

Review: The preparation of Hydantoins

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By Heinrich Biltz and Karl Slotta

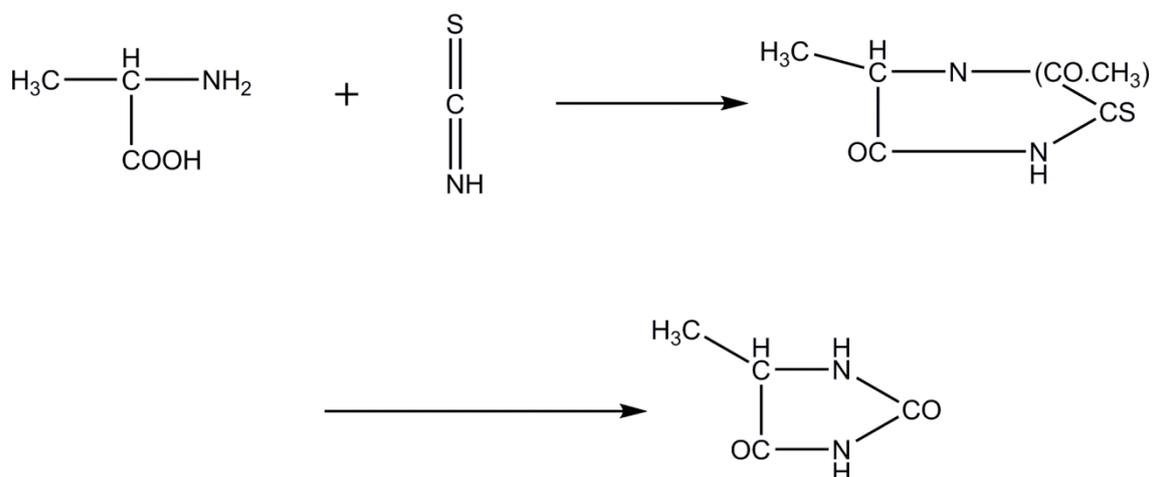
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The degradation of uric acid derivatives into hydantoins that often occur are here compared in order to identify those that give desirable products; we longed for a more thorough discussion and analysis of the problems surrounding the preparation of larger quantities of the variously substituted hydantoins. This led us into a systematic examination and characterization of the recommended hydantoin preparations.

We have repeated most of the numerous recipes that are described in the literature, and, we feel that this repetition proved valuable as the yields are often not given especially in older releases. Our experience has led to nail down a few of the more typical methods that need only be changed slightly in some cases. The following is an overview of what are in our view the more important methods. While we have searched thoroughly, we do not claim to have encompassed all of the reported hydantoin syntheses, and it is possible that we have overlooked some good examples.

Hydantoin and its homologues that are alkylated in the 5-position can be prepared from α -amino acids, either with urea and boiling in barium hydroxide solution, or by the cheaper and more convenient potassium cyanate technical preparations which are now available in admirable purity. The initially formed hydantoic acids have hydrochloric acid strongly bound to the rings.

Instead of urea or potassium cyanate the amino acids can be reacted with potassium thiocyanate in the presence of acetic anhydride to give 2-thio-hydantoins, this can be oxide of mercury or better desulphurisation with chloroacetic acid.

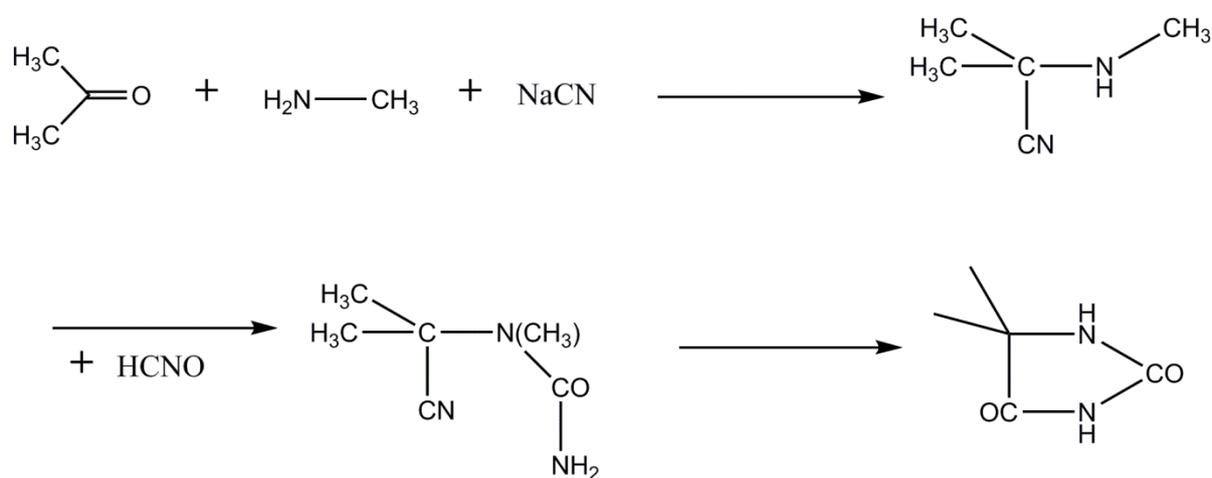


For preparative purposes the reaction with potassium cyanate is preferable.

For the preparation of hydantoin itself Harries and Weiss have used Glykokollester hydrochloride consisting of formaldehyde, ammonium chloride and sodium cyanide on methylene

aminoacetonitrile, (H₂C:N.CH₂.CN). They have reported that it is easy to prepare and carry out using potassium cyanate.

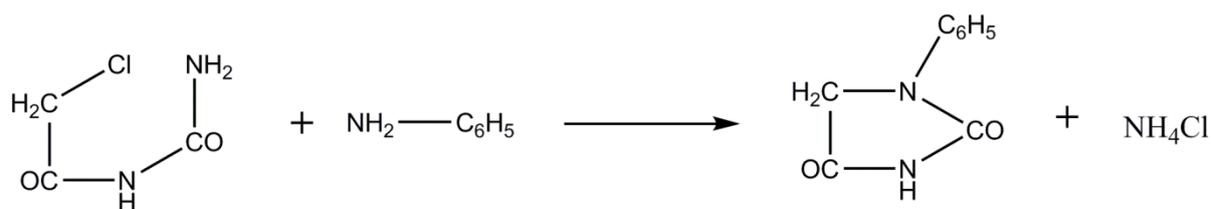
Because of our aforementioned approach towards the hydantoin itself, its substitution with 1 or 2 substituents in position 5 and hydantoin with alkyl on the nitrogen can be made in Figure 1. Especially for alkyl hydantoin, which were previously difficult to access to the point that you would sometimes have to prepare them from the reduction of suitably substituted uric acid derivatives. It is much more convenient to synthesize them treating an amino acetonitrile in the form of its hydrochloride or sulfate salt with potassium cyanide. A hydantoic nitrile intermediate is then saponified with strong hydrochloric acid and to give ring closure to the hydantoin. Using the amino-acetonitrile, any substituents that can be readily attached to a carbon or a nitrogen can be made available to the end hydantoin compound. These amino-acetonitriles can be prepared subject to certain conditions, including with cooling easily in ammonia or a primary aliphatic amine whose alkyl will attach to position 1 of the hydantoin in the form of its hydrochloric acid salts with sodium cyanide and formaldehyde, or when substituents of 5 should enter as the correspondingly higher aldehydes or ketones. These imines are converted as hydrochloride or sulfate hydrochloride with potassium cyanide, which is very smooth and transferred to the hydantoin.



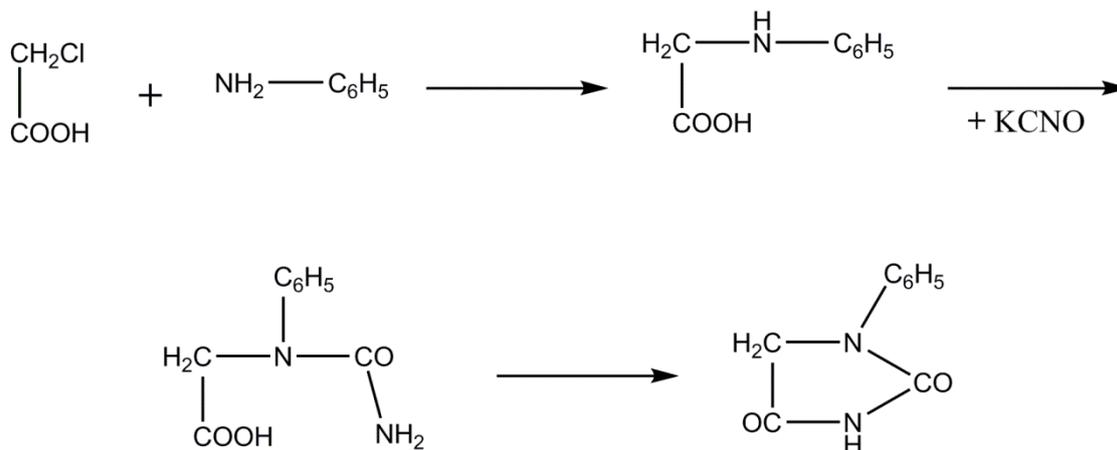
We believe the above pathway offers advantages over those executed in the past.

3-Alkyl hydantoin is easy to obtain. You go from any hydantoin which is unsubstituted in position 3 and then convert it in a customary manner with a controllable alkylating reagent such as diazomethane or dimethyl sulfate or haloalkyls and brine. Also the bottom of the extraction of 3-aryl-hydantoin recommends procedures to be implemented with amino acids or better with amino nitriles. Isocyanates may also prove occasionally useful.

