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The Aminobarbituric Acid−Hydantoin Rearrangement

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A general synthesis protocol for the generation of tri- and tetrasubstituted 5-carbamoylhydantoins is described. Starting from barbituric acids and following bromination and reaction with primary amines, 5-aminobarbituric acids **3a**−**s** and **8** were prepared. Compounds **3** and **8** were subjected to different conditions of a base-catalyzed rearrangement reaction to yield the 1,5,5-trisubstituted hydantoins **4a**−**s** and the 1,3,5,5-tetrasubstituted hydantoin **5c**, respectively. Alkylation of **4a**−**s** afforded 1,3,5,5-tetrasubstituted hydantoins **5a**−**h**. Mechanisms that explain the transformation of corresponding aminobarbituric acids to hydantoins **4a**−**s** and **5c** were discussed in terms of the formation of ring-opened intermediates. Aminobarbituric acids **3a**−**s** unsubstituted at position 3 underwent a ring contraction via intermediate isocyanates which were trapped by the amino function. A different mechanism involving a carbamate intermediate was concluded for conversion of the 1,3,5,5-tetrasubstituted aminobarbituric acid **8**.

Introduction

Hydantoins have long been the focus of attention as a ubiquitous moiety incorporated into compounds with numerous biological activities and therapeutic applications,[1,2] e.g., as anticonvulsants,[3] antiarrhythmics,[4] antidiabetics,[5] serotonin and fibrinogen receptor antagonists.[6] Moreover, a class of tetrasubstituted hydantoins were reported as antagonists of leukocyte cell adhesion acting as allosteric inhibitors of the protein−protein interaction.[7] Some bioactive natural products were found which contain a hydantoin or related moiety, such as hydantocidins from *Streptomyces hygroscopicus*[8] and aplysinopsins isolated from marine organisms.[9]

Small, substituted heterocyclic compounds play an important role in the development of biologically active substances by offering a high structural diversity. Among such heterocycles, particularly the hydantoin scaffold opens the possibility of different kinds and degrees of substitution. A variety of combinatorial approaches have been described by which pharmacophoric groups were attached to such a relatively rigid scaffold.[10−12] Therefore, the chemistry of multiple substituted hydantoins has newly attracted much interest, and traditional approaches have been combined with recently developed strategies. General accesses to 5-mono- and 5,5-disubstituted hydantoins were provided early by Read synthesis and by Bucherer−Bergs method. The former comprised the reaction of amino acids and cyanate salts and the latter the condensation of carbonyl compounds with potassium cyanide and ammonium carbonate.[1,13] The condensation of α-dicarbonyl compounds with ureas

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represented another classical methodology that involved a step similar to the benzilic acid rearrangement.[1,14]

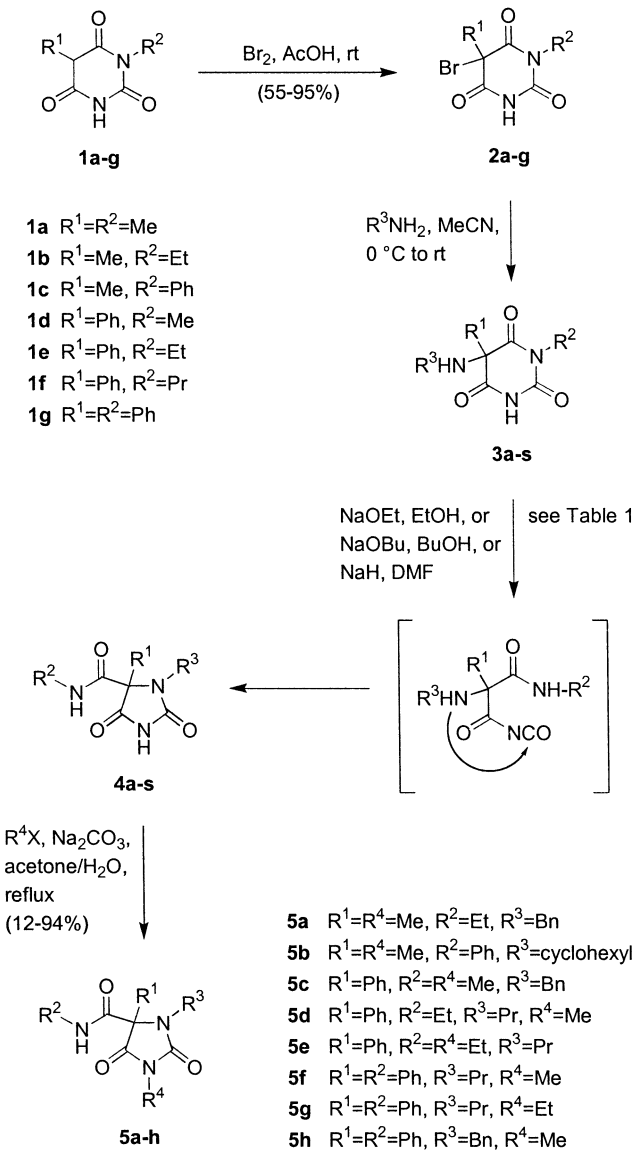
Hydantoins were prepared by acid-catalyzed cyclization of ureido acids obtained from reactions of amino acids or amino nitriles with alkyl, aryl, or chlorosulfonyl isocyanates, respectively.[1,15] This type of cyclization has widely been used in combinatorial chemistry,[11] and modifications have been applied. For example, *N*,*N*-disubstituted hydantoins have been synthesized by a route that involved condensation with aromatic aldehydes and reduction *prior* to urea formation to introduce substituents at position N-1 of the final products.[12]

1,3,5,5-Tetrasubstituted hydantoins were accessible by 1,3-dipolar cycloaddition reactions of 1-oxa-4-azabutadienes with aryl isocyanates.[16,17] The reaction of ureas with dimethyl acetylenedicarboxylate afforded 5-carbomethoxymethylidenehydantoins.[18] A one-pot multicomponent reaction was developed to prepare hydantoins from aldehydes, carbon monoxide, and ureas employing palladium catalysis.[19] Lately, 1,3,5-trisubstituted hydantoins were made available using a novel application of the Ugi five-component condensation.[20]

In a previous report, it was shown that 5-NH_2-substituted barbituric acids undergo a ring contraction to give 5,5-disubstituted hydantoins.[21] This transformation was accomplished by treating the barbituric acids with sodium ethoxide in ethanol. Alkaline hydrolysis of barbituric acids have been investigated frequently. The reaction center was found to be that carbonyl carbon close to the undissociated nitrogen (e.g., 1-methylbarbituric acids dissociated at N-3 and attacked at C-6). Nucleophilic attack resulted in ring opening and irreversible decarboxylation of the malonuric acids formed. 1,3-Dialkyl substitution shifted the ring cleavage to the N−C-2 bonds.[22,23] It stands to reason that alcoholysis of barbituric acids under nonaqueous conditions was rarely examined, since these were the usual conditions of their preparation. However, the usage of alkoxide prevents any decarboxylation and might allow for alternative ring closure reactions, other than the recyclization to the parent barbituric acids. Herein we present a novel application of this concept by converting 5-aminobarbituric acids with alkali alkoxide to hydantoins.

It was the priority objective of the present study to prepare 1,5-substituted barbituric acids with an additional substituted amino group at position 5 and to investigate their conversion to hydantoins. As anticipated, such aminobarbituric acids **3** (Scheme 1) represent suitable substrates for a rearrangement reaction to 1,5,5-trisubstituted hydantoins **4**. A fourth substituent might then easily be introduced at position 3 to furnish tetrasubstituted hydantoins. Furthermore, the mechanism of the rearrangement should be elucidated.

