Chemistry of Heterocyclic Compounds, Vol. 41, No. 11, 2005

SYNTHESES BASED ON NATURAL α-AMINO ACIDS. CYANOETHYLATION OF 3-SUBSTITUTED 5-METHYL-2-THIOHYDANTOINS

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Starting from α-alanine, the C- and S-cyanoethyl derivatives of 5-methyl-3-phenyl(allyl)-2-thiohydantoins have been synthesized. It was shown that the products of hydrolysis of C-cyanoethyl derivatives, 5-methyl-3-phenyl(allyl)-(β-carboxyethyl)-2-thiohydantoins, are formed in addition.

Keywords: acrylonitrile, α-alanine, 2-thiohydantoin, cyanoethylation.

The wide distribution of hydantoins in nature and the presence among them of active regulators of plant growth [1, 2] has defined the problem of the present work, *viz*. the synthesis of analogs of these compounds, substituted 2-thiohydantoins. The closeness of the latter in structure to compounds isolated from a whole family of plant sources [3], guarantees the safety of their practical use, since degrading enzyme systems exist in plants preventing an excessive accumulation of both the natural compounds and their analogs [4].

To solve this problem we have studied the cyanoethylation of the known 5-methyl-3-phenyl(allyl)-2-thiohydantoins **1a,b** obtained previously by the interaction of α-alanine with phenyl and allyl isothiocyanates [5].

When using 2-thiohydantoins in synthesis it is necessary to consider the readily occurring isomeric and tautomeric conversions of these molecules. Its thioamide fragment S=C–NH_2 is a tautomeric triad, in which the equilibrium is displaced in the direction of the NH form [6]. The latter circumstance determines the ambiguity of the reactivity of anions of compounds of type **1**. Investigations showed that predominantly N-alkyl derivatives are formed on alkylation of 2-thioxoimidazolidines with hard reagents in polar solvents [7, 8]. At the same time the predominant formation of S-alkylation products is observed in reactions with soft alkylating agents in solvents of low polarity [9]. In other words, in polar solvents the reaction is directed to the center of basicity, the N atom of the triad [10-12]. In nonpolar solvents a determining role is played by the polarizability of the reaction center, which is greater at the sulfur atom than at the nitrogen. It is also known that on alkylation of imidazolidinethiones the alkylation begins at the more nucleophilic sulfur atom [13], but alkylation of N-aminoazolinethiones occurs exclusively at the sulfur atom [14] and in this respect they do not differ from other heterocyclic thiones [15]. In compounds **1a,b** there is an additional reaction center at the $C_{(5)}$ atom, at which alkylation may also occur. Because of this there is undoubted interest in clarifying the direction of alkylation of thiohydantoins **1a,b**.

By cyanoethylating compounds **1a,b** with an excess of acrylonitrile in alcohohol in the presence of a catalytic amount of sodium hydroxide at room temperature, a mixture was obtained in both cases consisting mainly of products of C and S alkylation **2a,b** to **4a,b** (overall yield up to 90%, see Table 1), among which the double alkylation products **3a,b** (yields up to 50%) predominated.

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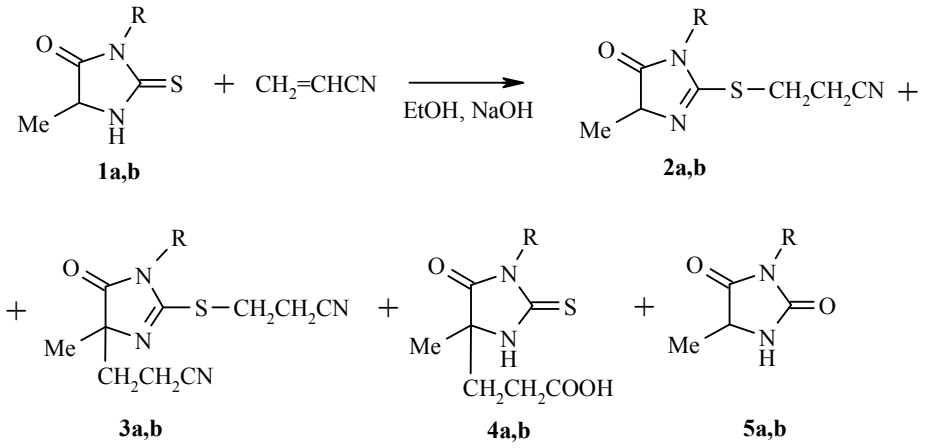

1-5 a R = Ph, **b** R = $CH_2CH{=}CH_2$

The possibility of the reaction occurring at two reactive centers has been described in the literature [16]. It should be mentioned that in the case of products of alkylation only at the carbon atom no corresponding 5-(β-cyanoethyl) derivatives were obtained, but β-substituted propionic acids **4a,b** are formed as a result of hydrolysis of the latter. Small quantities (up to 10%) of hydantoins **5a,b,** products of hydrolytic desulfurization of the initial compounds **1a,b**, were also isolated from the reaction mixtures. The formation of hydantoins on alkylating thiohydantoins in the presence of alkali has been noted previously [3].