1-arylhydantoin is particularly convenient to prepare. There are two ways: either one merges [α-halo-acyl]-urethanes or [α-halo-acyl]-ureas, in the simplest case chloroacetylurethane; or



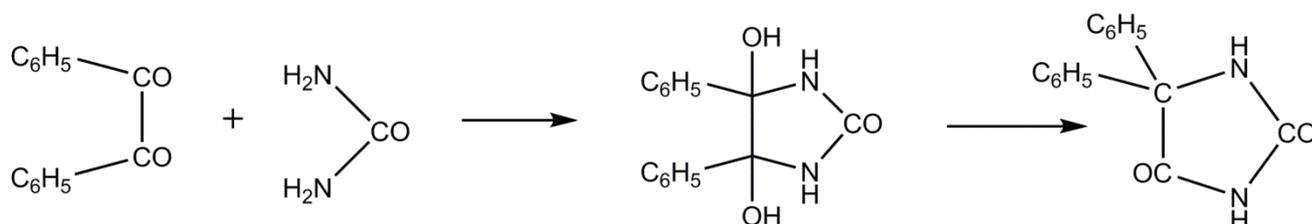
chloroacetylurea with primary aromatic amines or one merges chloroacetic acid with primary aromatic amines and sodium acetate, in the most convenient manner, α -arylamino-acetic acids produced are readily converted by reaction with urea to give the desired hydantoins.



Alkyl groups can be easily inserted in position 3 of said hydantoins in the manner indicated above.

3-phenyl-hydantoins finally, can be obtained by the action of phenyl isocyanate to alkaline aqueous solutions of α -amino acids and boiling the terminal phenylated-hydantoic acid with strong hydrochloric acid instead of the free amino acids, which may be that their more accessible hydrochlorides are taken under doubling the hydroxide level. In our experience, it is preferable to convert the nitriles of free amino acids with phenyl isocyanate, because this is carried out in non-aqueous solution, whereby unwanted side reactions of the phenyl isocyanate are avoided.

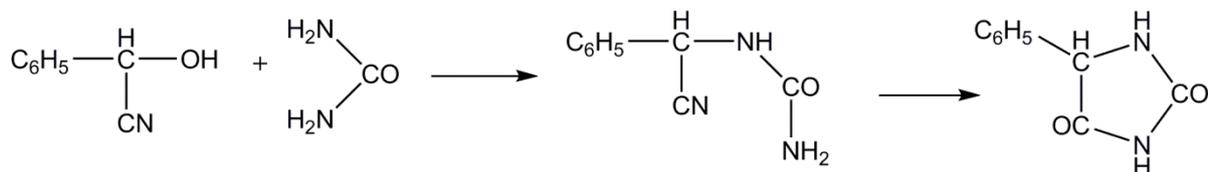
It was only noted at this point the methods that have proven useful in special cases. So, the effect of urea on α -dicarbonyl compounds, such as of urea to benzil.



It is this way that one of the related pinacol rearrangements occurs. Similarly, urea or glyoxal acting on dioxo-succinic acid with exchange of the simple hydantoin H and OH - in the latter case with elimination of carbon dioxide - is formed.

For the production of 5,5-dialkyl hydantoin the exposure of dialkyl-cyano-aminoaceticacids to hypobromite, are amide acid depleting, hydrolysis of the CN followed by ring closure. Nirvanol (5-phenyl-ethyl-hydantoin) is prepared this way.

Cyanohydrins react with urea only cleanly if they carry larger alkyl groups such as phenyl or isobutyl. The initially formed Hydantoic acid-nitrile is hydrolyzed in the usual manner and the rings closed together.



Two methyls can suffice. My own tests showed that only a little acetone cyanohydrin 5,5-dimethyl hydantoin and hydantoin that glycolic acid nitrile provides no more.

Hydantoin

Hydantoin was obtained by Baeyer in a clean synthesis from bromoacetyl-urea, although in poor yield. We presented some experiments with the easily accessible chloroacetyl-urea, but could get out of it no more than Baeyer's hydantoin.

Chloroacetyl-urea was prepared by Tomasi with 84% of the calculated yield. (decomposition point: 195 °C). Neither heating in alcoholic solution with sodium carbonate, nor heating in sodium hydroxide solution, nor dimethylaniline, pyridine or zinc dust in the presence of acids or bases, nor heating with acetic anhydride with the addition of sodium acetate lead to the targets. Nor heating with ammonia fumes at 140-150 °C, nor heating by itself.

Another series of experiments was intended to use the Errerasche synthesis for production of hydantoin itself. By the action of hypobromite to cyanoacetamide only smearing were obtained, no doubt because the two hydrogens next to CN were a bother.

Finally, an attempt was made to couple glycolic acid nitrile with urea and fuse them into a hydantoin in the presence of hydrochloric acid. We boiled at 100 °C and 140 °C, but could come to no recrystallization of compounds.

An excellent synthesis of hydantoin proved to be the path via the amino-acetic ester. To prepare its hydrochloride, the instructions of Klages and Curtius, Welde proved well founded. Formaldehyde solution (1000 g) was treated with ammonium chloride (360 g) and sodium cyanate (250-300 g) gave methyleneamino-acetonitrile (440 g) with good cooling in harmony with the data obtained from Klages, and from this about 430 g glycolester hydrochloride.

Hydantoin preparation was by starting with a solution of 40 g glycolester hydrochloride in 80 mL of water was added at room temperature with a solution of 30 g of potassium cyanate in 90 mL of water. When stirring and cooling, hydantoic ester (31.5 g) separated out from its solution in 100 mL 25% Hydrochloric acid was obtained by evaporation of 24 g of crude hydantoin. Recrystallization

gave 20 g of pure product, (quantitative yield = 28.9 g). The yield increased to 24 g of pure hydantoin when the mother liquor was evaporated from hydantoic ester and the residue with 50 mL of fuming concentrated hydrochloric acid and 5 g of crude product was thus obtained by recrystallization.

Preparation of Hydantoin via amino acetonitrile sulfate

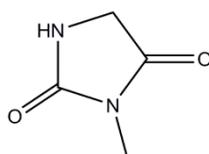
The preparation of hydantoin by Harries and Weiss has the defect of the production of glycolester hydrochloride from methyleneamino-acetonitrile and as it uses a lot of alcohol is also awkward. It is more advantageous to convert methyleneamino-acetonitrile in aminoacetonitrile hydrosulfate to implement this idea with potassium cyanate, which is added to the complete saturation of the sulfuric acid 0.5 mol of sodium carbonate, to saponify the acetonitrile-urea to fuse and arrive at hydantoin. In this way we obtain 200 g of hydantoin for almost 17 - M material consumption, while the commercial 400 - M are required.

For processing of 1 kg methyleneamino formol-acetonitrile (280-300 g) was obtained. Upon reaction with sulfuric acid and alcohol (425 g) it furnished aminoacetonitrile hydrosulfate while Klages reached a much higher yield in processing small quantities and by the addition of ether. This 425 g was gradually added to a cooled solution of 130 g of anhydrous sodium carbonate in 750 mL of water and this solution in about 45 min to a filtered solution of 250 g of technical grade potassium cyanate in 750 mL of water, avoiding exposure to bright light dropwise. The mixture was allowed to stand for 1 hour in the dark and was then concentrated in a large fractionation flask placed in a water bath not exceeding 70 °C at reduced pressure to about 600 mL. Slowly and while shaking, 600 mL of concentrated hydrochloric acid were added and the solution heated on a water bath for 4 hours. Then for dewatering the residue was evaporated under reduced pressure to dryness and extracted twice with 20 mL of dehydrated alcohol. These extracts gave ~ 245 g of crude crystalline hydantoin, which was heavily contaminated with inorganic salts. It was recrystallized from glacial acetic acid in several portions to obtain 175 g of hydantoin, MP 207-210 °C. As noted, the yield can be improved by working up the mother liquor.

On the first day one comes to the instances of the amino-acetonitrile-sulfate, the second to the hydantoin, the third it is evaporated and started to take off with alcohol, it takes depending on the effectiveness of the apparatus a few days until everything is dissolved and then recrystallized.

On the observed solubility of hydantoin: it is very readily soluble in hot water; dissolves comfortably in cold water and methanol; dissolves in ethanol when heated for 5 min; marginally soluble in chloroform, benzene and ethyl acetate; practically insoluble in diethyl ether or petroleum ether. Glacial acetic acid is recommended for recrystallization; hydantoin dissolves in about 10 parts of boiling glacial acetic acid and crystallizes on cooling to about 9/10.

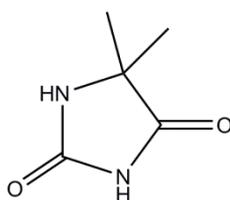
3-Methyl-hydantoin



3-methyl-hydantoin has been well prepared recently, mostly by reduction of 3-methyl-allantoin with hydrogen iodide. Since, as shown above, hydantoin can be easily synthesized, its methylation was tested. Instead of methyl iodide we used dimethyl sulfate.

Pure hydantoin (5 g) was shaken with 50 mL of 10 % NaOH solution and dimethyl sulfate (9.5 g) at room temperature until the oil layer had disappeared. The next day it was made strongly acidic with hydrochloric acid and evaporated in a 500 mL flask on a water bath under vacuum. For drying, the residue was twice fumed off with 10 mL of alcohol. The dry residue was boiled in the same flask with 100 mL of dehydrated alcohol. The filtrate was recrystallized from acetone to give beautiful, small prisms with an attached rectangular end face. Mp 182 °C; easily soluble in water and organic solvents except diethyl ether and petroleum ether.

5,5-Dimethyl-hydantoin

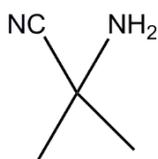


5,5-dimethyl hydantoin has not yet been studied in particular detail. It was discovered by dropwise addition of hydrochloric acid to a mixture of acetone and cyanide containing potassium cyanide (KCN). Data concerning the yield are missing. As we found, which is understandable given the peculiar and complicated synthesis, the yield is very low, just as in the corresponding preparation of 5-methyl-hydantoin from acetaldehyde, noted by Andreasch. In this way we made 0.8 g of dimethyl hydantoin from acetone (12 g), potassium cyanide (9 g) and sodium cyanide (15 g).