SCHEME 1



Results and Discussion

The synthetic route to 5-aminobarbituric acids **3** is shown in Scheme 1. 1,5-Disubstituted barbituric acids **1a**−**g** were brominated at position 5 using bromine in acetic acid. The resulting bromobarbituric acids **2** were reacted with various primary amines to obtain **3a**−**s** (Table 1) as the first representatives of this type of trisubstituted aminobarbituric acids. The nucleophilic substitution reactions were performed with 2 equiv of the amine and acetonitrile as the suitable solvent. After dilution with water, the products were isolated by extraction with ethyl acetate. This procedure allowed the

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TABLE 1. Preparation of Aminobarbituric Acids 3 and Rearrangement to Hydantoins 4

entry	R^1	R^2	R^3	**3** (yield, %)	**4**	conditions[a]	yield, %
1	Me	Me	*i*-Pr	**3a** (71)[b]	**4a**	B	36[b]
2						C	30[b]
3	Me	Me	Bn	**3b** (82)[c]	**4b**	B	43[c]
4						E	21[b]
5	Me	Me	cyclohexyl	**3c** (60)[b]	**4c**	B	56[c]
6	Me	Et	Pr	**3d** (68)[c]	**4d**	B	17[b]
7	Me	Et	*i*-Pr	**3e** (81)[b]	**4e**	B	16[b]
8						C	28[b]
9	Me	Et	Bn	**3f** (66)[b]	**4f**	B	81[c]
10	Me	Et	cyclohexyl	**3g** (92)[c]	**4g**	B	36[b]
11	Me	Ph	Bn	**3h** (59)[b]	**4h**	A	28[c]
12	Me	Ph	cyclohexyl	**3i** (74)[b]	**4i**	A	35[b]
13						D	56[c]
14	Ph	Me	Pr	**3k** (70)[c]	**4k**	B	66[c]
15	Ph	Me	Bn	**3l** (55)[b]	**4l**	B	38[b]
16	Ph	Et	Pr	**3m** (92)[c]	**4m**	B	58[c]
17						C	15[c]
18	Ph	Et	Bn	**3n** (51)[b]	**4n**	B	28[b]
19	Ph	Pr	Bn	**3o** (74)[b]	**4o**	B	38[b]
20	Ph	Ph	Pr	**3p** (72)[b]	**4p**	A	64[c]
21	Ph	Ph	*i*-Pr	**3r** (96)[c]	**4r**	A	28[c]
22	Ph	Ph	Bn	**3s** (67)[b]	**4s**	A	85[b]

[a] All reactions were performed under an argon atmosphere. Conditions A: Reactions were performed for 3 h in refluxing EtOH in the presence of sodium ethoxide (4 equiv, 0.3 M). B: Reactions were performed for 5 h in a sealed tube at 120 °C with EtOH in the presence of sodium ethoxide (4 equiv, 0.8 M). C: Reactions were performed for 5 h in refluxing BuOH in the presence of sodium butoxide (4 equiv, 0.8 M). D: Reactions were performed for 3 h at 78 °C in DMF in the presence of sodium hydride (4 equiv). E: Reactions were performed for 5 h at 78 °C in DMF in the presence of sodium hydride (4 equiv). Refer to the Experimental Section for details. [b] Yields refer to products recrystallized or purified as indicated (Experimental Section). [c] Yields refer to pure crude products.

removal of the corresponding ammonium barbiturates. Such salts had been observed as impurities in certain cases under other workup conditions.

Seventeen aminobarbituric acids **3** were converted to hydantoins **4**, and the ring contraction was examined under different conditions. The transformations of 1-phenyl aminobarbituric acids (**3**, R^2 = Ph) were performed in refluxing ethanol in the presence of 4 equiv of sodium ethoxide (0.3 M) over 3 h (conditions A, Table 1). However, to successfully accomplish the conversions of 1-alkyl aminobarbituric acids (**3**, R^2 = Me, Et, Pr), stronger conditions were needed. These barbituric acids were treated in a closed reaction vessel at 120 °C for 5 h with an 0.8 M solution of sodium ethoxide (4 equiv) in ethanol (conditions B). It was shown exemplarily that ethanol could be replaced by higher-boiling 1-butanol, and thus sodium ethoxide by butoxide, to allow for a reaction process in an open vessel (conditions C). Moreover, the rearrangement was studied in the absence of a nucleophilic coreactant with sodium hydride in DMF at 78 °C (conditions D, E, respectively). Under these conditions, hydantoins **4b** and **4i** were obtained and proved to be identical with the corresponding products obtained with sodium ethoxide.

As expected, 1,5,5-trisubstituted hydantoins could be alkylated at the only remaining position 3. This was shown for the reactions of several hydantoins **4** with methyl iodide or ethyl bromide. The tetrasubstituted hydantoins **5a**−**h** are outlined in Scheme 1.

Constitution of the products **4** and **5** was unambiguously elucidated as 5-carbamoyl hydantoins, which are ultimately distinguishable from corresponding aminobarbituric acids on the basis of spectral data. ^{13}C NMR spectra of 5-carbamoyl hydantoins showed three distinct carbonyl signals at 155−157 ppm (C-2), 163−167 ppm (exocyclic CO), and 170−174 (C-4), the first and the last being characteristic of the hydantoin scaffold. In contrast, the first carbonyl resonance of aminobarbituric acids **3** appeared at 150 ppm (C-2), and the ^{13}C NMR shifts of the two other carbonyl carbons (C-4, C-6) occurred close together at 170−173 ppm.[24] Depending on the nature of R^1, C-5 signals of hydantoins **4** and **5** were observed either between 69 and 71 ppm for alkyl, or between 75 and 77 ppm for phenyl substitution. These values lay downfield compared to those of the aminobarbituric acids at 62−64 ppm and 71−72 ppm, respectively. According to ^1H NMR data for compounds **4** and **5**, the residue R^2 was determined as part of the exocyclic carboxamide moiety. The spectra showed characteristic splitting patterns for the side-chain NH and the attached methyl or methylene protons. Compared to 5-benzylaminobarbituric acids, 1-benzylhydantoins showed clearly different chemical shifts of their diastereotopic benzylic protons.

We have analyzed the mass spectra of all aminobarbituric acids and hydantoins prepared. Fragmentation of aminobarbituric acids was not uniform but depended on the amino residue introduced at position 5.[25−28] For 5-carbamoyl hydantoins, the elimination of R^2NCO was the significant fragmentation[29,34] accompanied by further decay that included the substituent at position 1.[30−33]

Aminobarbituric acids **3** and hydantoins **4** could easily be detected by a color reaction using cobalt(II) nitrate/piperidine in methanol to give a violet complex.[23,35] As expected in the cases of tetrasubstituted hydantoins **5**, the reaction was negative.[36]

(24) For ^{13}C NMR data of barbituric acids, see: (a) De Meester, P.; Jovanovic, M. V.; Chu, S. S. C.; Biehl, E. R. *J. Heterocycl. Chem.* **1986**, *23*, 337−341. (b) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246−2254.

(25) MS fragmentation of 5-isopropylaminobarbituric acids (**3**, R^3 = *i*-Pr): ($M^+ - CH_3$), ($M^+ - C_3H_7N$). Relative intensities are noted in the Experimental Section.

(26) MS fragmentation of 5-benzylaminobarbituric acids (**3**, R^3 = Bn; **8**): ($M^+ - C_7H_7N$), 106 ($C_7H_8N^+$). Relative intensities are noted in the Experimental Section.

(27) MS fragmentation of 5-cyclohexylaminobarbituric acids (**3**, R^3 = cyclohexyl): (M^+ − HCNO), 98 ($C_6H_{12}N^+$). Relative intensities are noted in the Experimental Section.

(28) MS fragmentation of 5-propylaminobarbituric acids (**3**, R^3 = Pr): ($M^+ - C_2H_5$). Relative intensities are noted in the Experimental Section.

(29) MS fragmentation of hydantoins **4**: ($M^+ - R^2NCO$). Relative intensities are noted in the Experimental Section.

(30) MS fragmentation of 1-isopropylhydantoins (**4**, R^3 = *i*-Pr): ($M^+ - R^2NCO - C_3H_6$). Relative intensities are noted in the Experimental Section.

(31) MS fragmentation of 1-benzylhydantoins (**4**, **5**, R^3 = Bn): ($M^+ - R^2NCO - C_7H_7$), 91 ($C_7H_7^+$). Relative intensities are noted in the Experimental Section.

(32) MS fragmentation of 1-cyclohexylhydantoins (**4**, **5**, R^3 = cyclohexyl): ($M^+ - R^2NCO - C_6H_{10}$). Relative intensities are noted in the Experimental Section.

(33) MS fragmentation of 1-propylhydantoins (**4**, **5**; R^3 = Pr): ($M^+ - R^2NCO - C_3H_6$). Relative intensities are noted in the Experimental Section.

(34) This has also been reported for a few 5-carbamoylhydantoins known so far: Zanotti, G.; Pinnen, F. *J. Heterocycl. Chem.* **1981**, *18*, 1629−1633. See also refs 16, 17, 21.

