it recyclized to (I).

For the reaction product of phenylglyoxal and phenylurea in alkali the American authors[1] put forward the expression (IV).



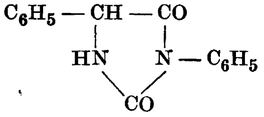
IV.



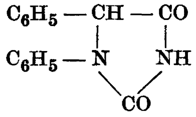
$C_6H_5-NH-CO-NH-\underset{C_6H_5}{\underset{|}{CH}}-COOH$

V.

This structure also has proved untenable. The reaction product gave analytical figures corresponding with the formula $C_{15}H_{14}N_2O_3 + \frac{1}{2}H_2O$. The water of crystallization was given off only after heating at 100° *in vacuo* over phosphorus pentoxide for 2 hours. The product was freely soluble in aqueous sodium bicarbonate and could be titrated as a mono-carboxylic acid. It was remarkably stable towards alkali whereas acidic reagents readily transformed it into a new compound (VI), $C_{15}H_{12}N_2O_2$, differing from (V) by the elements of water, and having all the characteristics of a hydantoin.



VI.

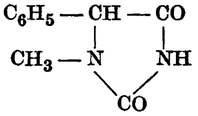


VII.

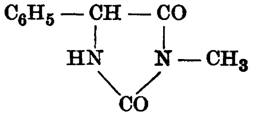
The ring-closed compound was formulated as 1,5-diphenylhydantoin (VII) by Fisher *et al.*[1] though this is obviously inconsistent with its insolubility in aqueous alkali. In the literature the authentic 1,5-diphenylhydantoin is described by Aspelund[4], the two compounds being distinctly different with regard to melting point and chemical properties *. A *levo*-rotatory stereoisomeride of 3,5-diphenylhydantoin (VI) has been reported previously by Ehrlich[5], whereas the corresponding racemic substance was a hitherto unknown compound.

The structure (V) was confirmed in this laboratory by an independent synthesis from DL-C-phenylglycine and phenyl isocyanate, yielding the hydantoic acid with m.p. 168°, thereby demonstrating the statement of Kossel[6], that the compound melts at 154°, to be erroneous. On treating the compound with ethanolic hydrogen chloride, water was readily split off and racemic 3,5-diphenylhydantoin (VI) resulted which was proved identical with the $C_{15}H_{12}N_2O_2$ compound mentioned above.

Analogously, Fisher *et al.*[1] pictured the condensation product (m. p. 174°) of phenylglyoxal and methylurea as 1-methyl-5-phenylhydantoin (VIII).



VIII.



IX.

On repeating the reaction in this laboratory a 28 % yield of a substance, $C_{10}H_{10}O_2N_2$, melting at 163°, was obtained. Gabriel[7] prepared the authentic 1-methyl-5-phenylhydantoin many years ago by a procedure which left no doubt as to its correct structure, and reported the melting point to be 177°, corroborated recently by Long, Miller and Troutman[8]. The isomeric 3-methyl-5-phenylhydantoin (IX) (m. p. 161°-162°) has been described by Pinner[2]. The identity of the C_{10}-compound with (IX) was established by comparison with a sample prepared by methylation of 5-phenylhydantoin with methyl sulphate. (IX) was readily soluble in dilute alkali, a feature generally excluding substitution in the 3-position of the hydantoin ring. On standing, however, the alkaline solution soon deposited a high-melting crystalline compound (X), formed by oxidation of (IX), and this proved identical with dimethyldiphenylhydantil previously prepared by Gabriel[7], using a different procedure. The true nature of this behaviour in alkali may have been overlooked

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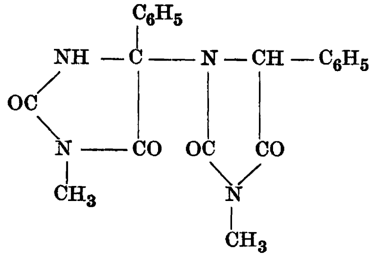
* A sample of 1,5-diphenylhydantoin for comparison was kindly supplied by Professor Aspelund.