A satisfactory way to recover 5,5-dimethylhydantoin was found only when the reaction was carried out stepwise. α -Amino-isobutyric acid nitrile was first prepared from acetone, ammonium sulfate and sodium cyanide. Its hydrochloride salt was reacted with potassium cyanide to [α -Cyanisopropyl] urea and this was then hydrolyzed with hydrochloric acid and underwent a ring-closure to form the dimethyl-hydantoin. The intermediates are individually described in detail, followed by an easy to follow procedure to prepare 5,5-dimethyl-hydantoin.

Not recommended is to obtain 5,5-dimethyl-hydantoin by reacting acetone with urea. We reacted acetone (8 g) with urea (6 g) in a flask for 30 min at 80 °C. The molten mixture was evaporated from 30 mL of half-concentrated hydrochloric acid on a water bath. Extraction of the residue with diethyl ether produced very little 5,5-dimethyl-hydantoin; just enough for its recognition, MP 175 °C. An increase of the reaction temperature to 100 °C prevented the formation of any 5,5-dimethyl-hydantoin.

α -Amino-isobutyric-nitrile



The above mentioned nitrile can be obtained from acetone cyanohydrin and ammonia. To avoid working with free hydrogen cyanide a two-step process is adopted. First acetone is treated with ammonium sulfate to quickly and cleanly yield the amino nitrile. This is then treated with sodium cyanide. Only certain conditions have to be met. We recommend the following procedure:

In a sealable flask a solution was prepared by the addition of ammonium sulfate (73 g) to a well-cooled solution of sodium cyanide (54 g) in water (250 mL) and acetone (58 g). The mixture was warmed gently with occasional shaking, then allowed to stand for two days at RT. We do not recommend the other possible conditions of heating at 70-80 °C for 2 h as this produces a much less pure product which tends to spontaneously decompose. The precipitated sodium sulfate is extracted with 10 mL of alcohol and washed with diethyl ether. By repeated washing and filtering the remaining sodium sulfate is cleaned and cooled with ice to give a deposit. The deep red-brown oily liquid is then extracted several times with a large amount of diethyl ether (5-10 times if necessary). The ether extracts are evaporated after dehydration with sodium sulfate to leave 65 g of α -amino-isobutyric acid-nitrile as a reddish brown raw product, ie 77% of the calculated amount. Vacuum distillation at 55-60 °C and 20 mmHg gave 55 g of pure product as a pale yellowish thick liquid.

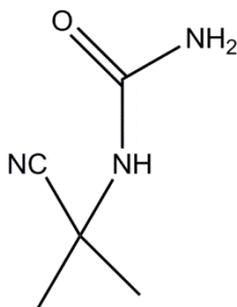
Hydrochloride salt. Amino-isobutyric acid nitrile (50 g) was placed in a 500 mL perforated top beaker and 100 g of an alcoholic hydrogen chloride solution (~ 30% HCl content) was added dropwise. The beaker was then covered with a watch-glass and cooled in ice. A thick, white crystal pulp was produced and kept until the next day in an ice bound container. It was then suction filtered and washed with cold alcohol where we obtained 45-50 g of the pure hydrochloride. Evaporation of the filtrate at low temperature and low pressure or precipitation using diethyl ether could give another 12-15 g of less pure afterproduct. The pure compound manifested as little crystalline platelets mostly rectangular in shape. Decomposition began at 175 °C, which is considerably higher than what Gulewitsch and Wasmus specified (144-146 °C).

Calculated for C ₄ H ₉ N ₂ Cl:		Found:	
N	23.2%	23.5%	23.5%

It is not recommended to produce the hydrochloride salt of this compound by passing HCl through it in an alcoholic solution as the temperature increase is hard to sufficiently suppress and leads to partial hydrolysis of the nitrile. It was concluded from the amount of deposited ammonium chloride that 2 h of this heat is enough to completely hydrolyze the nitrile. 30 g of the amino nitrile gave only 20 g of the hydrochloride compound when prepared by bubbling HCl gas through the solution.

Amino-isobutyric acid hydrochloride was prepared by Tiemann and Friedlander. 140 g of amino-isobutyric acid-nitrile was treated with 330 g of concentrated hydrochloric acid with the contents left together overnight. This was then evaporated by placing in a hot water bath. The residue obtained was extracted with 300 g of dehydrated alcohol which yielded 160 g of the hydrochloride compound (two thirds of the calculated amount). Crystals were grown from slow evaporation of water to form rectangular tablets, often with two opposing beveled-edged corners. It decomposed at 236-237 °C. N calculated: 10.0%, observed: 9.7% and 10.0%. Readily soluble in water, methanol and ethanol.

[α -cyano-isopropyl]-urea



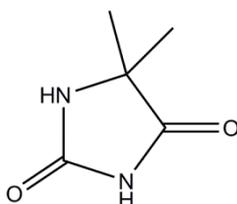
Attempts to obtain the compound from acetone cyanohydrin and urea have failed, however it was obtained readily from amino-isobutyric acid hydrochloride and potassium cyanate.

A cold solution of 20 g of amino-isobutyric acid nitrile hydrochloride in 40 mL of water was prepared and mixed with a filtered solution of 15 g of technical grade potassium cyanate (KCNO) in 45 mL water at low temperature. The mixture was then evaporated on a water bath under vacuum. The residue was dehydrated by evaporation with a 10 mL portion of alcohol followed by a further 50 mL of alcohol. The solids were absorbed in diethyl ether which was then evaporated to yield 16.5 g of product (calculated 21 g) which exists as four-sided prisms with an attached rectangular end face. Mp 157 °C without decomposition.

	Calculated for C ₅ H ₉ ON ₃ :	Found:
C	47.2%	46.9%
H	7.1%	7.4%
N	33.1%	32.7%

This compound was very readily soluble in glacial acetic acid, alcohol and water; easily soluble in methanol; less soluble in chloroform and petroleum ether; barely soluble in diethyl ether. Methanol is best for recrystallization.

5,5-Dimethyl-hydantoin



A. From amino-isobutyric acid hydrochloride.

A solution of amino-isobutyric acid hydrochloride (25 g) in water (50 mL) was added to potassium cyanate (15 g) in water (50 mL) at RT and then evaporated on a water bath. The residue was heated with 100 mL of concentrated hydrochloric acid on a water bath and suction filtered after cooling to

remove potassium chloride. Evaporation of the water gave 18 g of crude product which yielded 15 g of pure 5,5-dimethyl-hydantoin when recrystallized from alcohol.

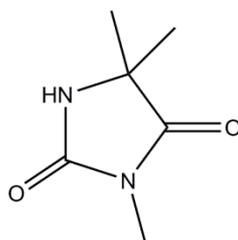
For illustration the following rule is convenient, as it combines the hydrolysis of the nitrile with the ring closure to hydantoin. A special experiment showed that cyanoisopropyl urea quantitatively underwent ring closure to form dimethyl hydantoin when boiled in conc. hydrochloric acid for 30 min.

B. From amino-isobutyric acid hydrochloride.

A cooled solution of amino-isobutyric acid hydrochloride (40 g) in water (80 mL) was mixed slowly with potassium cyanate (KCNO) (30 g) in water (120 mL). Small gas bubbles were observed. The solution was almost completely evaporated in a 500 mL distillation flask under vacuum on a water bath. The residue was heated in 150 mL of 25% hydrochloric for 30 min. Upon thorough cooling, 25 g of potassium chloride (almost free of ammonium chloride) was suction filtered and the filtrate again evaporated on a water bath under vacuum. 10 mL of fuming alcohol was twice removed in order to dry the product. From the remaining solids 15 g of ammonium chloride crystallized after concentration and left behind 31 g of 5,5-dimethyl-hydantoin (calculated 42.6 g), Mp 175 °C.

Very easily soluble in acetone, glacial acetic acid, ethyl acetate, alcohol; Less in benzene, chloroform, methanol; Even less in diethyl ether; Barely in petroleum ether. It recrystallized from alcohol as large, shiny glass prisms with hemihedral or straight ends. Evaporation from a solution in chloroform gave lovely even needles as a snowy cushion. From diethyl ether came a beautiful jumble of pointed needles. Sublimation is possible when sand is added but losses due to decomposition are unavoidable. The yield is easily improved when the reaction is done under vacuum.

3,5,5-Trimethylhydantoin



The above named trimethyl-hydantoin was first prepared by desulfurization of the corresponding thiohydantoin. We gained it readily by methylation of 5,5-dimethyl-hydantoin.

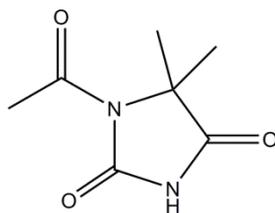
A. From diazomethane.

The reaction proceeded very vividly. From 2.3 g of crude product, 2.0 g was recrystallized from a small amount of alcohol to give six-sided prisms pointed in two major directions. MP 148 °C. Easily soluble in water and the common organic solvents except for diethyl ether and petroleum ether.

B. From dimethylsulfate.

Dimethylhydantoin (6 g) was placed in a 10% sodium hydroxide solution (50 mL) and freshly distilled dimethyl sulfate (10 g) was added and the flask shaken until the latter was consumed. The next day it was acidified with hydrochloric acid and evaporated under vacuum on a water bath. The residue

was dried of its water by boiling off two 50 mL portions of fuming alcohol. The filtrate was trimethylhydantoin. The yield by working up the mother liquor was 4 g when using an identical preparation to that above.

1-Acetyl-5,5-dimethylhydantoin

5,5-dimethyl hydantoin is subjected to acetylation and takes an acetyl at the less acidic N1 position on the compound. This was proven by methylation of the product as after acetylation a methyl can only occupy the other free place (namely N3). It was also proven by saponification of the product to 3,5,5-trimethyl-hydantoin (the compound described above). Note that we were able to introduce only one acetyl group as while it is possible to diacetylate hydantoin, an acetyl group on position 3 is labile.

