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A NEW SYNTHESIS FOR 1-AMINOHYDANTOIN AND NITROFURANTOIN

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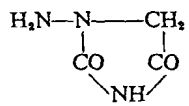
A new synthesis for 1-aminohydantoin and nitrofurantoin is described. Derivatives of 1-aminohydantoin were prepared by condensation of semicarbazones with ethyl monochloroacetate in presence of sodium alkoxide in dry ethanol. The nature of this reaction is discussed and semicarbazones were shown to react as nucleophilic anions.

Nitrofurantoin, 1-(5′-nitro-2′-furfurylideneamino)hydantoin, is an important antibacterial drug in the treatment of infections of the urinary tract. It is prepared by condensing 5-nitro-2-furaldehyde or its diacetate with 1-aminohydantoin. The furan derivative may be prepared in good yield from furfural by nitration[1] but, until recently, 1-aminohydantoin (I) was obtained in relatively low yield by a rather slow process from monochloroacetic acid through hydrazino-monoacetic acid and 2-semicarbazido-acetic acid. In these reactions, the yield of 1-aminohydantoin is low mainly because of the formation of a large proportion of hydrazinodiacetic acid from the condensation of hydrazine and monochloroacetic acid. Even when 6 times excess of hydrazine is used, the yield of 1-aminohydantoin is only about 35 to 40 per cent[2] when allowance is made for hydrazine recovered by distillation. Accordingly, an improved synthesis for 1-aminohydantoin was desirable.



(I)

Simple semicarbazones such as benzaldehyde or acetone semicarbazone condense with ethyl monochloroacetate to form aldehydic or ketonic derivatives of 1-aminohydantoin in good yield. These derivatives are easily hydrolysed by mineral acids to give 1-aminohydantoin which may be condensed with 5-nitro-2-furaldehyde or its diacetate to give nitrofurantoin in about 60 per cent yield based on starting hydrazine compared with 35 to 40 per cent by the best previously known route. In addition, the new process is quicker and involves no hydrazine recovery or other potentially hazardous stage.

The improved yield of 1-aminohydantoin is due mainly to the selection of a starting hydrazine derivative which contains only one residual hydrogen atom for substitution. Usually, hydrazine forms preferentially gem-disubstituted derivatives with alkylating agents since mono-alkyl hydrazines are more basic than hydrazine[3,4]. But, in semicarbazones, two

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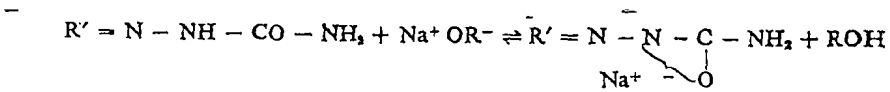
of the hydrazine hydrogen atoms are replaced by an aldehydic or ketonic residue which is easily removed after the condensation to hydantoin is complete, and a third by an amide group which takes part in the reaction to form the hydantoin structure. However, semicarbazones are not basic and do not react spontaneously with chloroacetic acid derivatives and so reaction conditions have to be used to form highly reactive semicarbazone anions. The reaction is discussed further below.

The use of semicarbazones in the synthesis of *N*-aminoheterocycles is novel. Other applications of this type of reaction have been investigated and will be reported soon.

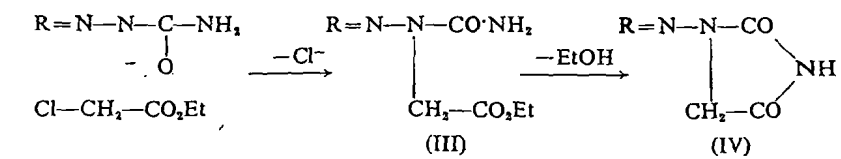
The Reaction between Semicarbazones and Ethyl Monochloroacetate

The basis of the new reaction is the formation of strongly nucleophilic semicarbazone anions (II) by treating the semicarbazone with a strong base under anhydrous conditions, for example with a sodium alkoxide in dry alcohol.



(II)

The semicarbazone ion reacts with added ethyl monochloroacetate, by a nucleophilic attack on the α-carbon of the ester with formation of a C–N bond and elimination of chloride ion, and by an ester-amide condensation resulting in the formation of a second C–N bond with elimination of ethanol and completion of the hydantoin structure (IV). The reaction is strongly exothermic and sodium chloride precipitates almost immediately the ester addition is begun. No intermediate 2-semicarbazidoacetic ester (III) could be isolated presumably because in it, the ester and amide groups are held close together in an environment ideal for their condensation.