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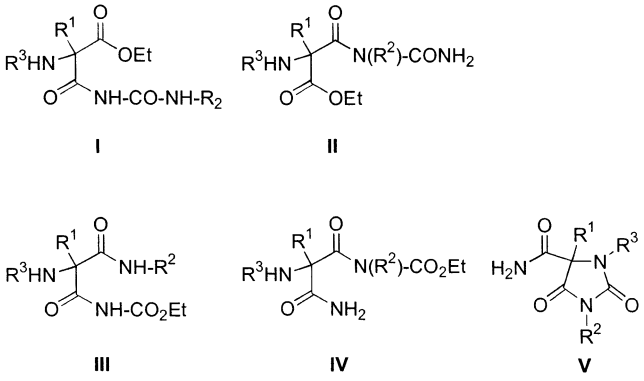
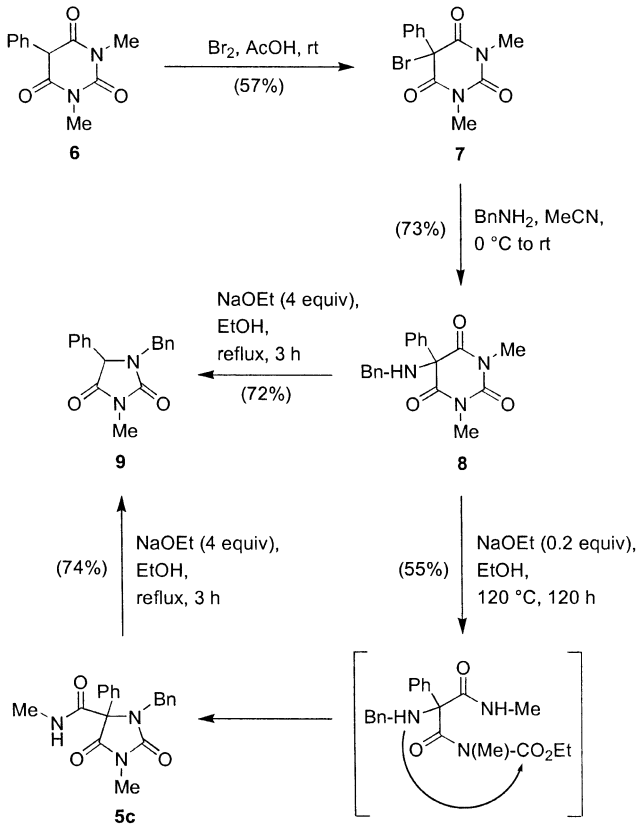
The aminobarbituric acid−hydantoin rearrangement could be envisaged to follow two different mechanisms. One possible mechanism involved the addition of the nucleophile, ring opening, and ring closure (ANRORC-type reaction).[37] Ring cleavage might result from a nucleophilic attack of ethoxide (or butoxide) at one carbonyl carbon of substrates **3**. With such a nucleophilic displacement being operative in the rearrangement, intermediates **I**−**IV** had to be considered. As it has been shown for the alkaline hydrolysis of 1,5,5-trisubstituted barbiturates,[23,38] carbon C-6 should preferably be attacked. However, the corresponding ester intermediates **I** might recyclize to **3** or undergo an intermolecular reaction but could not form the hydantoins **4**. This is also true for ester intermediates **II** which might result from an attack of ethoxide at C-4. Nucleophilic addition of ethoxide at C-2 and subsequent cleavage of either the 1,2-bond or the 2,3-bond might afford carbamate intermediates **III** and **IV**. Both of them are capable to generate 5-carbamoyl hydantoins by ring closure reactions. The possible products of these ring transformations are **4** and **V**, respectively. At least for 1-alkyl-substituted aminobarbituric acids **3,** intermediates **IV** and thus products **V** should be considered. However, in the course of our investigations on ethoxide-promoted conversions of **3**, hydantoins **V** were not isolated. The major products were always compounds **4** which could surely be distinguished from **V** by means of ^{1}H NMR. These findings indicated that the ANRORC-type reaction was not operative in the conversion of aminobarbituric acids **3** to hydantoins **4**.



Alternatively, the formation of hydantoins **4** followed an elimination−addition mechanism, known from E1cB processes in acyl transfer reactions.[39−41] According to this elimination−addition mechanism, an initial deprotonation of the aminobarbituric acids **3** was followed by the ring-opening elimination of the carboxamide moiety. Thereby, an intermediate isocyanate[42] was formed as shown in Scheme 1. Intramolecular addition of the amino group completed the rearrangement.

SCHEME 2



It was considered that the elimination−addition mechanism did not require the presence of ethoxide (or butoxide). Thus, the rearrangement was performed in the absence of any nucleophilic coreactant by hydride-promoted deprotonation of the aminobarbituric acids. Indeed, the respective hydantoins were formed under these conditions (conditions D, E; Table 1) to provide final evidence for the elimination−addition mechanism.

It was intended to study the reaction with a tetrasubstituted aminobarbituric acid as substrate. For that purpose, compound **8** was synthesized by a pathway outlined in Scheme 2. Initially, **8** was treated with sodium ethoxide in ethanol under conditions that have been applied for the conversion of trisubstituted aminobarbituric acids (conditions A, B; Table 1). Unexpectedly, the treatment of **8** with 4 equiv of sodium ethoxide in refluxing ethanol yielded the 1,3,5-trisubstituted hydantoin **9**. Clearly, the formation of **9** from **8** was a result of a consecutive transformation, and the 1,3,5,5-tetrasubstituted hydantoin **5c** was assumed as an intermediate which underwent a decarbamoylation. This was confirmed when **5c** was subjected to the same conditions and compound **9** was reobtained.

Compound **5c** has already been obtained by methylation of the trisubstituted hydantoin **4l** (Scheme 1). It should be noted that **4l** resisted to decarbamoylation under the stronger conditions of its preparation. An easy explanation for the different stability is the neutral

(36) N-Substituted compounds **8** and **9** failed to react with cobalt(II) nitrate, too.

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(42) Intermediate acylisocyanates were generated by phosgenation of the carboxamide moiety of cyclic imines and underwent a trapping reaction to fused hydantoin iminium chlorides: Jaunin, R.; Arnold, W. *Helv. Chim. Acta* **1973**, *56*, 2569−2583. For further examples to prepare fused imidazo derivatives by trapping reactions, see ref 43.

hydantoin unit in **5c** which served as a better leaving group compared to the negatively charged hydantoin moiety in **4l**. It was established that decarbamoylation reactions showed a high sensitivity to the nature of the leaving group.[40] A reaction similar to formation of **9** from **5c** has been described for 1,3,5-triaryl-5-arylcarbamoylhydantoins which lost an aryl isocyanate by thermal elimination.[16] Decarbamoylation reactions have also been reported for other α-acceptor-substituted amides under conditions of pyrolysis[44] or alcoholysis.[45] For the cleavage of the α-acceptor-substituted amide side chain of certain penicillins, an elimination of an isocyanate was suggested.[46]

Next, the reaction of compound **8** with sodium ethoxide in ethanol was studied under various conditions to prepare **5c** and prevent a further degradation to **9** as well (Scheme 2). This was accomplished by using a catalytic amount of ethoxide and an explicitly prolonged reaction time. However, covalent nucleophilic catalysis was necessary for the conversion of **8** since no reaction was observed in the absence of sodium ethoxide, maintaining the other conditions. The ring contraction of the tetrasubstituted aminobarbituric acid **8** had to process in a different way compared to the elimination−addition mechanism discussed above for the trisubstituted aminobarbituric acids **3**. In contrast to **3**, N-3 deprotonation of the substrate **8** is not possible. This led to an enhanced susceptibility of the carbonyl C-2 to nucleophilic attacks. Therefore, an ANRORC-type reaction was proposed for the ring contraction of **8** to produce **5c**. This transformation involved the addition of ethoxide, ring opening to the carbamate intermediate and ring closure by attack of the amino group at the carbamate carbon.

Compound **5c** was concluded to be the intermediate in the conversion of **8** to **9**, and the further degradation of **5c** was a decarbamoylation reaction. On the other hand, aminobarbituric acids could be transformed to corresponding 3-unsubstituted 5-carbamoylhydantoins **4** (Scheme 1) showing a less susceptibility to decarbamoylation. This was also the case for 1,3-unsubstituted 5-carbamoylhydantoins.[21] In an earlier report,[47] 3,5-dimethyl-1-*p*-tolylhydantoin was obtained by the treatment of 1,3,5-trimethyl-5-*p*-tolylaminobarbituric acid with ethanolic potassium hydroxide, and this reaction can now be attributed to a ring transformation−decarbamoylation pathway similar to that outlined in Scheme 2. There are some further examples known for ring contractions of six-membered rings to form hydantoins. Methyl dihydroorotate underwent a methoxide-catalyzed conversion to methyl hydantoin-5-acetate, and dimethyl 2-ureidosuccinate was supposed to be the intermediate; thus, the exocyclic ester moiety served as an electrophile for the recyclization.[48] However, in the aminobarbituric acid−hydantoin rearrangement reported herein, a nucleophilic attack of the exocyclic amino function completed the ring closure. Hydantoins were also prepared from six-membered heterocyclic compounds without an exocyclic moiety being incorporated into the newly formed hydantoin skeleton.[49]

In summary, an efficient synthetic entry to 1,5,5-trisubstituted hydantoins **4** based on a conversion of 1,5,5-trisubstituted barbituric acids **3** has been found. To introduce a 5-amino function into barbituric acids, corresponding bromobarbituric acids **2** can be reacted with primary amines. The nitrogen atom of this functionality is then incorporated into the newly formed five-membered ring. Thus, diversity at position 1 of the hydantoins **4** can be attained using different primary amines (defining R^3). In the course of the ring contraction, expulsion of the cyclic O═C(6)−NR^2 moiety of the aminobarbituric acids generates the exocyclic carbamoyl function of the hydantoin products. The substitution pattern at position 5 of the hydantoins is derived from the ureas (defining R^2) and dialkyl malonates (defining R^1) which can be used as diverse starting materials for the preparation of the corresponding barbituric acids **1**. The present procedure enables regioselective introduction of the three substituents into the hydantoin scaffold of **4**. Moreover, the fourth substituent can easily be attached to the unsubstituted position 3 to obtain hydantoins **5**. It is known that hydantoins undergo alkylation and acylation reactions preferably at position 3,[55] whereas substitution at position 1 (and 5) occurs under more severe conditions.[1,6,48]

The aminobarbituric acid−hydantoin rearrangement follows a deprotonation−elimination−addition mechanism. However, if 1,3-disubstition of the aminobarbituric acids prevents the formation of an intermediate isocyanate, a mechanism involving nucleophilic addition, ring opening, and ring closure becomes operative. The rearrangement will be applied in our ongoing efforts toward the chemistry of multisubstituted heterocyclic compounds.