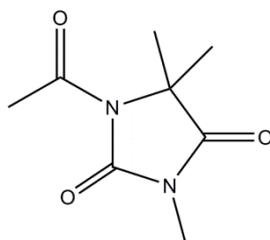
A solution of 5,5-dimethyl hydantoin (5 g) in acetic anhydride (32 g) was boiled for one hour under reflux. A crude crystal mass was gathered from the highly concentrated solution upon cooling which was then recrystallized from acetone. Yield 4 g of fine, transparent, six-sided prisms with straight or hemihedral pointed ends. Mp 192 °C.

	Calculated for $C_7H_{10}O_3N_2$:	Found:
C	49.4%	49.3%
H	5.9%	5.9%
N	16.5%	16.6%

The compound dissolved easily in water, ethanol, methanol, acetone, acetic acid, ethyl acetate; slightly in chloroform; barely in petroleum ether.

To verify the mono-acetylation, the diacetyl compound was first produced. As this loses an acetyl only upon workup and recrystallization, the crude version was crystallized from acetic anhydride and analyzed. A nitrogen determination indicated 16.9% N, which disproved the diacetyl compound which required 13.2% N.

This acetyl did not hydrolyze even when heated for 30 min. Treatment with sodium hydroxide allowed clean 5,5-dimethyl-hydantoin to be recovered.

1-Acetyl-3,5,5-dimethylhydantoin

The acetyl compound described above retained its acetyl group even when boiled in alcohol even in the presence of diazomethane, which is in agreement with Herzig's rule.

1 g of 1-acetyl-5,5-dimethyl-hydantoin was methylated with diazomethane. The crude product was recrystallized from alcohol to yield 0.8 g of fine, intergrowing, pointed needles with Mp 99-100 °C. Very easily soluble in water and most organic solvents; slightly in ether; barely in petroleum ether. It sublimated to very long, fine needles.

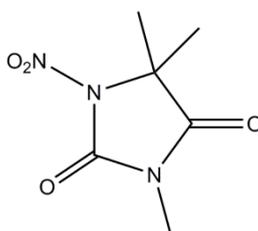
0.1364 g gave 0.2608 g CO₂ and 0.0837 g H₂O
0.1097 g gave 14.5 mL N (18°, 757 mm, 50% KOH).

Calculated for C ₈ H ₁₂ O ₃ N ₂ :		Found:
C	52.2%	52.1%
H	6.5%	6.9%
N	15.2%	15.4%

Saponification with sodium hydroxide yielded 0.3 g from 0.5 g of 3,5,5-trimethyl-hydantoin, Mp 148 °C.

One benzoyl derivative prepared from a 5,5-dimethyl-hydantoin did not succeed in spite of repeated efforts. Under different conditions it was treated with benzoic anhydride, but only the unchanged dimethyl-hydantoin was recovered.

1-Nitro-3,5,5-trimethylhydantoin



This compound was formed by nitration of 3,5,5-trimethyl-hydantoin. This indicates that the nitro version of 5,5-dimethyl-hydantoin is also formed under the same conditions.

A. From trimethyl-hydantoin.

A solution of 1 g of 3,5,5-trimethyl-hydantoin was placed into 5 g of a high percentage nitrogen oxides made from nitric acid. The solution was then gently evaporated on a water bath to about half of its starting volume. On cooling and adding pieces of ice, 1.1 g of nitro compound crystallized (calculated 1.3 g). It was recrystallized from diethyl ether or alcohol as flat prisms with oblique or hemihedral pointed ends. Mp 115-116 °C without decomposition.

0.1179 g gave 0.1661 g CO₂ and 0.0516 g H₂O
0.0920 g gave 18.5 mL N (18°, 757 mm, 23% KOH).

Calculated for C ₆ H ₉ O ₄ N ₃ :		Found:
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C	30.5%	30.8%
H	3.1%	3.1%
N	14.2%	14.6%
Cl	36.0%	36.4%

The compound dissolves reasonably easily in most organic solvents at room temperature; it dissolves very little in water even when heated; it is even less soluble in petroleum ether. The boiling aqueous solution smells - as a sign of hydrolysis - of hypochlorous acid. Boiling in alcohol quickly reduces it back to dimethyl-hydantoin. Similarly, the chlorines are easily removed by potassium iodide, especially a strong solution which was quantitatively followed.

0.1281 g consumed 25.9 mL n/10 $\text{Na}_2\text{S}_2\text{O}_3$ solution

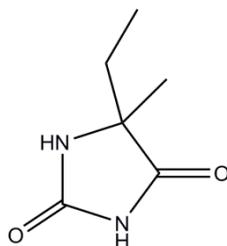
0.1094 g consumed 22.4 mL

Calculated for $\text{C}_5\text{H}_6\text{O}_2\text{N}_2\text{Cl}_2$:

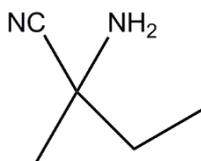
Found:

C	36.0%	35.8%	36.2%
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5-Methyl-5-ethylhydantoin



The principles set out by the experiences in the previous chapter could be readily transferred to methyl ethyl ketone to access 5-methyl-5-ethyl-hydantoin.

α -Amino-methyl-ethyl-carboxylic-nitrile

According to the above procedure 72 g of methyl ethyl ketone, 54 g of sodium cyanide and 73 g of ammonium sulfate were reacted at room temperature. After removal of the bulk of the sulfate, the residue was extracted with ether, the ether evaporated and the residue distilled under reduced pressure to yield 50 g of a colorless oil with a density of about 0.9. One reference gave a Bp of 68 °C, another gave a bp of 72 °C.

0.1032 g gave 0.2320 g CO₂ and 0.0961 g H₂O

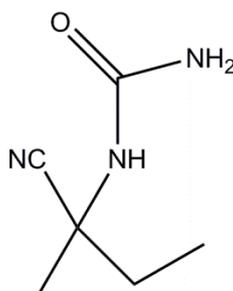
0.1636 g gave 40.4 mL N (18°, 751 mm, 50% KOH).

Calculated for C ₅ H ₁₀ N ₂ :		Found:
C	61.2%	61.3%
H	10.2%	10.4%
N	28.6%	28.6%

Hydrochloride salt. 50 g of the nitrile was transformed into its HCl salt by the dropwise addition of 100 ml of an alcoholic solution of hydrogen chloride. Despite good cooling, the formation of some ammonium chloride (5 g) could not be avoided. From the filtrate 45 g of almost pure hydrochloride separated out in a few days as colourless, lustrous flakes with blurred outlines. These decomposed at 110-115 °C. Easily soluble in hydroxylic solvents.

0.0868 g gave 15.95 mL N (18°, 752 mm, 23% KOH).

Calculated for C ₅ H ₁₀ N ₂ , HCl:		Found:
N	20.8%	20.9%

Methyl-ethyl-ureido-acetonitrile

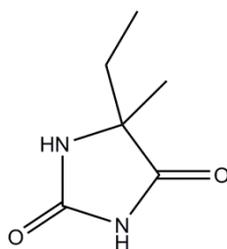
Cooled solutions of the hydrochloride salt just described (40 g into 80 mL of water) and 30 g of potassium cyanate in 120 mL of water were mixed. The next day it was evaporated under reduced pressure on a water bath and the residue extracted several times with dehydrated alcohol to yield

27 g of crude product. It was recrystallized from methanol or ethanol to give four-sided prisms with slanted pointy ends. The compound fell out as a fine crystal powder when they were dissolved in alcohol and diethyl ether was added. MP 142-143 °C. It is easily soluble in most organic solvents except for diethyl ether and petroleum ether.

0.1083 g gave 0.2039 g CO₂ and 0.0782 g H₂O

Calculated for C ₆ H ₁₁ ON ₃ :		Found:
C	51.1%	51.3%
H	7.8%	8.1%

5-Methyl-5-ethyl-hydantoin



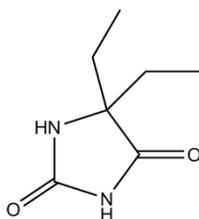
The ring closure to give the hydantoin was fuming done in fuming 25% hydrochloric acid on a water bath. This was carried out three times each of which gave an almost quantitative yield. Without isolation, the urea compounds were obtained from the hydrochloride in 45 to 50% yield. From methanol gave large beautiful, seemingly four-sided prisms with oblique ended faces with MP 149 °C. Easily soluble in the usual organic solvents except for diethyl ether and petroleum ether. The melting point stayed the same when a pure sample was sublimed careful from an admixture of sand and then recrystallized once from methanol.

0.1248 g gave 0.2334 g CO₂ and 0.0790 g H₂O

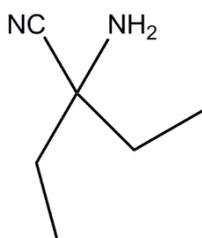
0.1246 g gave 22.1 mL N (18°, 744 mm, 23% KOH).

Calculated for C ₆ H ₁₀ O ₂ N ₂ :		Found:
C	50.7%	51.1%
H	7.0%	7.1%
N	19.7%	20.0%

The same methyl-ethyl-hydantoin was prepared by Ciamician and Silver from methyl ethyl ketone and by two years of exposure to dilute hydrogen cyanide. Mp 146 °C. A melting point of 141 °C is reported by Einhorn.

5,5-diethyl-hydantoin

The application of the above procedure to diethylketone also proceeded smoothly as follows.

 α -Amino-diethyl-carboxylic-nitrile

From 86 g of diethyl ketone, 54 g of sodium cyanide and 73 g of ammonium sulfate, the nitrile was obtained in a yield of 50 g. Bp 78 °C; Bp 81 °C.