(III) (IV)

The hydantoin formed, being a relatively strong acid, reacts with the sodium derivative of the semicarbazone to give a sodium hydantoin and free semicarbazone. Accordingly, the theoretical relative proportion for the reaction are semicarbazone (1 mole), sodium alkoxide (2 moles) and ethyl monochloroacetate (1 mole), but for best yields, not all of the ethoxide may be added at once since the excess would react readily with the chloro-ester to give an ethyl alkoxyacetate. The following scheme shows the theoretical optimum method of addition.

Semicarbazone (1 mole) + sodium alkoxide (1 mole)
↓ ethyl monochloroacetate (½ mole)
Sodium hydantoin (½ mole) + semicarbazone (½ mole) + sodium chloride (½ mole)
↓ 1. Sodium alkoxide (½ mole) 2. Ethyl monochloroacetate (¼ mole)
Sodium hydantoin (¼ mole) + semicarbazone (¼ mole) + sodium chloride (¼ mole)
↓ 1. Sodium alkoxide (¼ mole) 2. Ethyl monochloroacetate (⅛ mole)
Sodium hydantoin (⅛ mole) + semicarbazone (⅛ mole) + sodium chloride (⅛ mole)
↓ 1. Sodium alkoxide (⅛ mole) etc.

In practice, the scheme was followed to the second ester addition and thereafter the alkoxide and ester were added in alternate estimated equivalent additions since the quantities involved became small. Also, whilst the scheme allows theoretical conversion of semicarbazone to a 1-aminohydantoin derivative, lower yields are obtained because of the competing side-reaction between the alkoxide and chloroester yielding an ethyl alkoxyacetate. The yield of hydantoin obtained depends on the relative concentrations of semicarbazone and alkoxide ions and their relative reactivities towards the chloroester.

With benzaldehyde semicarbazone the reaction product was the sodium derivative of 1-benzylideneaminohydantoin. 1-Benzylideneaminohydantoin was easily isolated by acidification of the reaction mixture and separated from unchanged benzaldehyde semicarbazone by treatment with aqueous alkali in which the semicarbazone was sparingly soluble. 1-Aminohydantoin hydrochloride was obtained by hydrolysis of the benzylidene derivative with hydrochloric acid and was converted to free 1-aminohydantoin by treatment with an equivalent of aqueous alkali or with sodium methoxide in dry alcohol. With acetone semicarbazone the reaction product was the sodium salt of 1-isopropylideneaminohydantoin. The acid form of this hydantoin was not readily isolated but was converted to 1-benzylideneaminohydantoin or nitrofurantoin by reaction with benzaldehyde or 5-nitro-2-furaldehyde respectively in acid solution.

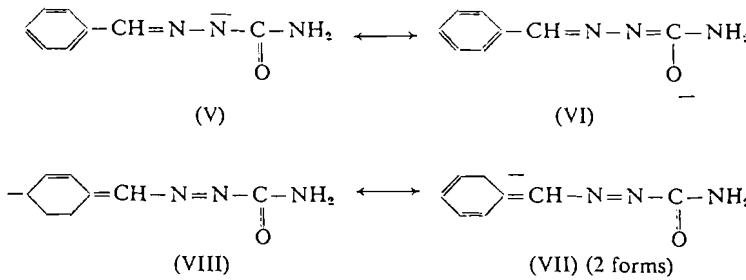
Semicarbazone Anions

The following evidence confirms the existence of semicarbazone anions.

Acetone and benzaldehyde semicarbazones are much more soluble in a solution of sodium ethoxide in dry ethanol than in ethanol alone.

Benzaldehyde semicarbazone could be titrated partially as an acid with sodium methoxide in ethylenediamine using azo-violet as indicator[5] but, under these conditions, acetone semicarbazone showed little or no acidity and is, therefore, a weaker acid than the benzaldehyde derivative. This would be expected because of the inductive effect (+I) of the isopropylidene group which partially satisfies the electron demand of the 2-nitrogen of acetone semicarbazone and so its substituent hydrogen atom ionises less readily, and because of the greater possibility for resonance and,

therefore, stability in benzaldehyde semicarbazone anion. Resonance forms are shown in V to VIII.



