Intramolecular Ring Opening in 3-Aminoalkyl Hydantoins

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Certain hydantoins substituted in the 3-position with aminoalkyl groups have been found to undergo hydrolytic ring-opening under very mild conditions. The effects of varying the side chain have been studied and an intramolecular mechanism is suggested.

During the preparation of a series of 3-aminoalkyl-1-(5-nitrofurfurylideneamino)hydantoins (1), an unexpected hydrolytic ring-opening of some of the compounds under very mild conditions occurred. Investigation has shown that the side-chain amino group, when properly located, participates intramolecularly. This paper describes the conditions under which this reaction takes place and the products that are formed.

It was found that the hydantoin ring in 3-(3-dimethylaminopropyl)-1-(5-nitrofurfurylideneamino)hydantoin (**1**) opens when the compound is shaken in water at room temperature. The reaction is complete in 2-3 hours, giving a high yield of the zwitterionic 5-dimethylaminopropyl-3-(5-nitrofurfurylideneamino)hydantoic acid (**2**). Compound **2** was characterized by elemental analysis, by its salt-like solubility characteristics and melting point, and by its infrared and ultraviolet absorption spectra, which are different from those of **1**.

Treatment of **2** with methanolic hydrogen chloride at room temperature gave the ester **3**. Heating **2** with dilute hydrochloric acid closed the hydantoin ring, regenerating the hydrochloride of **1**.

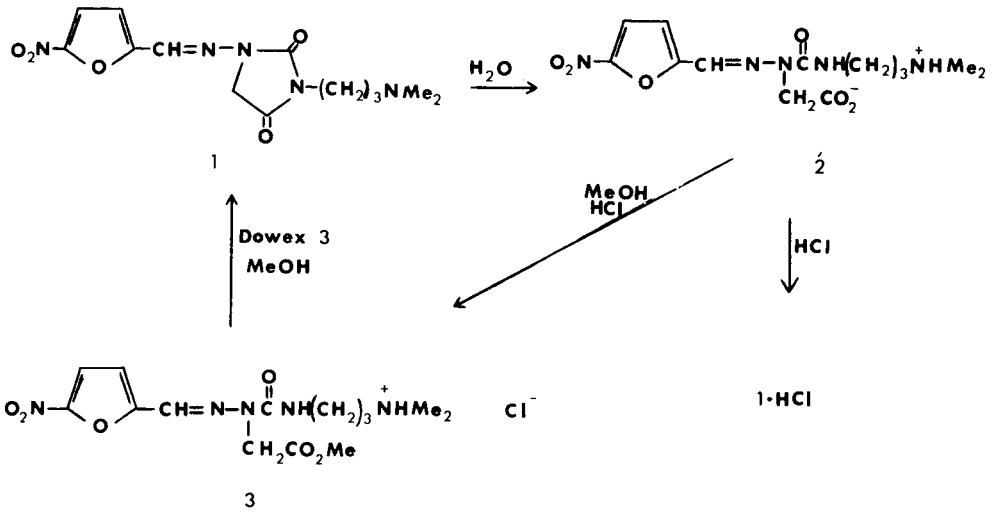
Although the conversion of hydantoins to hydantoic acids in basic medium and the reverse in acidic medium is well-known (2), this facile ring-opening in water is unusual. It can be interpreted as a nucleophilic attack by the terminal nitrogen atom on the more positive carbonyl carbon atom, accompanied by shifting of electrons as shown. Attack by a water molecule on intermediate **5** then gives the final product.