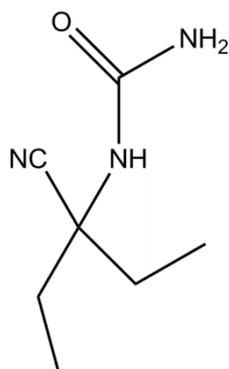
0.1254 g gave 0.2955 g CO₂ and 0.1192 g H₂O

Calculated for C ₆ H ₁₂ N ₂ :		Found:
C	64.3%	64.3%
H	10.7%	10.6%

Hydrochloride salt. 25 g of the nitrile was reacted with 50 mL of an alcoholic solution of hydrogen chloride; As this solution only gave about 1 g of precipitate it was concentrated on a water bath, after which the crystallization took place to yield 20 g of flakes of varying shapes. The compound sintered at 140 °C and decomposed at 155 °C. It was readily soluble in the usual organic solvents, except for diethyl ether and hydrocarbons.

0.1094 g gave 18.6 mL N (18°, 750 mm, 23% KOH).

Calculated for C ₆ H ₁₂ N ₂ , HCl:		Found:
N	18.9%	19.3%

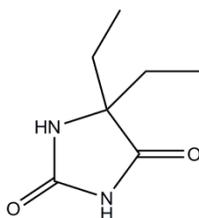
Diethyl-ureido-acetonitrile

A cooled solution of 20 g of potassium cyanate in 80 mL of water was added to a solution of 20 g of the above hydrochloride salt in 40 mL and the solution stirred. It was then evaporated under reduced pressure on a hot water bath and the residue extracted several times into alcohol. 9 g of crude product separated out from the concentrated alcoholic solution upon addition of ether. The compound was recrystallized from methanol to give fine needles that had a Mp of 255 °C with decomposition.

0.1034 g gave 25.0 mL N (18°, 741 mm, 23% KOH).

Calculated for C ₇ H ₁₃ ON ₃ :		Found:
N	27.1%	27.1%

The compound dissolved readily in alcohol, glacial acetic acid and ethyl acetate; scarcely in ether, petroleum ether.

5,5-diethyl-hydantoin

The ring closure of the urea compound to give the hydantoin was almost quantitative. From 10 g of the hydrochloride of the nitrile, 3-4 g of hydantoin were obtained with that were totally free of any of the urea compound. It was recrystallized from alcohol to give rough, four-sided, hemi-hedral ended prisms. Mp 166 °C. Readily soluble in the usual organic solvents, except for diethyl ether and petroleum ether.

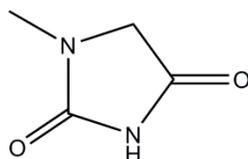
0.1002 g gave 15.9 mL N (18°, 741 mm, 23% KOH).

Calculated for C ₇ H ₁₂ O ₂ N ₂ :		Found:
N	17.9%	17.8%

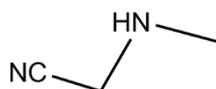
5,5-diethyl-hydantoin was prepared by Errera using a less convenient synthesis of diethyl cyanoacetamide and hypobromite; his preparation showed the same melting point.

Some experiments with semi-aromatic ketones, such as acetophenone, ethylphenyl ketone and benzophenone have shown that this method also allows access to these targets; this was allowed by the development of reaction conditions which provide a satisfactory yield.

1-Methyl-hydantoin



α -Methylamino-acetonitrile



The compound was prepared essentially by the procedure of Heimrod. The yield is excellent, if the reported procedure is respected and followed exactly as described below; otherwise the yield quickly becomes unsatisfactory.

34 g of methyl ammonium chloride were dissolved in 68 g of formaldehyde solution at room temperature. The solution was cooled to $\sim 0^\circ\text{C}$ and an equally strong cooled solution of 25 g of sodium cyanide in 50 mL of water was added dropwise (and no more!). Some sodium cyanide precipitated and was not brought back into solution. After a few minutes the reaction product began to separate as an oily layer, which separates more profoundly upon further cooling. After 0.5 hour, the oil layer was separated and diluted with ether. The aqueous layer was allowed to stand until the following day to complete the reaction and was then mixed with 10 g of sodium chloride and extracted with ether several times. The combined ethereal solutions were dried with sodium sulfate and freed of ether on a water bath. Yield was 33.5 g out of a maximum 35 g. Further purification of the light brownish oil is unnecessary; its hydrochloride is pure white. For the preparation from Sarkosin it is sufficient to let the raw nitrile sit with concentrated hydrochloric acid for several hours and then to proceed with the rest of the method according to that from Heimrod.

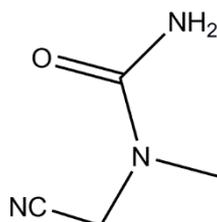
Hydrochloride salt. Methyl-amino-acetonitrile (30 g) was dissolved in 75 g of alcohol. To this solution 50 mL of a 30% alcoholic solution of hydrogen chloride was dripped in quick succession with the flask kept cold in an ice bath. Dilution with alcohol and good cooling are important because the reaction too easily becomes vigorous which results in impure preparations that are difficult to purify without loss. About 5 min after completion of the dropping the solution was heated for a few minutes on the water bath, then cooled again and brought out by grinding the wall to crystallize. Colourless, nearly centimeter-long, four-sided, flat prisms with oblique pointed ends were obtained. Yield was 35-40 g out of a possible 45 g. Mp 104°C .

0.1072 g gave 25.1 mL N (17° , 746 mm, 23% KOH).

Calculated for C ₃ H ₇ N ₂ Cl:		Found:
N	26.3%	26.5%

The salt dissolved very easily in water; soluble in methanol, ethanol and glacial acetic acid; little or no solubility in other organic solvents. It can be recrystallized alcohol.

N-[α -Cyanomethyl]-N-methyl-urea

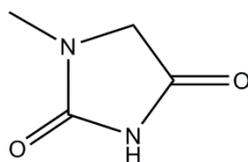


Thoroughly cooled solutions of 10 g methylamino-acetonitrile hydrochloride in 20 mL of water and 12 g of potassium cyanate in 36 mL of water were gradually mixed. Under these conditions, there were hardly any gases emitted. The solution was then concentrated using a water bath to about 30 mL, followed by the formation of 9-10 g of crystals overnight. Quantitative yield was calculated as 10.6 g. Broad, mostly yellowish prisms with oblique end faces. Readily soluble in water; little in organic solvents. It can be recrystallized from water but avoid high temperatures. Browning occurs at about 180 °C; Decomposition at 212 °C.

0.0920 g gave 29.9 mL N (16°, 744 mm, 23% KOH).

Calculated for C ₄ H ₇ ON ₃ :		Found:
N	37.3%	36.9%

1-Methyl-hydantoin

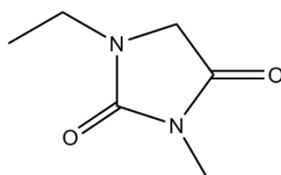


A mixture of 3 g of α -cyanomethyl- α -methyl-urea and 15 mL of concentrated hydrochloric acid was boiled for one hour and the solution brought to dryness. The residue was extracted by boiling in 10 mL of dehydrated alcohol. After concentration of the extract, 2.7 g of 1-methyl-hydantoin crystallized as a centimeter long, crude, four-sided prisms with pointed ends. They had a Mp of 156-157 °C which matches that reported by Horbaczewsky. Elemental analysis found C 41.9%, H 5.4%, N 24.8%; Calculated: C 42.1%, H 5.3%, N 24.6%.

Following this process, large quantities were produced repeatedly. Doing the process all in one day is the most efficient. When the preparation of α -methylamino-acetonitrile is left until the next day about a lower yield 10% is observed. The conversion to the hydrochloride salt was done in a distillation flask where the solution was evaporated under reduced pressure on a water bath. The

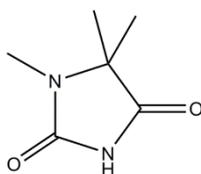
residue was treated with 250 mL of 25% hydrochloric acid with cooling, after which potassium chloride soon separated and was drawn off. The filtrate was boiled for an hour and then evaporated under reduced pressure on a water bath. The residue twice washed with 10 mL of hot dried alcohol. The remaining residue was slowly heated into 200 mL of alcohol which was decanted and then allowed to evaporate to crystallization. From 75 g of methyl ammonium chloride and 61 g of the nitrile were obtained 70 g of the hydrochloride salt and finally 57 g of pure 1-methyl-hydantoin. This has become a method to easily access 1-methyl-hydantoin.

1,3-Diethyl-hydantoin

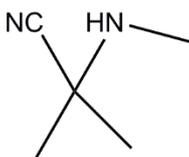


The previously obtained compound from the degradation of the uric acid derivative cleanly produced 1,3-dimethyl-hydantoin from reacting 1-methyl-hydantoin with diazomethane. The pale yellow oil was distilled at 34 mm pressure at $\sim 174^\circ\text{C}$, or 20 mm pressure at $\sim 150^\circ\text{C}$. In unison with the above information it boiled at atmospheric pressure at 262°C (according to the method from Siwoloboff).

1,5,5-Trimethyl-hydantoin



α -Methylamino-isobutyric acid-nitrile



A solution of 10 g of sodium cyanide in 50 mL of water was mixed at $\sim 0^\circ\text{C}$ with 14 g of methyl ammonium chloride and 12 g of acetone. After one day the solution had become homogeneous and 5 g of NaCl was added and the reaction extracted several times into ether. Yield 19 g. The crude product (analysis I) was not pure; it contained methylimino dibutyric acid-nitrile. It boiled between 50 and 70°C at 14 mm pressure. After repeated vacuum distillation an oil was obtained which boiled at 59°C at 20 mm of pressure and was nearly pure (analysis II).

- | | |
|-----|--|
| I. | 0.2065 g gave 0.4560 g CO_2 and 0.2067 g H_2O |
| | 0.0496 g gave 11.4 mL N (21° , 759 mm, 50% KOH). |
| II. | 0.0570 g gave 0.1289 g CO_2 and 0.0452 g H_2O |

Calculated for

Found:

C ₅ H ₁₀ N ₂ :		I.	II.
C	61.2%	60.3%	61.7%
H	10.2%	11.2%	8.9%
N	28.6%	26.6%	---

We have not used any special efforts to purify the nitrile as the crude product is suitable for further reactions, especially when the reaction was kept cool.