(V) (VI)

(VIII) (VII) (2 forms)

Acetone semicarbazone, being a weaker acid than benzaldehyde semicarbazone, should yield a lower concentration of anion than benzaldehyde semicarbazone under similar conditions, and, therefore, a lower yield of hydantoin in its reaction with ethyl monochloroacetate. The yields obtained, isolated as 1-benzylideneaminohydantoin in each case, were 60 to 65 per cent from acetone semicarbazone and 70 to 74 per cent from benzaldehyde semicarbazone. However, this difference might also be attributed to different reaction rates due to steric effects in the two ions.

The absorption spectrum of benzaldehyde semicarbazone showed a bathochromic shift when the solvent was changed from super-dry ethanol (λ max 283 mμ, ϵ 22,900) to 1·2N sodium methoxide in the same ethanol (λ max 323 mμ, ϵ 15,000) thus indicating probable anion formation.

The Effect of Water on the Reaction

Absence of water is essential for good yields in the new synthesis, the yield of hydantoin falling rapidly as the water content is increased. For good results the solvent should not contain more than about 0·1 per cent of water because semicarbazones, being very weak acids, do not form anions in the presence of water. In proof of this, it was shown that benzaldehyde semicarbazone did not exhibit a bathochromic shift in 0·1N sodium methoxide in methanol containing 0·2 per cent of water. Also, it is well known that in ester-amide condensation reactions good yields depend on the absence of water, the preparation of barbituric acids from malonic esters and urea being a good example[6].

Experimental

Melting points are uncorrected.

Ultra-violet spectra were determined with a Beckman DK2 recording spectrophotometer.

1-Benzylideneaminohydantoin

From 1-Aminohydantoin hydrochloride. Benzaldehyde (10·6 g.) was added to a solution of 1-aminohydantoin hydrochloride (15·2 g.) in a mixture of water (150 ml.) and ethanol (150 ml.). A white crystalline

solid separated almost immediately, was filtered off, washed with water and dried at 80° *in vacuo* to give 1-benzylideneaminohydantoin (19·4 g.; 95·5 per cent), m.p. 252 to 254°. Needles from 50 per cent v/v aqueous ethanol, m.p. 254 to 255°. (Traube and Hoffa[7] give 244°, Carrara and others[8] 249 to 250° and Uota and others[9] 245°.)

From benzaldehyde semicarbazone. Benzaldehyde semicarbazone (16·3 g.) was dissolved with heating and stirring in a solution of sodium (2·3 g.) in dry ethanol (50 ml.). Ethyl monochloroacetate (6·2 g.) was added at such a rate as to maintain refluxing without external heating (3 to 4 min.), then the mixture was refluxed for 10 minutes. A solution of sodium (1·15 g.) in dry ethanol (25 ml.) was added and the mixture heated at reflux and stirred for about one minute. Ethyl monochloroacetate (3·1 g.) was added as before and the mixture refluxed for 10 minutes. Sodium (1·15 g.) dissolved in dry ethanol (25 ml.) and ethyl monochloroacetate (3·1 g.) were added in that order in alternate small estimated equivalent additions refluxing briefly after each addition. Finally, the mixture was refluxed for 30 minutes and then most of the ethanol removed by distillation to give an alkaline pasty solid. Concentrated hydrochloric acid (15 ml.) mixed with water (80 ml.) and crushed ice (100 g.) was added, the mixture stirred and the insoluble white solid filtered off, washed and dried at 100 to 110° to give 18·5 g. solid, m.p. 228 to 240°. The solid was triturated with aqueous sodium hydroxide solution (250 ml. of 5 per cent w/v) and then filtered. The filter residue was slightly impure benzaldehyde semicarbazone (2·9 g.), m.p. 218 to 222°. The filtrate was acidified with hydrochloric acid (100 ml. of 15 per cent w/v HCl) and the precipitated white solid filtered off, washed with water and dried at 100 to 110° to give crude 1-benzylideneaminohydantoin (15·2 g.; 75 per cent) m.p. 246 to 250° which crystallised from aqueous acetic acid (250 ml. of 50 per cent v/v) giving 1-benzylideneaminohydantoin as colourless rods (14·2 g.; 70 per cent), m.p. 254 to 255°. Found: equiv. wt. 209 (sodium methoxide in benzene-methanol solution), 204 (sodium methoxide with dimethyl formamide as solvent). Required: equiv. wt. 203. The melting point was not depressed in admixture with 1-benzylideneaminohydantoin prepared from 1-aminohydantoin hydrochloride and the infra-red absorption spectra were identical for the two samples.