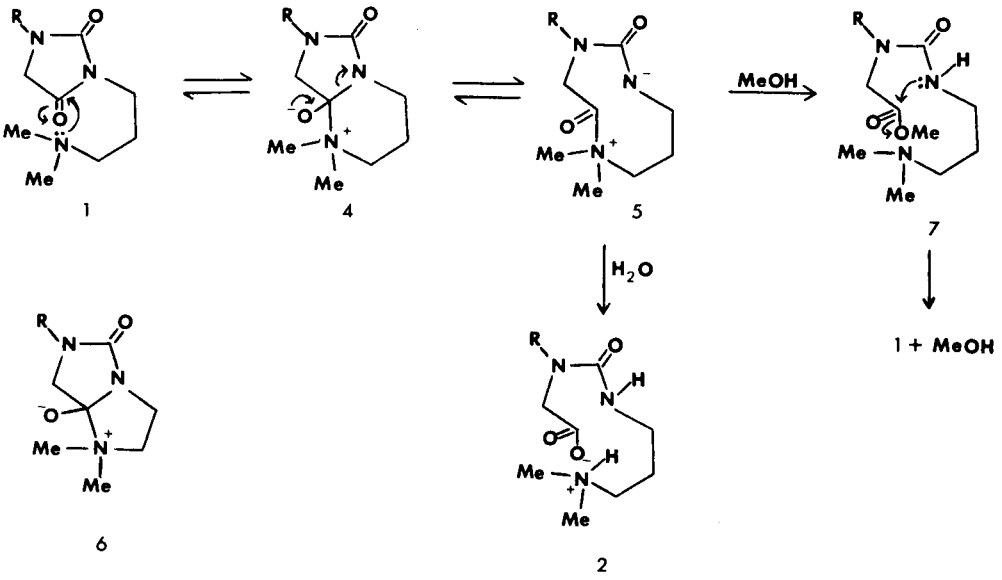
Evidence for intramolecular catalysis rather than general base catalysis was provided by: (a) substitution of bulkier groups on the terminal nitrogen and (b) variation in length of the carbon chain. Treatment of the sterically hindered diisopropylamino analog of **1** with water for 20 hours resulted in 80% recovery of pure starting material. The infrared spectrum of the remainder indicated that it was a mixture of hydantoic acid and unchanged hydantoin.

When the length of the carbon chain was increased to five methylene groups, so that the intermediate analogous to **4** would require the formation of an eight-membered ring, no discernible hydrolysis occurred on shaking with water. In this case the position of the nitrogen atom is not favorable for attack on the carbonyl carbon atom.

The analog of **1** with the carbon chain shortened to two methylene groups was also prepared. This compound showed about the same reactivity as **1** toward water, as expected. Hydrolysis was complete in 2 hours, resulting in a high yield of the hydantoic acid. Here the proximity of the nitrogen atom is favorable for formation of a 5-membered ring intermediate **6**.

Compound **1** was also subjected to methanolysis to learn whether the free base of ester **3** could be obtained by attack of a methanol molecule on intermediate **5**; no reaction occurred and **1** was recovered quantitatively. This observation may be rationalized in the following way. If the intermediate **5** did form and react with methanol, the product **7** presents another opportunity for internal reaction. Another nitrogen atom also is in position for nucleophilic attack on the ester carbonyl carbon atom, displacing methoxide ion and returning to **1**. In support of this hypothesis, compound **3** (the hydrochloride of **7**) was neutralized in dry methanol solution by means of a weakly basic anion exchange resin (Dowex 3). After removal of the methanol, the infrared absorption spectrum of the residue was identical with that of **1**, showing that ring closure of **7** had occurred rapidly and completely. It is entirely reasonable that this reaction does not occur in the case of the free acid **2** because zwitterion formation can take place and is the preferred process.





EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded as mineral oil mulls and ultraviolet spectra as aqueous solutions.

5-(3-Dimethylaminopropyl)-3-(5-nitrofurfurylideneamino)hydantoic Acid (**2**).

A solution of 11.5 ml. (0.17 mole) of ammonium hydroxide in 50 ml. of water was added in 5 minutes to a solution of 62 g. (0.17 mole) of 3-(3-dimethylaminopropyl)-1-(5-nitrofurfurylideneamino)hydantoin hydrochloride (**1**) in 2 l. of water with rapid stirring. After stirring for an additional 5 minutes, the mixture was filtered and the precipitate was washed with cold water, suspended in 2-propanol, again filtered, washed with ether, and air-dried, giving 45 g. (81%) of crude free base. Recrystallization from 2-propanol gave 32 g. (59%) of yellow crystalline **1**, m.p. 153-155° dec.; ir 5.65, 5.85 μ; uv 265, 365 nm.

Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.43; H, 5.52; N, 21.59.