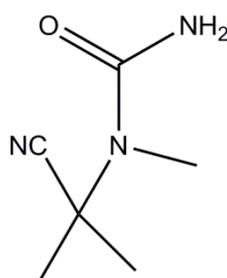
Hydrochloride salt. To a solution of methylamino-isobutyric acid-nitrile (15 g) in alcohol (35 g) that was kept cool by ice water, 50 g of cold HCl in alcohol solution was added dropwise. The salt was filtered from the mother liquor after very careful concentration by evaporation. Yield 16-17 g (calculated 20 g). It was recrystallized from alcohol. Decomposition point 196 °C.

0.0965 g gave 17.4 mL N (20°, 754 mm, 50% KOH).

Calculated for C ₅ H ₁₁ N ₂ Cl:		Found:
N	20.8%	20.8%

The salt dissolved very easily in water; easily in ethanol, methanol and glacial acetic acid; far less in any other solvent. It recrystallizes from alcohol as dendritic shaped needles.

N-[α-cyano-isopropyl]-N-methylurea



A cooled solution of the hydrochloride (13 g) in water (25 mL) was added in several portions to a cooled solution of potassium cyanate (10 g) in water (30 mL). After concentration of this solution to a half of its volume, 10 g of N-[α-cyano-isopropyl]-N-methyl-urea crystallized as fine-pointed needles. These were recrystallized from alcohol. The decomposition point was remarkably high, namely 305 °C. Care is required for its combustion as small amounts of methane easily escape.

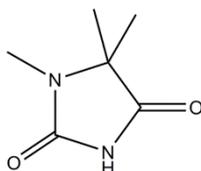
0.1242 g gave 0.2307 g CO₂ and 0.0931 g H₂O

0.1128 g gave 30.7 mL N (19°, 754 mm, 23% KOH).

Calculated for C ₆ H ₁₁ ON ₃ :		Found:
C	51.1%	50.7%
H	7.8%	8.4%
N	29.8%	30.9%

The compound dissolved very abundant in water, methanol and glacial acetic acid; easily in ethanol and phenol; less easily in ethyl acetate, acetone or chloroform; scarcely in diethyl ether or petroleum ether. It can be precipitated from aqueous or alcoholic solution by addition of diethyl ether.

1,5,5-Trimethyl-hydantoin



10 g of N-cyanisopropyl-N-methyl-urea was placed into 50 g of 25% hydrochloric acid and the mixture heated at reflux for one hour. The evaporation residue obtained under reduced pressure was dried by azeotropeing with dehydrated alcohol. The evaporation residue of this extract was expediently distilled under reduced pressure to obtain beautiful, colorless needles with attached rectangular end faces. If the product was not distilled it crystallized only with difficulty. Yield 5.4 g.

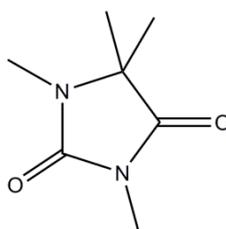
0.1174 g gave 0.2180 g CO₂ and 0.0691 g H₂O
0.0894 g gave 15.5 mL N (21°, 747 mm, 50% KOH).

Calculated for C ₆ H ₁₁ ON ₃ :		Found:
C	50.7%	50.6%
H	7.0%	6.6%
N	19.7%	19.8%

The compound dissolved abundantly in alcohol, acetone, glacial acetic acid or ethyl acetate; only partially in chloroform and diethyl ether; hardly at all in petroleum ether. Large six-sided prisms were obtained when crystallizing from alcohol.

If it is not to give the intermediates, the hydrochloride salt of the methylamino-isobutyric acid-nitrile is reacted with potassium cyanate in the manner described, the solution was evaporated at reduced pressure and the residue immediately further hydrolyzed with hydrochloric acid to bring about the ring closure.

1,3,5,5-Tetramethyl-hydantoin



The up until now little known 'Per-methyl-hydantoin' was easily obtained from treating the trimethyl compound (above) with diazomethane. 2 g of product came from 2 g of start material. Large, six-

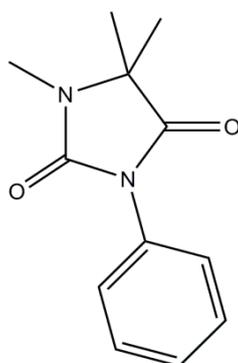
sided prisms were recrystallized from diethyl ether with a mp of 85 °C. Careful analysis was required as methane is easily emitted by this compound.

0.1290 g gave 0.2530 g CO₂ and 0.0919 g H₂O
 0.0943 g gave 14.8 mL N (17°, 754 mm, 50% KOH).

Calculated for C ₇ H ₁₂ O ₂ N ₂ :		Found:
C	53.8%	53.5%
H	7.7%	8.0%
N	18.0%	18.4%

Easily soluble in the usual solvents; not in petroleum ether.

1,5,5-Trimethyl-3-phenyl-hydantoin



Hydantoin phenylated in position 3 are most easily obtained by treatment of the free α -amino-fatty acid-nitriles with phenyl isocyanate followed by hydrolysis of the resulting cyanoacetyl-phenyl-ureas. The following implementation is described as an example.

N-[α -Cyano-isopropyl]-N-methyl-N'-phenyl-urea.

A solution of α -methylamino-isobutyric nitrile (9 g) in anhydrous benzene (50 mL) was shaken vigorously with 8 g of phenyl isocyanate, until a thick crystalline slurry was formed (1 hour). Work up of the mother liquor gave 13 g of product, which recrystallized from alcohol as four-sided hemihedral prisms with mp 118-120 °C.

0.1596 g gave 25.8 mL N (16°, 762 mm, 23% KOH).

Calculated for C ₁₂ H ₁₅ ON ₃ :		Found:
N	19.3%	18.8%

Very easily soluble in water and in the usual organic solvents, except for diethyl ether and petroleum ether.

1,5,5-Tetramethyl-3-phenyl-hydantoin. Preparing the hydantoin required a longer heating time than usual. It was obtained by placing the above described urea (5 g) into concentrated hydrochloric acid

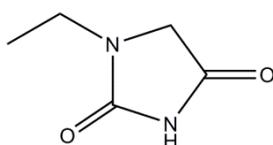
(50 mL) and heating at reflux for 3 hours. After concentrating the solution, 3.5 g of pure product crystallized out as thin, beautifully refined, seemingly monoclinic prisms with six sided outlines. Mp 98-100 °C.

0.1363 g gave 15.3 mL N (17°, 756 mm, 50% KOH).

Calculated for C ₁₂ H ₁₄ O ₂ N ₂ :		Found:
N	12.8%	13.1%

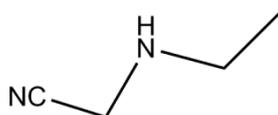
Very readily soluble in alcohol, acetic acid, benzene, ethyl acetate; easily in diethyl ether or water; practically insoluble in petroleum ether.

1-Ethyl-hydantoin



The Preparation of ethyl-hydantoin occupied us with multiple attempts until we found the right way. We first used glycolic acid nitrile and exposed it to ethylamine. A solution of glycolonitrile (4 g) in dehydrated alcohol (4 g) was added to a solution of ethylamine (4 g) in dehydrated alcohol (10 g) to obtain a solution with 4 g ethylamino-acetonitrile. The yield may have been improved by prolonged standing before heating the mixture; such attempts have been disregarded a direct synthesis was since found. For the preparation of the ethylamino-acetonitrile, the procedure from Knoevenagel and Mercklin and was initially used; A sodium bisulfite solution containing formaldehyde and ethylamine were reacted by adding sodium cyanide. With this method the reported yield of 13 g of ethylamino-acetonitrile was sometimes obtained, but more often the yield was reduced to low levels. Meanwhile, the above-reported observations in the preparation of amino-isobutyric acid were made, namely that the addition of sodium hydrosulfite is unnecessary if ethylammonium chloride is removed and that good cooling during mixing is important. This led to the following procedure.

α-Ethylamino-acetonitrile



A solution of ethylammonium chloride (33 g) in formalin (54 g) was, under careful cooling with ice, gradually added to a cooled solution of sodium cyanide (20 g) in water (40 mL). An oil separated which could soon be decanted off. The aqueous portion was treated the next day with sodium chloride and extracted repeatedly into diethyl ether. Nearly the whole 30 g of crude nitrile were obtained (90% of calculated) that were brighter and purer than after the bisulfite method. The yield was about 1/5 lower when the reaction was extracted immediately into ether; apparently the reaction is slow and only comes to completion when left overnight. The crude product was distilled at 30 mm between 75 and 90 °C. After repeated distillation under the same pressure it boiled at 85 °C which matched what Knoevenagel and Mercklin had reported.

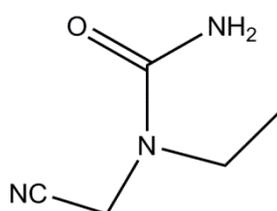
Hydrochloride salt. To a well cooled by ice water solution of ethylamino-acetonitrile (30 g) - the crude product was good enough - in alcohol (75 g), a solution of ~30% hydrogen chloride in alcohol (50 mL) was added dropwise. The salt crystallized as tiny, pretty, uniform, pure looking crystals, which grew into fine, seemingly four sided prisms with flat ends. Yield 21 g. Sintered at 125 °C; Browning and the onset of decomposition occurred at 150-160 °C.

0.1105 g gave 22.3 mL N (18°, 755 mm, 50% KOH).

Calculated for C ₄ H ₉ N ₂ Cl:		Found:
N	23.2%	23.5%

The salt dissolved very easily in acetic acid, methanol, ethanol and water; little else.