Experimental Section

Melting points are not corrected. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded in DMSO-d_6, unless otherwise stated. Mass spectra were obtained from using electron impact ionization (EI, 70 eV). Thin-layer chromatography was performed on Merck aluminum sheets, silica gel 60 F_{254}. The solvent system used for TLC was toluene/acetone/methanol (5:3:2). Barbituric acids **1a**−**g**, **6** were prepared following literature procedures.[50−52]

Synthesis of 5-Bromobarbituric Acids 2a−g: General Procedure. A solution of barbituric acid **1** (20 mmol) in acetic

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(55) Mixtures of N-3 and N-1 alkylation products have also been obtained, see ref 13.

acid (300 mL) was stirred at room temperature. A solution of bromine in acetic acid (20% solution, 16 g, 20 mmol) was added dropwise over 20 min. When the addition was completed, the mixture was stirred for 1 h at room temperature, the solvent was evaporated under reduced pressure, and the residue was dissolved in diethyl ether. After addition of charcoal and filtration into the same amount of petroleum ether, the mixture was kept at room temperature in an open dish. The residue after evaporation was suspended in petroleum ether and filtered off.

5-Bromo-1,5-dimethylbarbituric acid (**2a**): yield 78%, mp 119−122 °C, lit.[51,52] mp 94−95 °C, 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.33 (s, 3H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 28.9, 45.1, 148.7, 165.6, 167.1.

5-Bromo-1-ethyl-5-methylbarbituric acid (**2b**): yield 84%, mp 121−123 °C, lit.[51] mp 121−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 2.07 (s, 3H), 3.87−4.01 (m, 2H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 21.5, 37.7, 45.4, 148.4, 165.7, 166.6.

5-Bromo-5-methyl-1-phenylbarbituric acid (**2c**): yield 82%, mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 7.22−7.54 (m, 5H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 45.8, 128.0, 129.6, 129.6, 133.3, 148.3, 165.4, 166.8.

5-Bromo-1-methyl-5-phenylbarbituric acid (**2d**): yield 95%, mp 124−126 °C, lit.[53] mp 128−129 °C; ^{1}H NMR ($CDCl_3$) δ 3.37 (s, 3H), 7.39−7.53 (m, 5H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3, 56.2, 128.3, 128.9, 130.0, 132.6, 148.3, 164.8, 166.4.

5-Bromo-1-ethyl-5-phenylbarbituric Acid (**2e**). The residue obtained after evaporation of acetic acid was suspended in diethyl ether (30 mL), and the product was filtered off: yield 93%, mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 3.99 (q, J = 7.2 Hz, 2H), 7.39−7.52 (m, 5H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 38.2, 56.4, 128.3, 128.8, 129.9, 132.6, 148.0, 164.8, 165.9.

5-Bromo-1-propyl-5-phenylbarbituric acid (**2f**): yield 55%, mp 87−90 °C, ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.64 (sext., J = 7.5 Hz, 2H), 3.89 (t, J = 7.5 Hz, 2H), 7.37−7.53 (m, 5H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0, 20.9, 44.2, 56.3, 128.3, 128.8, 129.9, 132.6, 148.4, 165.0, 166.2.

5-Bromo-1,5-diphenylbarbituric acid (**2g**): yield 89%, mp 157−158 °C, lit.[53] mp 158−158.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.16−7.61 (m, 10H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 128.1, 128.4, 129.0, 129.6, 129.7, 130.1, 132.3, 133.3, 148.1, 164.6, 166.0.

Synthesis of 5-Aminobarbituric Acids 3a−s: General Procedure. A solution of the appropriate amine (20 mmol) in cold anhydrous acetonitrile (5 mL) was added dropwise at 0 °C to a stirred solution of 5-bromobarbituric acid **2** (10 mmol) in cold anhydrous acetonitrile (25 mL). The mixture was stirred at room temperature for 1 h, diluted with brine (250 mL), and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. See Table 1 for yields.

1,5-Dimethyl-5-isopropylaminobarbituric acid (**3a**): mp 131−135 °C (ethyl acetate/petroleum ether); ^{1}H NMR δ 0.84 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H), 1.40 (s, 3H), 2.68 (sept., J = 6.3 Hz, 1H), 3.09 (s, 3H), 11.48 (s, 1H); ^{13}C NMR δ 24.1, 24.1, 26.2, 27.8, 45.6, 62.6, 150.3, 172.2, 173.2; EIMS (m/z)[25] 212 (M^+ − H, 2), 198 (100), 156 (57).

5-Benzylamino-1,5-dimethylbarbituric Acid (**3b**). The crude product was dried and washed with diethyl ether: mp 139−142 °C; ^{1}H NMR δ 1.46 (s, 3H), 3.03 (s, 3H), 3.00−3.10 (m, 1H), 3.44−3.53 (m, 2H), 7.18−7.29 (m, 5H), 11.77 (s, br, 1H); ^{13}C NMR δ 25.1, 27.7, 48.5, 63.6, 126.9, 128.1, 128.2, 140.0, 150.3, 171.5, 172.4; EIMS (m/z)[26] 261 (M^+, 2), 156 (5), 106 (100).

5-Cyclohexylamino-1,5-dimethylbarbituric acid (**3c**): mp 198−199 °C (ethyl acetate/cyclohexane); ^{1}H NMR δ 0.90−1.60 (m, 10H), 1.40 (s, 3H), 2.28−2.44 (m, 2H); 3.09 (s, 3H), 11.47 (s, br, 1H); ^{13}C NMR δ 24.7, 25.5, 34.1, 34.1, 26.2, 27.8, 53.2, 63.3, 150.3, 172.2, 173.1; EIMS (m/z)[27] 253 (M^+, 11), 210 (100), 98 (53).

1-Ethyl-5-methyl-5-propylaminobarbituric acid (**3d**): mp 86−89 °C; ^{1}H NMR δ 0.80 (t, J = 7.4 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H), 1.29−1.36 (m, 2H), 1.40 (s, 3H), 2.21 (t, J = 7.1 Hz, 2H), 3.73 (q, J = 7.1 Hz, 2H), 11.45 (s, 1H); ^{13}C NMR δ 11.8, 13.2, 23.0, 24.4, 36.0, 46.3, 63.5, 149.9, 171.6, 172.1; EIMS (m/z)[28] 226 (M^+ − H, 1), 198 (100).

1-Ethyl-5-isopropylamino-5-methylbarbituric acid (**3e**): mp 96−99 °C (ethyl acetate/petroleum ether); ^{1}H NMR δ 0.84 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H), 1.40 (s, 3H), 2.65−2.73 (m, 1H), 3.74 (q, J = 7.1 Hz, 2H), 11.50 (s, 1H); ^{13}C NMR δ 13.0, 24.0, 26.3, 36.0, 45.5, 62.5, 149.8, 172.1, 172.7; EIMS (m/z)[25] 226 (M^+ − H), 212 (100), 170 (6).

5-Benzylamino-1-ethyl-5-methylbarbituric acid (**3f**): mp 118−120 °C (MeOH/diethyl ether); ^{1}H NMR δ 1.05 (t, J = 7.1 Hz, 3H), 1.46 (s, 3H); 3.01−3.12 (m, 1H), 3.43−3.55 (m, 2H), 3.69 (q, J = 7.1 Hz, 2H), 7.18−7.29 (m, 5H), 11.47 (s, 1H); ^{13}C NMR δ 13.1, 24.9, 35.9, 48.3, 63.5, 126.8, 128.0, 128.1, 139.8, 149.7, 171.3, 171.8; EIMS (m/z)[26] 275 (M^+, 1), 170 (3), 106 (100).