A suspension of 5 g. (0.15 mole) of **1** in 600 ml. of water was shaken at room temperature for 3 hours. The clear solution was concentrated to dryness *in vacuo*. The residue was suspended in a little water, filtered, and recrystallized from ethanol-water to give 3.1 g. (61%) of **2** as yellow crystals, m.p. 235-238° dec.; ir 5.96, 6.20 μ; uv 275, 390 nm.

Anal. Calcd. for $C_{13}H_{19}N_5O_6$: C, 45.74; H, 5.61; N, 20.52. Found: C, 45.59; H, 5.63; N, 20.49.

Methyl 5-Dimethylaminopropyl-3-(5-nitrofurfurylideneamino)hydantoate Hydrochloride (**3**).

A solution of 11.1 g. of **2** in 500 ml. of methanol saturated with dry hydrogen chloride was kept at room temperature for 20 hours, protected from moisture by a Drierite tube, then concentrated *in vacuo* to a residue, keeping the temperature below 40°. A solution of the residue in 500 ml. of methanol was concentrated

in vacuo to *ca.* 40 ml. to remove excess hydrogen chloride, and then cooled in ice. The crystalline product was filtered, washed with methanol-ether (1:1), and dried at 60° to give 10.3 g. (81%) of **3**. Recrystallization from methanol-ether gave a 75% recovery, m.p. 152-153°.

Anal. Calcd. for $C_{14}H_{22}ClN_5O_6$: C, 42.91; H, 5.66; N, 17.88. Found: C, 42.67; H, 5.88; N, 17.68.

Reconversion of **2** to **1**·Hydrochloride.

A solution of 0.50 g. of **2** in 20 ml. of 4 *N* hydrochloric acid was heated under reflux for 0.5 hour. Most of the water was distilled *in vacuo*, several volumes of ethanol was added, and the mixture was chilled thoroughly. Filtration, washing and drying gave 0.32 g. of **1**·Hydrochloride, identified by its ir spectrum.

Reconversion of **3** to **1**.

A solution of 0.50 g. of **3** in 25 ml. of dry methanol was poured through an 8 x 100 mm column of Dowex 3, 20-50 mesh, hydroxide form, prepared in dry methanol. Evaporation of the effluent to dryness *in vacuo* gave 0.40 g. of **1**, identified by its ir spectrum.

3-(2-Dimethylaminoethyl)-1-(5-nitrofurfurylideneamino)hydantoin.

This compound was prepared from its hydrochloride (1) in the same manner as described above for **1**; m.p. 140-141°.

Anal. Calcd. for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.65. Found: C, 46.36; H, 4.97; N, 22.59.

5-(2-Dimethylaminoethyl)-3-(5-nitrofurfurylideneamino)hydantoic Acid.

This compound was prepared from the corresponding hydantoin by the same procedure as **2**, m.p. 156-157° dec.

Anal. Calcd. for $C_{12}H_{17}N_5O_6 \cdot H_2O$: C, 41.74; H, 5.55; N, 20.28. Found: C, 42.04; H, 5.54; N, 20.00.

The presence of water was confirmed by differential thermal analysis.

Attempted Hydrolysis of 3-(3-diisopropylaminopropyl)-1-(5-nitrofurfurylideneamino)hydantoin.

The hydrochloride (1.00 g.) of this compound (1) was converted to its free base by the procedure described above for the dimethylamino compound. The free base was then shaken in water for 20 hours and the undissolved material was filtered and dried; 0.63 g. of unchanged hydantoin was recovered.

Evaporation of the filtrate to dryness *in vacuo* gave 0.25 g. of material whose ir spectrum showed the presence of both hydantoin and hydantoic acid.

Attempted Hydrolysis of 3-(5-Dimethylaminopentyl)-1-(5-nitrofurfurylideneamino)hydantoin.

The hydrochloride (0.79 g.) of this compound (1) was converted to is free base as described above for **1**. This free base (0.66 g.) was shaken in water for 17 hours, the brown solution was filtered to remove a trace of insoluble material, and the filtrate was concentrated to dryness *in vacuo*. The ir spectrum of this residue (0.58 g.) was identical with that of the free base.

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REFERENCES

(1) C. F. Spencer, J. G. Michels, G. C. Wright and C. N. Yu, *J. Med. Chem.*, in press.

(2) E. Ware, *Chem. Rev.*, **46**, 403 (1950).