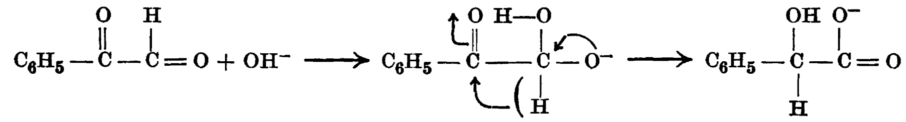
by Fisher *et al.*[1]* and may have influenced these authors in their choice of structure (VIII), whereas no satisfactory explanation can be given for the discrepancy in melting points between their and our product.



X.

DISCUSSION

Some comments may be made regarding the mechanism of the reactions in question. It is well known that phenylglyoxal rearranges in alkali to mandelic acid; this reaction has been studied *inter alia* by Alexander[9] who proved it to be of the second order. Doering *et al.*[10] presented evidence that the reaction proceeds without interruption of the linkage between the phenyl- and the keto-group, and suggested the mechanism



which involves the transfer of a hydride ion.

In the course of the present study it was shown that the condensation of phenylglyoxal with ureas precedes the rearrangement, because mandelic acid and phenylurea do not interact under the conditions used in the condensation.

It will be remembered that phenylglyoxal with urea and methylurea yielded the hydantoins, whereas phenylurea reacted to form the hydantoic acid under similar conditions. The question therefore arises as to whether the rearrangements take place in an open or in a cyclic structure. It was proved that none of the hydantoic acids in question suffered ring-closure under the conditions used in working up the reaction mixtures. Submitted to an alkaline

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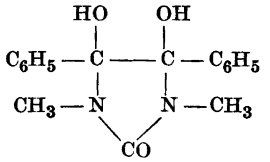
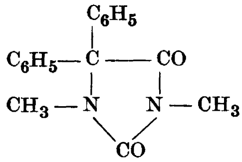
* *e. g.* The statement from ref. 1 as to the reaction product forming "a monopotassium salt which hydrolyzes readily with water".

treatment, identical with the one used in performing the reactions, 3,5-diphenylhydantoin was ring-opened to the corresponding hydantoic acid, whereas 5-phenyl- and 3-methyl-5-phenyl-hydantoin were recovered in high yields. This fact makes it appear probable, that *a*,*δ*-diphenylhydantoic acid (V) is a secondary reaction product and that the rearrangement consequently is preceded by cyclization. Supporting evidence for this view may be found in the observation by Biltz[3], that 1,3-dimethyl-4,5-diphenyl-4,5-dihydroxy-2-imidazolidone (XI) could easily be transformed into 5,5-diphenyl-1,3-dimethyl-hydantoin (XII) in alkaline solution.

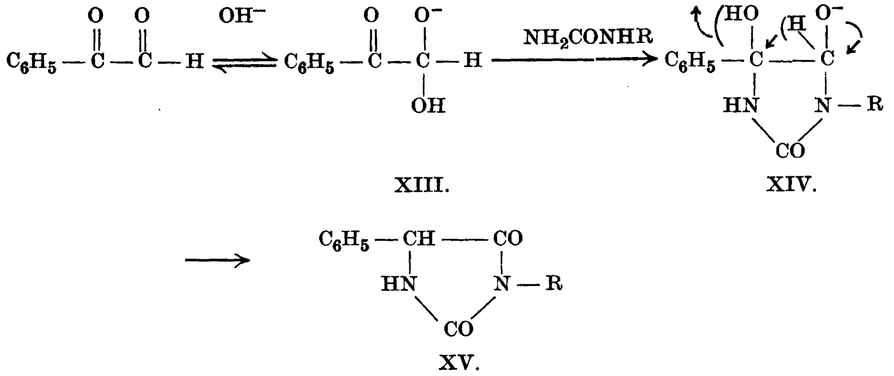


XI.



XII.

Thus, the reactions in question may be pictured as follows:



XIII.

