SYNTHESIS AND NITROSATION OF 3- AND 3,5-SUBSTITUTED HYDANTOINS

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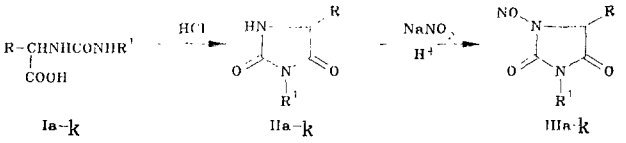
UDC 547.783'495.4.542.953.2.543.422.25

The cyclization of N-alkylated(arylated) α-ureidocarboxylic acids gives a series of 3-mono- and 3,5-disubstituted hydantoins, and nitrosation of the latter yields their nitroso derivatives. The rotational isomerism of 3-(α-naphthyl)hydantoins has been studied by PMR spectroscopy.

The synthesis and several conversions of α-ureidocarboxylic acids were previously studied in [1, 2]. As a continuation of these investigations, we synthesized the series of 3-mono- and 3,5-disubstituted hydantoins IIa-k (Table 1) by dehydration of α-ureidocarboxylic acids Ia-k.



I—III a—d R=H; e—h R=CH_3; i—k R=C_6H_5; a, e, i R^1=C_6H_{13}; b, f, j R^1=C_6H_6; c, g, k R^1=α-$C_{10}H_7$; d, h R^1=β-$C_{10}H_7$

A characteristic feature of the PMR spectra of hydantoins IIa-k is the decrease in the spin—spin coupling constant J_{HCNH} to 1.0-1.5 Hz in comparison to the original ureido acids (J_{HCNH} = 7 Hz), which is due to the planar conformation of the hydantoin ring [3-6], the spin—spin coupling constants of the 3-monosubstituted hydantoins being somewhat smaller (1.0-1.3 Hz) than the 3,5-disubstituted derivatives (1.3-1.5 Hz). When there are identical substituents in position 5, the PMR spectra of 3-phenyl- and 3-(β-naphthyl)hydantoin scarcely differ. The PMR spectra of hydantoins IIc, g, and k are more complex: Doubling of the signals of the methine, methylene, and methyl protons was observed in them. When the samples were heated, reversible averaging of the signals took place due to the slowing of the rotation around the C—N bond coining the heterocyle to the α-naphthyl group. The ratio of the rotamers was ∿1:1 and was not dependent on the temperature. The values of E_a for hydantoins IIg and IIk differ only slightly within the range of accuracy of the measurements and are comparable to the literature data [7-9].

The nitrosation of hydantoins has scarcely been studied, although nitrosohydantoins,

TABLE 1. Characteristics of Hydantoins II and 1-Nitrosohydantoins III

Compound	mp, ℃	Found, %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
IIc	220—222	68,9	4,5	12,4	$C_{13}H_{10}N_2O_2$	69,0	4,5	12,4
IId	201—203	69,1	4,5	12,6	$C_{13}H_{10}N_2O_2$	69,0	4,5	12,4
IIg	177—179	69,9	4,9	11,7	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7
IIh	207—210	70,1	5,2	11,6	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7
IIi	65—67	69,2	7,4	11,0	$C_{15}H_{20}N_2O_2$	69,2	7,7	10,8
IIk	186—188	75,3	4,7	9,1	$C_{19}H_{14}N_2O_2$	75,5	4,7	9,3
IIIc	156—158	61,1	3,6	16,5	$C_{13}H_9N_3O_3$	61,2	3,6	16,5
IId	223—225	60,9	3,7	16,6	$C_{13}H_9N_3O_3$	61,2	3,6	16,5
IIIg	162—164	62,3	4,1	15,7	$C_{14}H_{11}N_3O_3$	62,5	4,1	15,6
IIIi	84—86	62,1	6,5	14,6	$C_{15}H_{19}N_3O_3$	62,3	6,6	14,5
IIIj	159—161	64,0	4,2	14,8	$C_{15}H_{11}N_3O_3$	64,1	3,9	14,8

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1404-1406, October, 1984. Original article submitted March 6, 1984; revision submitted April 19, 1984.

 0009-3122/84/2010-1160$08.50

TABLE 2. PMR spectra of Hydantoins IIa-k and 1-Nitrosohydantoins IIIa-k

Compound	CH, ppm	J_{HCNH}, Hz	5-CH_3
IIa	3,85, s	1,2	—
IIb	4,02, s	1,3	—
IIc	4,28, AB system	1,2	—
IId	4,13, s	1,0	—
IIe	4,08, q	1,4	1,26, d
IIf	4,17, q	1,4	1,34, d
IIg	4,28, q; 4,40, q	1,4; 1,3	1,40, d; 1,47, d
IIh	4,33, q	1,35	1,45, d
IIi	5,14, s	1,4	—
IIj	5,34, s	1,5	—
IIk	5,51, s, 5,67, s	1,4; 1,2	—
IIIa	4,30, s	—	—
IIIb	4,43, s	—	—
IIIc	4,64, AB system	—	—
IIId	4,49, s	—	—
IIIe	4,69, q	—	1,39, d
IIIf	4,72, q	—	1,42, d
IIIg	4,91, q; 5,06, q	—	1,61, d; 1,68, d
IIIh	4,76, q	—	1,49, d
IIIi	5,65, s	—	—
IIIj	5,81, s	—	—
IIIk	5,89, s, 6,06, s	—	—

being cyclic analogs of N-nitrosoureas, are of interest as biologically active substances [10, 11]. We obtained the series of 1-nitrosohydantoins IIIa-k (Table 1). The PMR spectra of the latter revealed downfield shifts of the signals of the methylene and methine protons of the heterocycle in comparison to hydantoins IIa-k, which amounted to 0.3-0.4 (for the 1-nitroso-3-substituted hydantoins) and 0.4-0.65 ppm (for the 1-nitroso-3,5-disubstituted hydantoins). Hydantoins IIIc, g, and k are also mixtures of two rotamers; however, it was difficult to determine the coalescence temperatures for them due to their denitrosation upon heating.