5-Cyclohexylamino-1-ethyl-5-methylbarbituric Acid (**3g**). The crude product was dried and washed with diethyl ether: mp 110−113 °C; ^{1}H NMR δ 0.90−1.65 (m, 10H), 1.06 (t, J = 7.1 Hz, 3H), 1.45 (s, 3H), 2.28−2.42 (m, 1H), 3.74 (q, J = 7.1 Hz, 2H), 11.51 (s, 1H); ^{13}C NMR δ 12.9, 23.8, 24.6, 25.4, 26.2, 30.5, 34.0, 36.0, 53.2, 61.2, 149.8, 172.1, 172.7; EIMS (m/z)[27] 267 (M^+, 4), 24 (52), 98 (100).

5-Benzylamino-5-methyl-1-phenylbarbituric Acid (**3h**). The crude product was purified by column chromatography (eluent, 1:1 ethyl acetate/petroleum ether): mp 86−89 °C; ^{1}H NMR δ 1.60 (s, 3H), 3.17 (s, br, 1H), 3.62 (s, br, 2H), 7.21−7.47 (m, 10H), 11.60 (s, 1H); ^{13}C NMR δ 24.5, 48.4, 64.0, 126.9, 128.2, 128.3, 128.5, 128.9, 129.1, 135.3, 140.2, 150.0, 171.5, 172.1; EIMS (m/z)[26] 322 (M^+ − H), 218 (5), 106 (100).

5-Cyclohexylamino-5-methyl-1-phenylbarbituric acid (**3i**): mp 201−203 °C (toluene); ^{1}H NMR δ 0.96−1.70 (m, 10H), 1.52 (s, 3H), 2.43−2.50 (m, 1H), 7.21−7.26 (m, 2H), 7.40−7.52 (m, 3H), 10.83 (s, br, 1H); ^{13}C NMR δ 24.8, 24.8, 25.5, 25.6, 34.3, 34.3, 53.1, 62.6, 128.6, 129.0, 129.1, 135.2, 150.0, 172.2, 172.9; EIMS (m/z)[27] 315 (M^+, 14), 272 (86), 98 (100).

1-Methyl-5-phenyl-5-propylaminobarbituric acid (**3k**): mp 106−110 °C; ^{1}H NMR δ 0.85 (t, J = 7.4 Hz, 3H), 1.44 (sext., J = 7.4 Hz, 2H), 2.34−2.36 (m, 2H), 2.83 (s, br, 1H), 3.17 (s, 3H), 7.32−7.42 (m, 5H), 11.75 (s, 1H); ^{13}C NMR δ 11.8, 23.2, 28.0, 46.6, 71.3, 126.5, 128.8, 128.9, 138.3, 150.1, 169.7, 171.1; EIMS (m/z)[28] 275 (M^+, 10), 246 (100).

5-Benzylamino-1-methyl-5-phenylbarbituric acid (**3l**): mp 147−148 °C (EtOH/cyclohexane); ^{1}H NMR δ 3.15 (s, 3H), 3.26−3.32 (m, 1H), 3.60−3.69 (m, 2H), 7.20−7.49 (m, 10H), 11.73 (s, 1H); ^{13}C NMR δ 28.1, 48.7, 71.2, 126.5, 126.9, 128.2, 128.2, 128.9, 129.0, 138.2, 140.3, 150.2, 170.0, 171.0; EIMS (m/z)[26] 323 (M^+, 3), 218 (16), 106 (100).

1-Ethyl-5-phenyl-5-propylaminobarbituric acid (**3m**): mp 101−105 °C; ^{1}H NMR δ 0.85 (t, J = 7.3 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H), 1.44 (sext., J = 7.3 Hz, 2H), 2.32−2.39 (m, 2H), 2.86 (s, br, 1H), 3.73−3.87 (m, 2H), 7.33−7.42 (m, 5H), 11.76 (s, 1H); ^{13}C NMR δ 11.8, 13.1, 23.2, 36.4, 46.6, 71.1, 126.3, 128.8, 128.9, 138.2, 149.7, 169.7, 170.6; EIMS (m/z)[28] 289 (M^+, 6), 260 (64).

5-Benzylamino-1-ethyl-5-phenylbarbituric acid (**3n**): mp 133−139 °C (diethyl ether/petroleum ether); ^{1}H NMR δ 1.08 (t, J = 6.9 Hz, 3H), 3.28−3.35 (m, 1H), 3.59−3.85 (m, 4H), 7.20−7.47 (m, 10H), 11.78 (s, 1H); ^{13}C NMR δ 13.1, 36.5, 48.6, 71.1, 126.4, 127.0, 128.2, 128.3, 129.0, 129.1, 138.0, 140.2, 149.7, 169.6, 170.5; EIMS (m/z)[26] 337 (M^+, 1), 232 (6), 106 (100).

5-Benzylamino-5-phenyl-1-propylbarbituric Acid (**3o**). The crude product was purified by column chromatography (eluent, 1:2 ethyl acetate/petroleum ether): mp 112−114 °C; ^{1}H NMR δ 0.77 (t, J = 7.4 Hz, 3H), 1.49 (sext., J = 7.4 Hz, 2H), 3.30−3.33 (m, 1H), 3.59−3.77 (m, 4H), 7.21−7.45 (m, 10H), 11.80 (s, 1H);^{13}C NMR δ 11.1, 20.8, 42.7, 48.6, 71.2, 126.4, 126.9,

128.2, 128.2, 128.9, 129.1, 138.0, 140.2, 150.0, 169.7, 170.6; EIMS (m/z)[26] 351 (M^+, 1), 246 (7), 106 (100).

1,5-Diphenyl-5-propylaminobarbituric acid (**3p**): mp 140−143 °C (diethyl ether); ^{1}H NMR δ 0.87 (t, J = 7.4 Hz, 3H), 1.42−1.50 (m, 2H), 2.44−2.49 (m, 2H), 2.94 (s, br, 1H), 7.25−7.54 (m, 10H), 11.90 (s, 1H); ^{13}C NMR δ 11.8, 23.3, 46.6, 71.6, 126.6, 128.8, 128.9, 129.0, 129.0, 129.2, 134.9, 138.0, 149.8, 169.7, 170.8; EIMS (m/z)[28] 337 (M^+, 15), 308 (100).

1,5-Diphenyl-5-isopropylaminobarbituric acid (**3r**): mp 44−48 °C; ^{1}H NMR δ 1.00 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 2.97 (sept., J = 6.3 Hz, 1H), 7.25−7.56 (m, 10H), 11.97 (s, 1H); ^{13}C NMR δ 24.5, 46.0, 70.9, 126.5, 128.8, 128.8, 128.9, 129.0, 129.3, 134.8, 138.8, 149.7, 170.1, 171.7; EIMS (m/z)[25] 337 (M^+, 12), 322 (100), 280 (34).

5-Benzylamino-1,5-diphenylbarbituric acid (**3s**): mp 205−210 °C (MeOH); ^{1}H NMR δ 3.37−3.40 (t, J = 7.4 Hz, 1H), 3.69−3.79 (m, 2H), 7.22−7.61 (m, 15H), 11.95 (s, 1H); ^{13}C NMR δ 48.7, 71.7, 126.6, 126.9, 128.2, 128.8, 128.9, 129.1, 129.2, 134.9, 137.8, 140.4, 149.8, 169.6, 170.6; EIMS (m/z)[26] 385 (M^+, 4), 280 (11), 106 (100).

Rearrangement of Aminobarbituric Acids 3a−s to Hydantoins 4a−s: General Procedures. **Conditions A**. To a solution of sodium (0.18 g, 8 mmol) in anhydrous ethanol (27 mL) was added aminobarbituric acid **3** (2 mmol). The mixture was refluxed for 3 h under an argon atmosphere. The solution was evaporated to dryness. The residue was taken up with a small amount of water, and insoluble material was removed by filtration. The filtrate was acidified with cold hydrochloric acid (1 N). The precipitate was filtered off and dried under reduced pressure. Working up was done as indicated below. **Conditions B**. To a solution of sodium (0.18 g, 8 mmol) in anhydrous ethanol (10 mL) was added aminobarbituric acid **3** (2 mmol). The mixture was heated in a sealed tube at 120 °C for 5 h under an argon atmosphere. The solution was evaporated to dryness under reduced pressure, the residue was taken up with a small amount of water, and insoluble material was removed by filtration. The filtrate was acidified with cold hydrochloric acid (1 N). The precipitate was filtered off and dried under reduced pressure. Further treatment or recrystallization of the crude product was performed as indicated below. **Conditions C**. To a solution of sodium (0.28 g, 12 mmol) in anhydrous butanol (15 mL) was added aminobarbituric acid **3** (3 mmol). The mixture was refluxed for 5 h under an argon atmosphere. Afterward, most of the solvent was removed under reduced pressure. Water (10 mL) was added, the mixture was stirred for 2 min, kept at room temperature for 30 min, and then the organic layer was removed. The aqueous phase was washed with ethyl acetate (4 × 5 mL), acidified with hydrochloric acid (2 N) to pH 2, and cooled. The precipitate was filtered off and dried under reduced pressure. If no crystallization was observed, the solution was extracted with ethyl acetate (4 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated to dryness. Further treatment or recrystallization was performed as indicated below. **Conditions D.** To a solution of sodium hydride (95%, dry, 0.20 g, 8 mmol) in anhydrous DMF (26.7 mL) was added aminobarbituric acid **3** (2 mmol). The solution was heated at 78 °C for 3 h under an argon atmosphere. The mixture was poured into hydrochloric acid (100 mL, 1 N) and cooled. The product was filtered off, washed with water, and dried under reduced pressure. **Conditions E.** To a solution of sodium hydride (95%, dry, 0.20 g, 8 mmol) in anhydrous DMF (10 mL) was added aminobarbituric acid **3** (2 mmol). The solution was heated at 78 °C for 5 h under an argon atmosphere. The mixture was poured into cold hydrochloric acid (100 mL, 1 N). The product was isolated by extracting the aqueous phase with ethyl acetate (4 × 25 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to dryness. The crude oil was dissolved in diethyl ether. After the solution was cooled for at least 5 days, pure crystals were separated by suction filtration and dried. See Table 1 for methods and yields.