N-Cyanomethyl-N-ethyl-urea

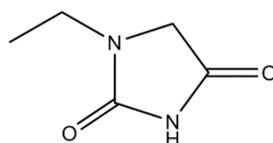


Under cooling, a solution of the hydrochloride salt (10 g) described above in water (20 mL) was added to a solution of potassium cyanate (12 g) in water (36 mL). From the carefully evaporated to half solution crystallized 5-6 g of product which was then recrystallized from alcohol. Pure yield 9-10 g (~90% of calculated). If the aqueous solution is heated too much or too long, the crude product becomes bright yellow; It is typically bright yellow. It can be purified by recrystallization from water at 60 °C to give crude, four-sided prisms which are usually combined into globular aggregates. Sparingly soluble in organic solvents (as was already observed for the methyl compound). Decomposed at 208 °C, having browned from 175 °C.

0.1255 g gave 36.3 mL N (17°, 743 mm, 50% KOH).

Calculated for C ₅ H ₉ ON ₃ :		Found:
N	33.1%	33.3%

1-Ethyl-hydantoin



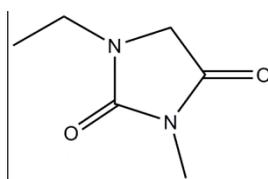
Pursuit of a 1-ethyl-hydantoin synthesis based upon the major solvents of was met with difficulties which are still not completely overcome in a satisfactory manner. Eventually a pathway was determined which provided a tolerable yield of pure product.

Either cyanomethyl-ethyl-urea was heated at reflux with five times the amount of half-concentrated hydrochloric acid and the evaporation residue extracted into dehydrated alcohol or ethyl acetate. Or

it was carried out with ethylglycol hydrochloride in the manner described with potassium cyanate, the evaporation residue was concentrated by fuming off the HCl and the product extracted into organic solvents. The yield of crystallized ethyl-hydantoin was always low and rarely exceeded 20%.

Even better was to completely evaporate the alcoholic extract and then purify the crude ethyl-hydantoin by distillation at reduced pressure. It was distilled from a small retort which was heated in an oil bath, the neck of which had been blown into a bulb shape to collect the distillate. The distillate was a solid needle-shaped mass which could be easily recrystallized from ethyl acetate. Its mp of 103-104 °C matched that of the same product when obtained using a 7-ethyl-uric acid glycol-ethylmonoether synthesis. From 10 g of cyanomethyl-ethyl-urea, up to 4 g of pure ethyl-hydantoin were obtained.

1-Ethyl-3-methyl-hydantoin

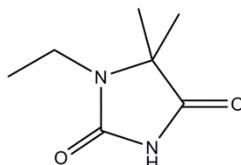


Ethyl-hydantoin was easily methylated with diazomethane. The crude product was distilled at reduced pressure into a curved test-tube apparatus. The oily distillate solidified slowly in a desiccator to give shiny-glasslike, six-sided hemihedral prisms. Mp 93 °C, Bp 278 °C (which matched that reported by Siwoloboff). Very easily soluble in water and organic solvents except for petroleum ether.

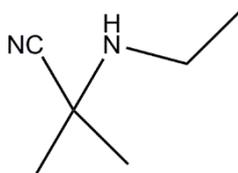
0.1207 g gave 20.9 mL N (18°, 747 mm, 50% KOH).

Calculated for C ₆ H ₁₀ O ₂ N ₂ :		Found:
N	19.7%	19.9%

1-Ethyl-5,5-dimethyl-hydantoin



α-Ethylamino-isobutyric-nitrile



A solution of sodium cyanide (25 g) in water (125 mL) was added to a flask with a sealed closure at room temperature that contained ethylammonium chloride (42 g) in acetone (30 g). After two days it was saturated with sodium chloride and extracted into diethyl ether. Yield 53 g (calculated 56 g).

The crude product boiled at 20 mm pressure at 70-80 °C to give a colourless oil. This nitrile proved relatively resistant to boiling in an alcoholic HCl solution.

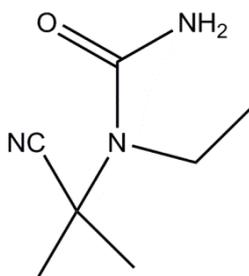
Hydrochloride salt. To an ice-cooled solution of ethylamino-isobutyric-nitrile (15 g) in alcohol (45 mL), a saturated solution of HCl in alcohol (50 g) was added dropwise. The precipitated hydrochloride was drawn off and the mother liquor worked up to yield 18 g of product as pointed needles. Decomposition point 110 °C.

0.1704 g gave 0.3042 g CO₂ and 0.1322 g H₂O
 0.1528 g gave 26.0 mL N (21°, 749 mm, 23% KOH).

Calculated for C ₆ H ₁₃ N ₂ Cl:		Found:
C	48.5%	48.7%
H	8.8%	8.7%
N	18.9%	19.0%

The HCl salt version of the compound dissolved easily in water, methanol and ethanol; less easily in acetic acid or acetone; insoluble in pretty much anything else.

N-[α-Cyano-isopropyl]-N-ethyl-urea



A cooled solution of the hydrochloride (18 g) in water (30 mL) was added in portions to a solution of potassium cyanate (15 g) in water (45 mL). After concentration on the water bath 12 g of product crystallized which was recrystallized from alcohol, possibly with the addition of some diethyl ether. Large four-sided prisms were obtained with slanted end faces that decomposed at 295-297 °C. To test whether the high decomposition point was caused by polymerization, the molecular weight was determined; it was found to be the value for the simple molecular mass.

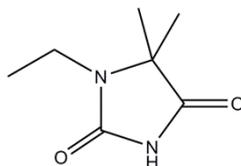
0.1089 g gave 25.4 mL N (16°, 763 mm, 23% KOH).

In 19.03 g phenol gave 0.2054 g Subst. 0.55° reduction.

Calculated for C ₇ H ₁₃ ON ₃ :		Found:
N	27.1%	27.2%
Molec. weight	155	141

Very easily soluble in water, acetic acid and methanol; easily in alcohol and phenol; somewhat less in acetone, chloroform, ethyl acetate; practically insoluble in diethyl ether, petroleum ether or camphor.

1-Ethyl-5,5-dimethyl-hydantoin



A solution of the above described urea (15 g) in half-concentrated hydrochloric acid (200 mL) was boiled for 2 hours and then evaporated under reduced pressure. The residue was boiled into anhydrous alcohol which was then decanted and evaporated to leave 12 g of ethyl-dimethyl-hydantoin as fine, sharp, little needles. These were recrystallized from a small amount of alcohol, possibly with the addition of some petroleum ether. Mp 138-139 °C.

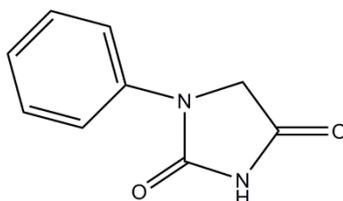
0.1158 g gave 0.2275 g CO₂ and 0.0824 g H₂O
0.0989 g gave 15.5 mL N (20°, 741 mm, 50% KOH).

Calculated for C ₇ H ₁₂ O ₂ N ₂ :		Found:
C	53.8%	53.6%
H	7.7%	8.0%
N	18.0%	17.8%

The compound dissolved very easily in organic solvents except for diethyl ether and petroleum ether. It can be distilled and crystallizes very well from organic solvents.

1-Aryl-hydantoins

1-Aryl-hydantoins are much easier to access than 1-Alkyl-hydantoins. Beckurts and Frerichs showed that they are obtained easily by fusing Chloro-acetyl-urea with 2 moles of arylamine and remove with alcohol, which we confirmed for 1-phenyl-hydantoin. To prepare larger amounts it is probably more convenient to use the method described by Hausdörfer, that is from chloroacetic acid and a primary arylamine to make the Arylaminoacetic acid and react it with potassium cyanate and use hydrochloric acid to close the ring. So we started with 1-phenyl-hydantoin, 1-anisyl-hydantoin and 1-phenethyl-hydantoin and set about converting them to their derivatives. Especially as we were interested in 1-phenyl-hydantoin, for the potassium salt Frerichs and Breustedt gave the formula of a derived addition product of 1-phenyl-hydantoin and potassium hydroxide, C₉H₈O₂N₂ + KOH, whereas Beckurts and Frerichs for the potassium salt of *p*-phenethyl-hydantoin gave the formula for what would be anticipated for the potassium salt of phenethyl hydantoinic acid. A careful examination of the potassium salts of 1-phenyl-hydantoin led us to a formula with one fewer H₂O which was C₉H₇O₂N₂K. Potassium has therefore replaced the hydrogen in position 3, probably by enolization.

1-Phenyl-hydantoin

For the preparation of phenylamino-acetic acid[†] following Hausdörfer's method, aniline (25 g), chloroacetic acid (25 g) and hydrous sodium acetate (40 g) were heated in a beaker on a water bath. Complete melting of a few cubic centimeters of water was followed by 3/4 of an hour of heating in which 200 to 300 mL of water was added. It was appropriately neutralized by dilute alkali and then just a little hydrochloric acid to obtain a red result on the congo red test (pH > 5.2). The crystal mass obtained upon cooling was washed with water, treated with ammonium carbonate solution, followed by acidification with strong hydrochloric acid, the resulting phenylamino-diacetic acid byproduct was removed by diethyl ether extraction. It was then made congo-neutral (pH 3-5.2) which was followed by the precipitation of 12-13 g of phenylamino-acetic acid. After recrystallization from water the mp was 121 °C.

To reach 1-phenyl-hydantoin, a solution of phenylamino-acetic acid (12 g) in water (150 mL) was mixed with a solution of potassium cyanate (8 g) in water (24 mL). After concentrating the solution to about 50 mL and adding 30 mL of concentrated hydrochloric acid, the 1-phenyl-hydantoin crystallized out on cooling. The ring closure takes place very easily. The product was recrystallized from alcohol to yield 9 g of oblique ended prisms. The mp of 191 °C matched that reported by Schwebel. It was soluble in NaOH or ammonia solution but precipitated with the addition of acids. Slightly soluble in cold water, more easily soluble in alcohol. 1-Phenyl-hydantoin could be reacted with either benzoyl chloride in the 3 position or with nitrosobenzene in the 5 position.