From Acetone Semicarbazone

This preparation was practically identical with that from benzaldehyde semicarbazone to the removal of ethanol stage substituting acetone semicarbazone (11·5 g.) for the benzaldehyde semicarbazone. No separation of 1-isopropylideneaminohydantoin occurred when the reaction mixture was acidified. Benzaldehyde (11·0 ml.) was added with ethanol (50 ml.) and the mixture heated to about 60° then cooled to 30° and filtered. The white filter residue was washed with water and dried to give slightly impure 1-benzylideneaminohydantoin (12·4 g.; 61 per cent) m.p. 248 to 252°. This material was almost completely soluble in aqueous sodium hydroxide or carbonate solution. After crystallisation

from aqueous ethanol the melting point was 254 to 255° which was not depressed when the sample was mixed with a known sample of 1-benzylideneaminohydantoin.

Nitrofurantoin: 1-(5′-*Nitro*-2′-*furfurylideneamino*)*hydantoin*

From 1-*Aminohydantoin hydrochloride.* A mixture of 5-nitro-2-furaldehyde diacetate (2·43 g.), 1-aminohydantoin hydrochloride (1·52 g.), ethanol (10 ml.), concentrated hydrochloric acid (5 ml.) and water (20 ml.) was refluxed for 30 minutes and then cooled. The yellow crystalline needles formed were filtered off, washed with water and dried at 80° *in vacuo* to give 1-(5′-nitro-2′-furfurylideneamino)hydantoin (2·2 g.; 91 per cent), m.p. 266 to 268° (decomp.).

From 1-*benzylideneaminohydantoin.* A mixture of 1-benzylideneaminohydantoin (2·03 g.) and dilute sulphuric acid (55 ml. of 10 per cent v/v H_2SO_4) was distilled until the distillate was free from benzaldehyde. Ethanol (10 ml.) and 5-nitro-2-furaldehyde diacetate (2·43 g.) were added and the mixture refluxed for 10 minutes and then cooled. The filtered and washed residue was dried at 80° *in vacuo* to give 1-(5′-nitro-2′-furfurylideneamino)hydantoin (2·18 g.; 92 per cent), m.p. 266 to 267° (decomp.).

From acetone semicarbazone. The preparation of 1-benzylideneaminohydantoin from acetone semicarbazone is described above. By a similar process acetone semicarbazone may be converted directly into nitrofurantoin in one reaction vessel by adding 5-nitro-2-furaldehyde diacetate instead of benzaldehyde in the final stage and refluxing for 15 minutes followed by cooling. The nitrofurantoin obtained is impure but may be purified by crystallisation from, for example, aqueous acetic acid. In one such experiment using acetone semicarbazone (11·5 g.) and later adding 5-nitro-2-furaldehyde diacetate (24·3 g.) there was obtained a crude product (16·9 g.; 67 per cent), m.p. 258 to 262° (decomp.) which after crystallisation from aqueous acetic acid (50 per cent v/v) gave 1-(5′-nitro-2′-furfurylideneamino)hydantoin (14·2 g.; 59 per cent), m.p. 266 to 268° (decomp.).

All of the above samples of nitrofurantoin showed no depression of melting point with an authentic sample and had practically identical ultra-violet and infra-red absorption characteristics.

1-*Aminohydantoin Hydrochloride*

From 2-*Semicarbazido-acetic acid.* 2-Semicarbazido-acetic acid (6·65 g.) was heated for 30 minutes at 100° with a mixture of concentrated hydrochloric acid (25 ml.) and water (10 ml.). The mixture was evaporated to near dryness with water-pump vacuum and absolute ethanol (20 ml.) was added. The white crystalline solid was filtered off, washed well with absolute ethanol and then dried to yield 1-aminohydantoin hydrochloride (6·5 g.; 86 per cent) m.p. 198 to 200° (decomp.) (Traube and Hoffa give 203° (decomp.)). Found: equiv. wt. 1. Aqueous NaOH to methyl red; 151. 2. Sodium methoxide in benzene/methanol; 75·3. Required: 1. 151·5. 2. 75·8.