1-Isopropyl-5-methyl-5-methylcarbamoylhydantoin (**4a**): mp 174−176 °C (ethyl acetate/cyclohexane); ^{1}H NMR δ 1.21 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.51 (s, 3H), 2.59 (d, J = 4.5 Hz, 3H), 3.44 (sept., J = 6.9 Hz, 1H), 7.97 (q, J = 4.5 Hz, 1H), 10.83 (s, 1H); ^{13}C NMR δ 18.9, 20.5, 20.8, 26.6, 45.4, 69.7, 155.1, 166.6, 173.0; MS (FAB) 214 (MH^+); EIMS (m/z)[29,30] 156 (100), 114 (99).

1-Benzyl-5-methyl-5-methylcarbamoylhydantoin (**4b**): mp 177−182 °C; ^{1}H NMR δ 1.36 (s, 3H), 2.49 (d, J = 4.6 Hz, 3H), 4.14 (d, J = 15.9 Hz, 1H), 4.60 (d, J = 15.9 Hz, 1H), 7.23−7.34 (m, 5H), 7.99 (q, J = 4.6 Hz, 1H), 11.16 (s, 1H); ^{13}C NMR δ 18.8, 26.7, 44.1, 69.9, 127.5, 128.2, 128.6, 137.9, 156.9, 166.1, 173.1; EIMS (m/z)[29,31] 261(M^+, 5), 204 (35), 113 (8), 91 (100).

1-Cyclohexyl-5-methyl-5-methylcarbamoylhydantoin (**4c**): mp 240−242 °C; ^{1}H NMR δ 1.00−1.77 (m, 10H), 1.53 (s, 3H), 2.58 (d, J = 4.6 Hz, 3H), 2.70−3.05 (m, 1H), 8.01 (q, J = 4.6 Hz, 1H), 10.87 (s, 1H); ^{13}C NMR δ 19.0, 25.1, 25.7, 25.8, 26.6, 30.2, 30.4, 53.4, 69.7, 155.2, 166.7, 173.0; EIMS (m/z)[29,32] 253 (M^+, 4), 196 (100), 114 (88).

5-Ethylcarbamoyl-5-methyl-1-propylhydantoin (**4d**): mp 132−138 °C (MeOH); ^{1}H NMR δ 0.82 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H), 1.50 (s, 3H), 1.43−1.50 (m, 2H), 2.93−3.19 (m, 4H), 8.06 (t, J = 5.4 Hz, 1H), 10.91 (s, 1H); ^{13}C NMR δ 11.4, 14.5, 18.4, 21.8, 34.4, 42.3, 69.4, 156.4, 165.7, 173.0; MS (FAB) 228 (MH^+); EIMS (m/z)[29,33] 156 (100), 114 (16).

5-Ethylcarbamoyl-1-isopropyl-5-methylhydantoin (**4e**). In performing method A, the crude oil was triturated with diethyl ether, and the product was filtered off: mp 183−186 °C (MeOH); ^{1}H NMR δ 0.99 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.51 (s, 3H), 3.00−3.16 (m, 2H), 3.44 (sept., J = 6.8 Hz, 1H), 8.04 (t, J = 5.4 Hz, 1H), 10.81 (s, 1H); ^{13}C NMR δ 15.3, 19.6, 21.2, 21.6, 35.1, 46.1, 70.4, 155.9, 166.6, 173.7; MS (FAB) 228 (MH^+); EIMS (m/z)[52,30] 156 (100), 114 (72).

1-Benzyl-5-ethylcarbamoyl-5-methylhydantoin (**4f**): mp 154−159 °C; ^{1}H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.33 (s, 3H), 2.94−3.00 (m, 2H), 4.10 (d, J = 16.1 Hz, 1H), 4.59 (d, J = 16.1 Hz, 1H), 7.21−7.32 (m, 5H), 8.01−8.04 (t, J = 5.5 Hz, 1H), 11.11 (s, br, 1H); ^{13}C NMR δ 14.4, 18.7, 34.4, 43.9, 69.7, 127.3, 128.0, 128.4, 137.8, 157.0, 165.2, 173.1; EIMS (m/z)[29,31] 275 (M^+, 2), 204 (69), 113 (18), 91 (100).

1-Cyclohexyl-5-ethylcarbamoyl-5-methylhydantoin (**4g**). The crude product was dried, triturated with diethyl ether, and filtered off: mp 168−175 °C; ^{1}H NMR δ 0.98 (t, J = 7.1 Hz, 3H), 1.03−1.96 (m, 10H), 1.50 (s, 3H), 2.95−3.20 (m, 3H), 8.09 (t, J = 5.5 Hz, 1H), 10.85 (s, 1H); ^{13}C NMR δ 14.5, 19.0, 25.1, 25.7, 25.8, 30.3, 30.5, 34.4, 53.5, 69.7, 155.2, 165.9, 173.0; EIMS (m/z)[29,32] 267 (M^+, 4), 196 (83), 114 (100).

1-Benzyl-5-methyl-5-phenylcarbamoylhydantoin (**4h**): mp 63−68 °C; ^{1}H NMR δ 1.52 (s, 3H), 4.34 (d, J = 16.0 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 7.06−7.46 (m, 10H), 9.64 (s, 1H), 11.23 (s, 1H); ^{13}C NMR δ 19.0, 44.0, 70.4, 121.3, 124.4, 127.3, 128.2, 128.4, 128.5, 137.5, 138.0, 156.8, 164.3, 172.6; EIMS (m/z)[29,31] 323 (M^+, 4), 204 (100), 113 (10), 91 (57).

1-Cyclohexyl-5-methyl-5-phenylcarbamoylhydantoin (**4i**): mp 133−137 °C (EtOH/cyclohexane); ^{1}H NMR δ 1.01−1.99 (m, 10H), 1.64 (s, 3H), 3.10−3.17 (m, 1H), 7.07−7.12 (m, 1H), 7.29−7.35 (m, 2H, 3′-H), 7.56−7.61 (m, 2H), 9.81 (s, 1H), 10.98 (s, 1H); ^{13}C NMR δ 19.7, 25.1, 26.6, 25.8, 30.1, 30.7, 53.6, 70.5, 121.1, 124.4, 128.7, 138.2, 155.3, 165.1, 172.6; EIMS (m/z)[29,32] 315 (M^+, 3), 196 (100), 114 (83).

5-Methylcarbamoyl-5-phenyl-1-propylhydantoin (**4k**): mp 200−204 °C; ^{1}H NMR δ 0.62 (t, J = 7.4 Hz, 3H), 1.08−1.29 (m, 2H), 2.67 (d, J = 4.4 Hz, 3H), 3.10−3.25 (m, 2H), 7.22−7.45 (m, 5H), 7.81 (q, J = 4.4 Hz, 1H), 11.25 (s, 1H); ^{13}C NMR δ 11.2, 21.1, 26.8, 43.5, 75.8, 127.9, 128.9, 129.1, 134.8, 156.0, 165.6, 171.6; MS (FAB) 276 (MH^+); EIMS (m/z)[29,33] 218 (100), 176 (13).