EXPERIMENTAL

The PMR spectra were recorded in acetone-d_6 on an Hitachi R-22 spectrometer (90 MHz) with HMDS as an internal reference. The calculations were performed on a BÉSM-6 computer. The rotation frequency τ^{-1} at a particular temperature was determined by means of a complete analysis of the shape of the spectral line with the use of an optimization program. The dependence of τ^{-1} on 1/T had a linear character, and the activation barriers to rotation were calculated according to the Arrhenius equation (for IIg: $T_{coalesc} = 113 \pm 1°C$, $E_a \approx 88.5 \pm 5.0$ kJ/mole: for IIk: $T_{coalesc} = 141.5 \pm 1°C$, $E_a = 96.3 \pm 6.3$ kJ/mole).

Compounds IIa, IIIa, IIe, and IIIe were synthesized according to [1], compounds IIb, IIIb, IIf, and IIIf were synthesized according to [2], compound IIIh was synthesized according to [10], and IIj was synthesized according to [12].

General Method for the Synthesis of Hydantoins IIa-k. A 20-mmole portion of the respective α-ureidocarboxylic acid (Ia-k) [1, 2] is boiled with 60 ml of conc. HCl for 2 h. Upon cooling the reaction mixture is diluted with water, and the precipitate of the hydantoin (70-88% yield) is filtered out and recrystallized from aqueous ethanol (1:1).

General Method for the Synthesis of 1-Nitrosohydantoins IIIa-k. A 10-mmole portion of hydantoin IIa-k is dissolved in a mixture of 10 ml of glacial acetic acid and 50 ml of acetic anhydride and given an addition of 50 mmole of sodium nitrite at 0°C over the course of 1.5 h with stirring, the stirring is continued for 2.5 h, the mixture is poured into 100 ml of ice water, and the precipitate (50-93% yield) is filtered out, washed with 50 ml of water, and dried in a vacuum over phosphorus anhydride.

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE JUNCTION POSITIONS. 11.* SYNTHESIS OF DIBENZO[b,e]-1,4-DIAZABICYCLO[2.2.2]OCTADIENE

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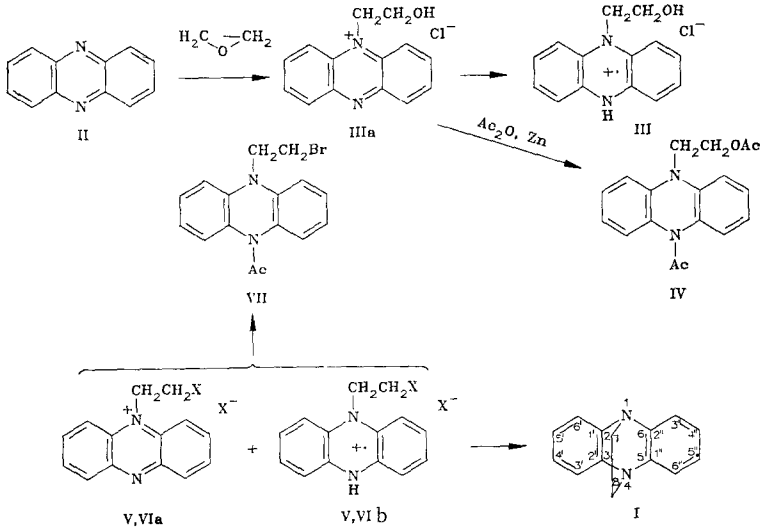
UDC 547.864:543.27

The reaction of ethylene oxide with phenazine followed by treatment with HCl gives N-(2-hydroxyethyl)phenazinium chloride, which yields N-2-haloethyl derivatives of phenazine in a mixture with products of their one-electron reduction when the hydroxyl group is exchanged for a halogen. Heating of these mixtures in the presence of sodium borohydride results in intramolecular cyclization with the formation of a new heterocyclic system, viz., dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene.

Continuing the investigation of the influence of the annelation of benzene rings on the properties of diazabicycloalkenes with nitrogen atoms in the junction positions [1], we carried out the synthesis of a new heterocyclic system, viz., dibenzo[b,e]-1,4-diazabicyclo [2.2.2]-octadiene (5,10-ethano-5,10-hydrophenazine) (I). The synthesis was carried out with phenazine (II) as the starting compound according to the following scheme:



Va, b X=Br; VIa,b X=Cl

*For report 10 see [1].

Novosibirsk Institute of Organic Chemistry, Academy of Sciences of the USSR, Siberian Branch, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1407-1411, October, 1984. Original article submitted March 29, 1984.

 0009-3122/84/2010-1162$08.50