From 1-*Benzylideneaminohydantoin.* A mixture of 1-benzylideneaminohydantoin (20·3 g.), concentrated hydrochloric acid (250 ml.) and water (250 ml.) was distilled until the distillate was free from benzaldehyde and then evaporated to near dryness under reduced pressure. Absolute ethanol (50 ml.) was added and the crystalline white solid filtered off, washed with ethanol and dried to give 1-aminohydantoin hydrochloride (13·3 g.; 88 per cent), m.p. 199 to 201° (decomp.).

1-*Aminohydantoin.* Sodium bicarbonate (5·55 g.) was added to a solution of 1-aminohydantoin hydrochloride (10·0 g.) in water (28 ml.). The resultant solution was cooled to 4° when colourless prisms separated, were filtered off, washed with a little water and then dried at 60° *in vacuo* to give 1-aminohydantoin (5·0 g.; 65·6 per cent), m.p. 195°. (Uota and others give 193° and Carrara and others 195 to 196°.) Found: equiv. wt., sodium methoxide in benzene/methanol 117. Required: equiv. wt. 115.

A mixture of 1-aminohydantoin hydrochloride (15·1 g.), sodium methoxide (5·4 g.) and absolute ethanol (200 ml.) was refluxed for 15 minutes and then filtered to remove sodium chloride. From the filtrate crystallised a colourless solid as rhombic prisms was filtered off, washed with ethanol and dried at 60° *in vacuo* to give 1-aminohydantoin (8·85 g.; 77 per cent), m.p. 194 to 195°.

The author thanks Dr. A. H. Beckett for help and advice and Mr. A. H. J. Cross and Mr. T. H. Watts for carrying out the infra-red absorption measurements.

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After the Author presented the paper there was a DISCUSSION.

A LIGHT-SCATTERING STUDY OF LYSOLECITHIN SOLS

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Sols of four samples of lysolecithin have been studied by means of a light-scattering apparatus. The results of a large number of measurements have been analysed statistically. They indicate that the mean molecular weight of the micelles in the sols is 92,400, the experimental error in this estimate being 7 per cent.

Light-scattering measurements can be used to provide information about the size and shape of macromolecules, a method we have applied to the further studies of the physical chemistry of phosphatide sols.

The theoretical foundations of light-scattering phenomena were laid by Rayleigh in 1871[1]. Since Debye's[2,3] recent development of the theory the method has made a large contribution to the understanding of biological substances, high polymers and other macromolecules.

The apparatus constructed in our laboratory is based on that described by Hughes, Johnson and Ottewill[4]; it was calibrated with Ludox (a silica sol) and several organic solvents. The apparatus which is shown in plan, in Figure 1, was then tested by examining aqueous sols of some fractionated proteins and non-aqueous sols of high polymers; all gave molecular weights in agreement with values obtained by other workers using this technique. The instrument was found to be suitable for molecular weight determinations in the range 5,000 to 500,000.

Before commencing a series of light-scattering experiments on phosphatide sols we have examined the reproducibility of determinations of the molecular weight of lysolecithin by making a large number of light-scattering measurements with aqueous sols of four different preparations of this substance.

Experimental

Four different samples of lysolecithin (A, B, C and D) were prepared by the action of viper venom on hen egg lecithin. Aqueous sols of this substance were obtained as previously described[5] and centrifuged at 8,300 *g*. Before the light-scattering measurements were made each sol was filtered through a fine sintered glass frit (1 μ) under a pressure of 10 cm. of mercury, to remove traces of dust.

The sol was transferred to a rectangular glass cell (5 × 5 × 1 cm.^{3}) and placed in a thermostat jacket in the path of a beam of parallel light of wavelength 4,358 Å. The light was scattered in all directions by the micelles in the sol and the intensity of scattering at 90° to the incident beam was measured by means of an 11-stage photomultiplier tube connected directly to a mirror galvanometer. The symmetry of the light scattered about the 90° angle was also examined, all the scattered intensities being related to those obtained with a standard lead glass block.