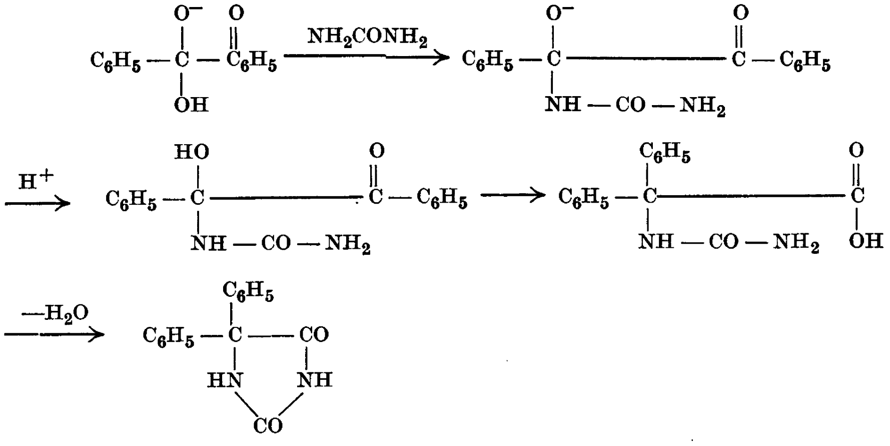
XIV.

XV.

The reversible addition of a hydroxyl-ion to (XIII) is followed by addition and dehydration giving (XIV), which in turn rearranges by displacement of a hydroxyl-ion by the migrating hydride-ion. This hydride-shift may be greatly facilitated by the negative charge on the adjacent oxygen-atom.

Although the 1,2-hydride shift is a common and generally accepted feature in intramolecular rearrangements, the displacement reaction suggested here does not appear to be generally recognized. Alexander[9], in studying the mechanism of the homogeneous Cannizzaro reaction, has suggested a somewhat similar displacement, taking place, however, over a 1,3-system, although a more recent paper[11] by the same author does not seem to support this view.

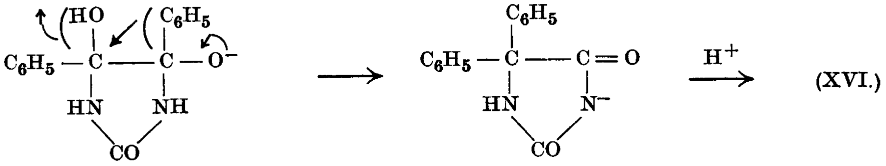
It may be worthy of note in this connection that Sikdar and Ghosh[12] recently suggested the following mechanism for the reaction between benzil and urea



XVI.

This series of steps, however, does not explicitly account for the necessity of maintaining alkaline conditions throughout the reaction, nor does the final spontaneous ring-closure appear to be a likely course of reaction.

By analogy with the suggestions presented above, this rearrangement may be pictured



involving a hydroxyl-ion displacement by the phenyl group with its bonding pair of electrons.

EXPERIMENTAL *

The reaction between phenylglyoxal and urea

Following the procedure of Fisher *et al.* (*l. c.*), a mixture of phenylglyoxal[13] (12.16 g) and urea (4.80 g) in 100 ml of water was heated to boiling for three minutes after addition of 50 % potassium hydroxide (24 ml). On cooling and acidification 4.48 g (32 %) of

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* All melting points are uncorrected. Analyses were carried out in this laboratory by Mr. A. Grossmann.

crude material separated. After recrystallization from aqueous ethanol and drying in the air, 4.40 g of 5-phenylhydantoin (I) was obtained as its monohydrate. M. p. 180°.

After two days the mother liquor had deposited 1.17 g (8 %) of α-phenylhydantoic acid (II), which after several recrystallizations from aqueous ethanol, separated in needles melting with strong effervescence at temperatures varying between 174° and 182°, depending on the rate of heating. Mixed m. p. with an authentic sample [2] was undepressed, whereas the m. p. on admixture with 5-phenylhydantoin was 160–64° (dec.).

The reaction between phenylglyoxal and phenylurea

The reaction between these compounds was conducted in accordance with the directions given [1], and a 72 % yield of crude α,δ-diphenylhydantoic acid (V) was obtained. An analytical sample was prepared by repeated crystallizations from ethanol. Colourless, silky needles, m. p. 168° (dec.).

$C_{15}H_{14}N_2O_3 + \frac{1}{2} H_2O$ (279.3)	Calc.	C 64.51	H 5.41	N 10.03
	Found	» 64.42	» 5.51	» 9.78

Neutr. equiv. 278.5

The water of crystallization was removed *in vacuo* over phosphorus pentoxide at 100° for two hours.

Calc.	H_2O	3.22 %
Found	»	3.22 »

The dried product (m. p. 168°) was analyzed for nitrogen.