1-Benzyl-5-methylcarbamoyl-5-phenylhydantoin (**4l**). The crude product was recrystallized from MeOH/diethyl ether (yield 32%). An analytic sample was obtained from recrystallization from EtOH: mp 182−189 °C; ^{1}H NMR δ 2.45 (d, J =

4.6 Hz, 3H), 4.45 (d, J = 16.3 Hz, 1H), 4.64 (d, J = 16.3 Hz, 1H), 6.97−7.38 (m, 10H), 7.77 (q, J = 4.6 Hz, 1H), 11.38 (s, 1H); ^{13}C NMR δ 26.5, 44.9, 76.1, 126.7, 127.3, 127.9, 128.0, 128.9, 129.0, 134.2, 137.4, 156.5, 165.5, 171.5; EIMS (m/z)[29,31] 323 (M^+, 4), 266 (59), 175 (19), 91 (100).

5-Ethylcarbamoyl-5-phenyl-1-propylhydantoin (**4m**): mp 148−152 °C; ^{1}H NMR δ 0.63 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 1.07−1.31 (m, 2H), 3.11−3.25 (m, 4H), 7.23−7.46 (m, 5H), 7.86 (t, J = 5.7 Hz, 1H), 11.25 (s, 1H); ^{13}C NMR δ 11.2, 14.4, 21.2, 34.6, 43.5, 75.8, 127.9, 128.9, 129.0, 134.8, 156.1, 164.9, 171.7; EIMS (m/z)[29,33] 289 (M^+, 1), 218 (100), 176 (24).

1-Benzyl-5-ethylcarbamoyl-5-phenylhydantoin (**4n**): mp 132−133 °C (ethyl acetate/petroleum ether); ^{1}H NMR δ 0.87 (t, J = 7.3 Hz, 3H), 2.90−3.03 (m, 2H), 4.48 (d, J = 16.2 Hz, 1H), 4.61 (d, J = 16.2 Hz, 1H), 6.97−7.39 (m, 10H), 7.80 (t, J = 5.4 Hz, 1H), 11.33 (s, br, 1H); ^{13}C NMR δ 14.1, 34.5, 44.9, 76.1, 126.7, 127.2, 127.9, 128.0, 128.9, 129.0, 134.4, 137.5, 156.6, 164.7, 171.6; EIMS (m/z)[29,31] 337 (M^+, 5), 266 (79), 175 (24), 91 (100).

1-Benzyl-5-phenyl-5-propylcarbamoylhydantoin (**4o**). The crude oil was triturated with ethyl acetate/petroleum ether, and the product was filtered off: mp 102−105 °C (MeOH); ^{1}H NMR δ 0.75 (t, J = 7.4 Hz, 3H), 1.29−1.36 (m, 2H), 2.82−2.98 (m, 2H), 4.50 (d, J = 16.2 Hz, 1H), 4.59 (d, J = 16.2 Hz, 1H), 6.96−7.40 (m, 10H), 7.78 (t, J = 5.7 Hz, 1H), 11.38 (s, 1H); ^{13}C NMR δ 11.4, 21.9, 41.3, 44.9, 76.3, 126.7, 127.2, 127.9, 128.1, 128.9, 129.0, 134.4, 137.5, 156.5, 164.9, 171.6; EIMS (m/z)[29,31] 351 (M^+, 3), 266 (52), 175 (11), 91 (76).

5-Phenyl-5-phenylcarbamoyl-1-propylhydantoin (**4p**): mp 75−79 °C; ^{1}H NMR δ 0.63 (t, J = 7.4 Hz, 3H), 1.12−1.19 (m, 1H), 1.25−1.34 (m, 1H), 3.21−3.35 (m, 2H), 7.11−7.60 (m, 10H), 9.69 (s, 1H), 11.38 (s, 1H); ^{13}C NMR δ 11.2, 21.2, 43.4, 76.7, 121.4, 124.8, 128.0, 128.7, 129.1, 129.2, 134.5, 137.8, 156.1, 164.2, 171.3; MS (FAB) 338 (MH^+); EIMS (m/z)[29,33] 218 (100), 176 (10).

1-Isopropyl-5-phenyl-5-phenylcarbamoylhydantoin (**4r**): mp 172−174 °C; ^{1}H NMR δ 0.91, (d, J = 6.9 Hz, 3H), 1.41 (d, J = 6.9 Hz, 3H), 3.50 (sept., J = 6.9 Hz, 1H), 7.11−7.62 (m, 10H), 9.54 (s, 1H), 11.37 (s, 1H); ^{13}C NMR δ 20.0, 20.3, 46.8, 77.3, 121.2, 124.7, 128.2, 128.8, 129.1, 129.4, 134.8, 137.7, 154.8, 163.9, 171.7; EIMS (m/z)[29,30] 337 (M^+, 2), 218 (100), 176 (43).

1-Benzyl-5-phenyl-5-phenylcarbamoylhydantoin (**4s**): mp 185−195 °C (EtOH/diethyl ether/cyclohexane); ^{1}H NMR δ 4.39 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 7.02−7.46 (m, 15H), 10.21 (s, 1H). One NH signal did not appear. ^{13}C NMR δ 45.3, 76.3, 120.3, 124.2, 125.1, 127.4, 127.6, 127.6, 128.3, 128.8, 128.8, 136.9, 137.8, 139.3, 165.6. Two carbonyl signals did not appear. MS (FAB) 386 (MH^+); EIMS (m/z)[29,31] 385 (M^+, 2), 266 (97), 175 (17), 91 (100).

1-Benzyl-3,5-dimethyl-5-ethylcarbamoylhydantoin (5a). To a solution of **4f** (0.29 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent, 2:1 ethyl acetate/petroleum ether) to give **5a** as a colorless oil (60 mg, 21%): ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H), 1.37 (s, 3H), 2.91 (s, 3H), 2.92−2.98 (m, 2H), 4.22 (d, J = 16.1 Hz, 1H), 4.59 (d, J = 16.1 Hz, 1H), 7.21−7.31 (m, 5H), 7.98 (t, J = 5.4 Hz, 1H); ^{13}C NMR δ 14.3, 18.5, 25.2, 34.4, 44.2, 68.6, 127.4, 128.0, 128.3, 137.4, 156.5, 164.9, 171.7; EIMS (m/z)[29,31] 289 (M^+, 1), 218 (100), 127 (75), 91 (100).

1-Cyclohexyl-3,5-dimethyl-5-phenylcarbamoylhydantoin (5b). To a solution of **4i** (0.32 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The filtrate was evaporated under reduced pressure. The crude product was recrystallized from ethanol to give **5b** (184 mg, 55%) as colorless crystals: mp 140−141 °C; ^{1}H NMR δ 1.03−2.03 (m, 10H), 1.64 (s, 3H), 2.88 (s, 3H), 3.13−3.20 (m, 1H), 7.08−7.13 (m, 1H), 7.29−7.35 (m, 2H), 7.51−7.57 (m, 2H), 9.76 (s, 1H); ^{13}C NMR δ 19.5, 25.0, 25.1, 25.5, 25.6, 30.3, 30.7, 53.9, 69.4, 121.2, 121.5, 128. 8, 138.1, 154.9, 164.8, 171.3; EIMS (m/z)[29,32] 329 (M^+, 4), 210 (100), 128 (83).

1-Benzyl-3-methyl-5-methylcarbamoyl-5-phenylhydantoin (5c). To a solution of **4l** (0.32 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The filtrate was evaporated under reduced pressure. The crude product was recrystallized from ethanol to give **5c** (120 mg, 35%) as colorless crystals: mp 148−150 °C; ^{1}H NMR δ 2.45 (d, J = 4.6 Hz, 3H), 2.98 (s, 3H), 4.49 (d, J = 16.1 Hz, 1H), 4.72 (d, J = 16.1 Hz, 1H), 6.99−7.40 (m, 10H), 7.88 (q, J = 4.6 Hz, 1H); ^{13}C NMR δ 25.6, 26.7, 45.4, 75.3, 127.1, 127.7, 128.1, 128.4, 129.1, 129.3, 134.2, 137.3, 156.4, 165.4, 170.5; EIMS (m/z)[29,31] 337 (M^+, 1), 280 (100), 189 (25), 91 (35).

5-Ethylcarbamoyl-3-methyl-5-phenyl-1-propylhydantoin (5d). To a solution of **4m** (0.29 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The volume of the solvent was reduced. After cooling, the precipitate was collected and recrystallized from EtOH to give **5d** (35 mg, 12%) as colorless crystals: mp 68−70 °C; ^{1}H NMR δ 0.64 (t, J = 7.4 Hz, 3H), 1.05 (t, J = 7.3 Hz, 3H), 1.09−1.36 (m, 2H), 2.94 (s, 3H), 3.14−3.31 (m, 4H), 7.25−7.45 (m, 5H), 7.92 (t, J = 5.7 Hz, 1H); ^{13}C NMR δ 11.1, 14.4, 21.1, 25.2, 34.7, 43.9, 74.8, 128.1, 128.9, 129.1, 134.5, 155.7, 164.6, 170.4; MS (FAB) 304 (MH^+); EIMS (m/z)[29,33] 232 (100), 190 (11).