[†]Phenylamino-acetic acid is also suitable for the production of 1,3-diphenyl-hydantoin. We heated 2.3 g in a flask an oil bath with phenyl-urea (2 g) at ~ 140 °C which released fumes of ammonia. When the reaction was complete it was recrystallized from benzene to yield 1.8 g of colourless, shimmering, elongated four sided flakes. Mp was 137 °C which matched that reported by H. L. Wheeler and C. Hoffman. Readily soluble in benzene and chloroform; less in alcohol; hardly in petroleum ether.

1-Phenyl-hydantoin potassium. 1-Phenyl-hydantoin (2.5 g) was dissolved in a solution of KOH (1.1 g) in warm alcohol (50 mL) as well as the dropwise addition of some water. Upon cooling came short, oblique ended prisms in the shape of intergrown rosettes. The product was recrystallized from 90% alcohol containing a little KOH. Decomposition point was 370-378 °C, exposure to boiling water induced hydrolysis; the potassium is therefore bound only weakly. Various preparations were dried at either 60 °C for 5 hours, 80 °C in vacuum or at 120 °C. We analyzed five preparations which consistently showed the formula as $C_9H_7O_2N_2K$.

0.0996 g gave 0.0395 g K_2SO_4 .
 0.1601 g gave 0.0655 g K_2SO_4 .
 0.1610 g gave 0.0644 g K_2SO_4 .
 0.0957 g gave 11.1 mL N (17°, 737 mm, 23% KOH).
 0.1203 g gave 13.5 mL N (15°, 756 mm, 23% KOH).
 0.1088 g gave 12.6 mL N (15°, 751 mm, 23% KOH).
 0.0919 g gave 10.8 mL N (16°, 742 mm, 23% KOH).

Calculated for $C_9H_7O_2N_2K$:

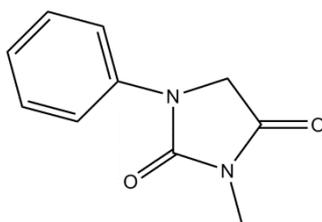
K	18.2	%	N	13.1	%
	17.8	18.4	17.9%	13.0	13.0
				13.3	13.5%

16.8% K and 12.1% N were calculated for $C_9H_9O_3N_2K$.

The error in the previous determinations are well explained by the fact that in the preparation of the salt, the residual water content of the KOH was not considered and therefore too little was used.

In accordance with our findings of the potassium salts, Pinner found the formula $C_9H_7O_2N_2K$ for that of 5-phenyl-hydantoin and Bailey found the formula $C_3H_3O_2N_2K$ for that of hydantoin.

1-Phenyl-3-methyl-hydantoin

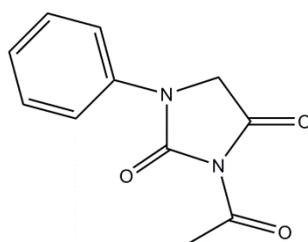


1-Phenyl-hydantoin was exposed to diazomethane to easily methylate position 3. The product was recrystallized from ethyl acetate to give crude but pretty, silvery-glazed, six-sided prisms with oblique end faces. Mp 185 °C.

0.1867 g gave 24.2 mL N (23°, 752 mm, 50% KOH).

Calculated for $C_{10}H_{10}O_2N_2$:	Found:
N	14.7%
	14.7%

Readily soluble in methanol, ethanol, acetic acid and toluene, less in ethyl acetate, little in water, practically insoluble in diethyl ether or petroleum ether.

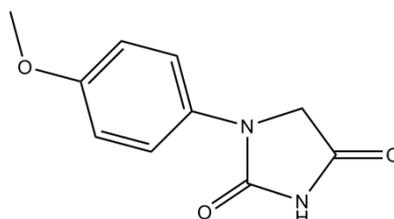
1-Phenyl-3-acetyl-hydantoin

1-Phenyl-hydantoin (3 g) and acetic anhydride (30 g) and were kept on the boil for 1 hour. From the concentrated solution crystallized 3 g of flat prisms with rectangular and attached end faces that had a mp of 145-146 °C.

0.1132 g gave 12.9 mL N (18°, 757 mm, 33% KOH).

Calculated for $C_{11}H_{10}O_3N_2$:		Found:
N	12.8%	13.1%

The acetyl compound dissolved readily in water and in common organic solvents; little in diethyl ether or petroleum ether. It is noteworthy that this compound keeps a firm hold on the acetyl as an acetyl group usually only loosely binds to the position 3 imide. For example hydantoin, when modified in this way, is not deacylated by half an hour of cooking in alcoholic solution. However, alkali or natural light will deacylate it.

1-Anisyl-hydantoin

Solutions of Anisylamino-acetic acid (12 g) in water (150 mL) and potassium cyanate (9 g) in water (30 mL) were mixed at room temperature and then evaporated on a water bath to a third. Following addition of 25 mL of concentrated hydrochloric acid to the hot solution, on cooling the anisyl-hydantoin product crystallized to yield 9 g of four-sided prisms with oblique pointed ends. For purification it was dissolved in very dilute sodium hydroxide solution and then precipitated out with hydrochloric acid. Melting point 201 °C. Frerichs and Breustedt, who produced the compound by other means reported a mp of 196-197 °C. Slightly soluble in water, alcohol and acetic acid.

1-Anisyl-3-acetyl-hydantoin. Made by two hours of boiling with a 10 molar excess of acetic anhydride. Gave fine, chopstick-like crystals. Recrystallized from Alcohol to give a mp of 172 °C. Easily dissolved in most organic solvents and in water; little in diethyl ether.

0.1073 g gave 10.7 mL N (18°, 758 mm, 33% KOH).

Calculated for $C_{12}H_{12}O_4N_2$:		Found:
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N	11.3%	11.5%
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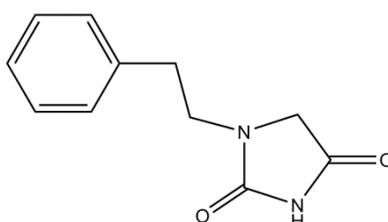
1-Anisyl-3-methyl-hydantoin. From 1 g of start material exposed to diazomethane gave the product in a nearly quantitative yield. Mp 194 °C. Easily dissolved in most organic solvents; little in diethyl ether or water.

0.1118 g gave 12.9 mL N (16°, 753 mm, 23% KOH).

Calculated for $C_{11}H_{12}O_3N_2$: Found:

N	12.7%	13.3%
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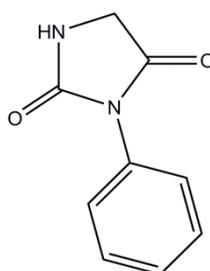
1-Phenethyl-hydantoin



It was prepared from the prepared according the procedure described by Halberkanns (Bericht **54**, p1154, 1921) using Phenethylamino-acetic acid in the same way. From 10 g of start material, 6 g of product were obtained with a mp of 232 °C. Frerichs and Beckurts reported 234 °C from using the same preparation. This products crystals took the form of four-sided, slanted-end prisms. It was purified by dissolving in alkali followed by precipitation with acid. The solubility was similar to the previous compound.

The obtained from treating this compound with diazomethane was 1-phenethyl-3-methyl-hydantoin which melted at 182 °C, which is slightly lower than what was previously reported.

3-Phenyl-hydantoin

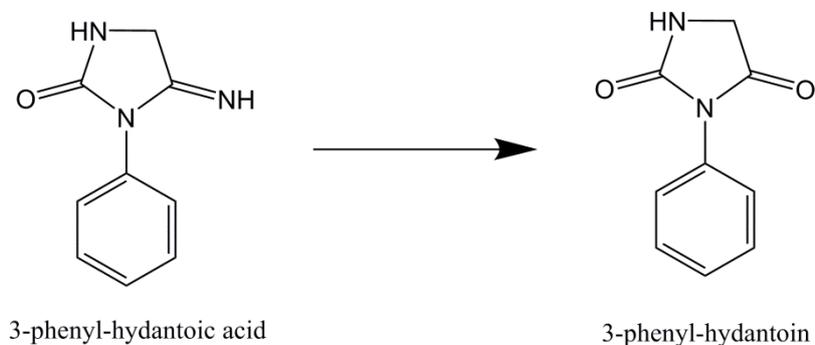


Phenyl-hydantoinic acid was obtained by Paal and Mouneyrat by fusing glycine and phenyl isocyanate, exposure to hydrochloric acid then converted it to 3-phenyl-hydantoin⁺⁺. Instead of the free glycine it is better to use the more convenient to be obtained Glycine ester hydrochloride, or better still to use amino-acetonitrile hydrochloride sulfate.

A solution of glycine ester hydrochloride (10.5 g) and sodium hydroxide (3.4 g) in water (140 mL) was prepared which was kept cool by a water pipe. Phenyl isocyanate (10 g) was added and the mixture shaken vigorously. After completion of the reaction (~ 5 minutes), the precipitated diphenyl-urea was drawn off and the filtrate treated with sulfuric acid to give a product with a mp of

about 195 °C, which is easily generated by hydrolysis of its ester (as reported by Paal). With half an hour of boiling in 80 mL of concentrated hydrochloric acid, 5 g of 3-phenyl-hydantoin were obtained. Our product melted at 168 °C, which is a few degrees higher than that stated by Mouneyrat.

†† Translator's note: Structures are not shown in the original for the above section but the author refers to a "Phenyl-hydantoinensäure" intermediate, which is treated with HCl to give the hydantoin. Hydantoinensäure doesn't translate well to English so I have used the term hydantoic acid. The structure of these compounds is as shown below.



End of Translation