Calc.	N	10.36
Found	»	10.52

α,δ-Diphenylhydantoic acid (500 mg) was dissolved in ethanol (7 ml), conc. hydrochloric acid (1 ml) added, and the solution refluxed for one hour. On cooling small needles, consisting of 3,5-diphenylhydantoin, separated in quantitative yield. Recrystallized twice from ethanol for analysis. M. p. 189°.

$C_{15}H_{12}N_2O_2$ (252.3)	Calc.	C 71.44	H 4.80	N 11.11
	Found	» 71.58	» 4.71	» 11.36

Synthesis of α,δ-diphenylhydantoic acid (V) and 3,5-diphenylhydantoin (VI)

To a well cooled and vigorously stirred solution of DL-α-aminophenylacetic acid (7.6 g) in 1 *N* sodium hydroxide (50 ml), phenyl isocyanate (5.5 ml) was dropwise added. A trace of *sym*-diphenylurea was filtered off and the filtrate carefully acidified, when a creamy separation resulted. Yield 95 %. Crystallized from aqueous ethanol as a mass of fine colourless needles containing half a molecule of water. M. p. 167–68° (dec.).

No depression of the m. p. was observed when mixed with the reaction product described above.

Calc.	*vide supra*						
Found	C	64.76	H	5.34	N	9.98	

On treating the hydantoic acid in ethanol with hydrochloric acid in the manner described above, it was transformed into 3,5-diphenylhydantoin of m. p. 189°. The identity of the two products was secured by mixed m. p.

The reaction between phenylglyoxal and methylurea

An alkaline solution of equimolar amounts of these two substances was heated to boiling for one minute, then cooled and acidified, when a brown syrup separated, which gradually became crystalline on standing. The mother liquor slowly deposited an additional crop of the same purity. Total yield 28 %. A sample was recrystallized twice from aqueous ethanol for analysis. M. p. 162—63°.

$C_{10}H_{10}O_2N_2$ (190.2)	Calc.	C	63.14	H	5.30	N	14.73
	Found	»	62.94	»	5.22	»	14.72

Synthesis of 3-methyl-5-phenyl-hydantoin (IX)

Methylation of 5-phenylhydantoin was previously carried out by Pinner [2], who used methyl iodide. Methyl sulphate has now been found to be a more convenient methylation agent. To a stirred solution of 5-phenylhydantoin (2.5 g) in 2.11 *N* sodium hydroxide (6.75 ml), methyl sulphate (1.4 ml) was added in small portions. Crystallization started within a few minutes. Yield 84 %. Separated from aqueous ethanol as a mass of fine needles. M. p. 162—63° alone or in mixture with the reaction product described above.

Diphenyldimethylhydantil (X)

3-Methyl-5-phenyl-hydantoin readily went into solution in diluted aqueous or methanolic potassium hydroxide. Within a few minutes a crystalline powder separated, slightly soluble in organic solvents. M. p. 325—30° (dec.). A sample was triturated several times with hot methanol and analyzed.

$C_{20}H_{18}O_4N_4$ (378.4)	Calc.	C	63.46	H	4.79	N	14.81
	Found	»	63.18	»	4.50	»	14.78

Phenylurea and mandelic acid

A mixture of mandelic acid (3.04 g) and phenylurea (2.72 g) in water (40 ml) containing 50 % potassium hydroxide (2 ml) was heated at the boiling temperature for 5 minutes. On cooling a 89 % yield (2.42 g) of unchanged phenylurea separated. The filtrate was acidified and extracted with ether, when a 84 % yield (2.55 g) of mandelic acid was recovered.

Stability of the hydantoins

Treating a) 3,5-diphenylhydantoin b) 3-methyl-5-phenylhydantoin and c) 5-phenylhydantoin in aqueous solutions with 50 % potassium hydroxide, under exactly the conditions used in the condensation experiments described above, [a] gave a 98 % yield of α,δ-diphenylhydantoic acid while [b] and [c] were recovered in 82 % and 89 % yields respectively.

SUMMARY

The reactions between phenylglyoxal and urea, phenylurea and methylurea have been studied, and the structures of the products previously reported in the literature revised.

Suggestions are presented as to the course and mechanism of the reactions involved.

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