3-Ethyl-5-ethylcarbamoyl-5-phenyl-1-propylhydantoin (5e). To a solution of **4m** (0.89 g, 3 mmol) in acetone 90% (135 mL) were added sodium carbonate (0.96 g, 9 mmol) and ethyl bromide (1.96 g, 1.34 mL, 18 mmol). The mixture was refluxed for 3 h and filtered. The filtrate was evaporated to dryness. The crude product was purified by column chromatography (eluent, 5:3 methanol/hexane) to give **5e** (156 mg, 16%) as a white solid: mp 86−88 °C; ^{1}H NMR δ 0.63 (t, J = 7.4 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H), 1.10 (t, J = 7.3 Hz, 3H), 1.10−1.34 (m, 2H), 3.14−3.27 (m, 4H), 3.45−3.51 (m, 2H), 7.22−7.46 (m, 5H), 7.90 (t, J = 5.7 Hz, 1H); ^{13}C NMR δ 11.1, 13.2, 14.4, 21.1, 33.9, 34.6, 43.8, 74.7, 128.0, 129.0, 129.2, 134.5, 155.4, 164.6, 170.1; MS (FAB) 318 (MH^+); EIMS (m/z)[29,33] 246 (100), 204 (5).

3-Methyl-5-phenyl-5-phenylcarbamoyl-1-propylhydantoin (5f). To a solution of **4p** (0.34 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The volume of the solvent was reduced. After cooling, the precipitate was collected by suction filtration to give **5f** (340 mg, 94%) as colorless crystals: mp 160−163 °C; ^{1}H NMR δ 0.67 (t, J = 7.4 Hz, 3H), 1.16−1.19 (m, 1H), 1.25−1.33 (m, 1H), 3.00 (s, 3H), 3.27−3.31 (m, 1H), 3.38−3.44 (m, 1H), 7.14−7.62 (m, 10H), 9.75 (s, 1H); ^{13}C NMR δ 11.2, 21.2, 25.4, 43.8, 75.6, 121.3, 124.8, 128.2, 128.8, 129.0, 129.3, 134.2, 137.8, 155.8, 163.9, 170.1; EIMS (m/z)[29,33] 351 (M^+, 1), 232 (100), 190 (7).

3-Ethyl-5-phenyl-5-phenylcarbamoyl-1-propylhydantoin (5g). To a solution of **4p** (1.01 g, 3 mmol) in acetone 90% (135 mL) were added sodium carbonate (0.96 g, 9 mmol) and ethyl bromide (1.96 g, 1.34 mL, 18 mmol). The mixture was refluxed for 3 h and filtered. The volume of the filtrate was reduced and cooled. The precipitate was filtered off and recrystallized from EtOH to give **5g** (781 mg, 71%) as colorless needles: mp 155−158 °C; ^{1}H NMR δ 0.63 (t, J = 7.3 Hz, 3H), 1.12 (t, J = 7.3 Hz, 3H), 1.08−1.19 (m, 1H), 1.24−1.33 (m, 1H), 3.27−3.39 (m, 2H), 3.48−3.57 (m, 2H), 7.11−7.60 (m, 10H), 9.75 (s, 1H); ^{13}C NMR δ 11.2, 13.2, 21.2, 34.1, 43.7, 75.5, 121.4, 124.8, 128.1, 128.8, 129.2, 129.4, 134.2, 137.8, 155.4, 163.9, 169.8; EIMS (m/z)[29,33] 365 (M^+, 1), 246 (100), 204 (15).

1-Benzyl-3-methyl-5-phenyl-5-phenylcarbamoylhydantoin (5h). To a solution of **4s** (0.41 g, 1 mmol) in acetone 90% (45 mL) were added sodium carbonate (0.21 g, 2 mmol) and

methyl iodide (0.57 g, 0.25 mL, 4 mmol). The mixture was refluxed for 90 min and filtered. The filtrate was evaporated under reduced pressure. The crude product was recrystallized from ethanol to give **5h** (230 mg, 56%) as a colorless solid: mp 64−66 °C; ^{1}H NMR δ 3.02 (s, 3H), 4.59 (d, J = 16.2 Hz, 1H), 4.77 (d, J = 16.2 Hz, 1H), 6.95−7.12 (m, 6H), 7.22−7.45 (m, 9H), 9.65 (s, 1H); ^{13}C NMR δ 25.4, 45.1, 75.7, 121.3, 124.6, 126.7, 127.3, 127.8, 128.2, 128.4, 128.8, 129.1, 133.7, 136.9, 137.4, 156.0, 163.4, 169.9; EIMS (m/z)[29,31] 399 (M^+, 4), 280 (92), 189 (39), 91 (100).

5-Bromo-1,3-dimethyl-5-phenylbarbituric Acid (7). A solution of barbituric acid **6** (3.07 g, 12 mmol) in acetic acid (180 mL) was stirred at room temperature. A solution of bromine in acetic acid (20% solution, 9.6 g, 12 mmol) was added dropwise over 20 min. When the addition was completed, it was stirred for 1 h at room temperature, and the solvent was evaporated under reduced pressure. The residue was diluted with water (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were stirred with charcoal and dried (Na_2SO_4). The filtrate was evaporated to dryness to give **7** (2.41 g, 57%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 6H), 7.36−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.0, 128.1, 128.8, 129.8, 133.4, 149.8, 165.8.

5-Benzylamino-1,3-dimethyl-5-phenylbarbituric Acid (8). A solution of the benzylamine (1.71 g, 1.75 mL, 16 mmol) in cold anhydrous acetonitrile (4 mL) was added dropwise at 0 °C to a stirred solution of **7** (2.60 g, 8 mmol) in cold anhydrous acetonitrile (20 mL). The mixture was stirred at room temperature for 1 h, diluted with brine (50 mL), and extracted with ethyl acetate (4 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The crude product was recrystallized from ethyl acetate to give **8** (1.97 g, 73%) as a white solid: mp 156−157 °C; ^{1}H NMR δ 3.18 (s, 6H), 3.39 (t, J = 7.3 Hz, 1H), 3.64 (d, J = 7.3 Hz, 2H), 7.20−7.46 (m, 10H); ^{13}C NMR δ 29.0, 48.7, 71.2, 126.6, 126.9, 128.2, 128.3, 128.9, 129.0, 138.2, 140.2, 150.7, 170.0; EIMS (m/z)[26] 336 (M^+ − H, 1), 232 (19), 106 (100).

Preparation of 1-Benzyl-3-methyl-5-methylcarbamoyl-5-phenylhydantoin (5c) from 5-Benzylamino-1,3-dimethyl-5-phenylbarbituric Acid (8). To a solution of **8** (0.34 g, 1 mmol) in anhydrous ethanol (12 mL) was added a stock solution of sodium ethoxide in anhydrous ethanol (0.2 M, 1 mL). The mixture was heated in a sealed tube at 120 °C for 120 h under an argon atmosphere. After cooling for a few days, the precipitate was collected by suction filtration and dried to give **5c** as colorless crystals (0.19 g, 55%), which was identical with the material obtained from methylation of **4l**.

Preparation of 1-Benzyl-3-methyl-5-phenylhydantoin (9) from 1-Benzyl-3-methyl-5-methylcarbamoyl-5-phenylhydantoin (5c). To a solution of sodium (0.18 g, 8 mmol) in anhydrous ethanol (26 mL) was added hydantoin **5c** (0.67 g, 2 mmol). The mixture was refluxed for 3 h under an argon atmosphere. The solution was evaporated to dryness, the residue was taken up with a small amount of water and acidified with cold hydrochloric acid (1 N). The precipitate was cooled, filtered off, and dried under reduced pressure to give **9** (0.44 g, 74%) as colorless crystalls: mp 103−105 °C, lit.[54] mp 120−121 °C; ^{1}H NMR δ 2.95 (s, 3H), 3.90 (d, J = 15.8 Hz, 1H), 4.78 (d, J = 15.8 Hz, 1H), 4.98 (s, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR δ 25.0, 44.6, 63.6, 127.6, 127.9, 128.1, 128.6, 129.0, 129.1, 133.5, 136.2, 156.6, 171.4; EIMS (m/z) 280 (M^+, 100), 91 ($C_7H_7^+$, 30).

Preparation of 1-Benzyl-3-methyl-5-phenylhydantoin (9) from 5-Benzylamino-1,3-dimethyl-5-phenylbarbituric Acid (8). Compound **8** (0.67 g, 2 mmol) was reacted with sodium ethoxide using the procedure described above to give **9** (0.43 g, 72%) which was identical with the material obtained from the conversion of **5c** to **9**.

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Supporting Information Available: Assignments to ^{1}H and ^{13}C NMR data, elemental analyses, and figures giving ^{1}H and ^{13}C NMR spectra for compounds **2a**−**g**, **3a**−**s**, **4a**−**s**, **5a**−**h**, **7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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