The results obtained indicate that under the conditions studied cyanoethylation occurs at two reactive centers of the molecule of compounds **1a,b**, the sulfur atom and the $C_{(5)}$ atom of the ring.

The structures of compounds **2a,b** to **5a,b** were confirmed by data of elemental analysis (Table 1) and IR, UV, and NMR spectra (Table 2).

Absorption bands are present in the IR spectra for C=O (**2a,b** to **5a,b**), C≡N (**2a,b** and **3a,b**), NH (**4a,b**, **5a,b**), and OH (**4a,b**) groups. The disposition of the absorption bands in the UV spectra of compounds **2a,b** and **3a,b** are characteristic of S-alkylation products [17]. In the ^{1}H NMR spectra of compounds **3a,b** and **4a,b** the singlet form for the signal of the 5-CH_3 group indicates the absence of proton from position 5, and consequently the presence in this position of a second substituent. The integrated intensity, shape, and position of the proton

TABLE 1. Characteristics of the Synthesized Compounds **2-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	R_f	M^+	Yield, %
		C	H	N				
2a	$C_{13}H_{13}N_3OS$	60.98 / 61.66	5.05 / 5.14	15.9 / 16.6	200-201 (benzene)	0.27	259	15
2b	$C_{10}H_{13}N_3OS$	58.39 / 58.81	5.19 / 5.83	17.19 / 18.83	Oil	0.18	223	25
3a	$C_{16}H_{16}N_4OS$	60.95 / 61.54	5.01 / 5.13	17.05 / 17.95	140-41 (alcohol)	0.60	312	50
3b	$C_{13}H_{16}N_4OS$	56.01 / 56.32	5.09 / 5.80	19.98 / 20.29	Oil	0.57	276	45
4a	$C_{13}H_{14}N_2O_3S$	55.98 / 56.12	4.98 / 5.04	9.97 / 10.07	220-221 (alcohol)	0.45	278	25
4b	$C_{10}H_{14}N_2O_3S$	49.02 / 49.59	5.04 / 5.79	10.98 / 11.57	Oil	0.35	242	22
5a	$C_{10}H_{10}N_2O_2$	62.98 / 63.16	5.01 / 5.29	14.01 / 14.74	160-162 (alcohol)	0.75	190	10
5b	$C_7H_{10}N_2O_2$	54.01 / 54.55	7.05 / 7.79	17.98 / 18.18	95-97 (alcohol)	0.27	154	8

TABLE 2. Spectral Characteristics of Compounds **2a,b** to **4a,b**

Com-pound*	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
2a	2253 (C≡N), 1749 (C=O), 3050 (s, C_6H_5)	1.68 (3H, d, *J* = 7.5, CH_3); 2.40 (2H, t, *J* = 7.0, CH_2-α); 7.00-7.50 (5H, m, Ar)
2b	2248 (C≡N), 1765 (C=O)	1.75 (3H, d, *J* = 7.0, CH_3); 2.42 (2H, *J* = 7.2, CH_2-α); 3.85 (2H, t, *J* = 7.2, CH_2-β); 4.12 (1H, qd, *J* = 7.0, *J* = 1.0, CH cycle); 4.20 (2H, dt, *J* = 5.6, *J* = 1.0, N–CH_2); 5.03 (2H, t, *J* = 10.4, =CH_2); 5.75 (1H, ddt, *J* = 15.5, *J* = 10.4, *J* = 5.6, =CH–)
3a	2252 (C≡N), 1750 (C=O), 3050 (s, C_6H_5)	1.60 (3H, s, CH_3); 2.40 (4H, m, CH_2-α); 3.12 (2H, t, *J* = 7.0, CH_2-α); 3.80 (1H, dt, *J* = 13.0, *J* = 7.0, CH_2-β); 4.05 (1H, dt, *J* = 13.0, *J* = 7.0, CH_2-β); 7.13-7.55 (5H, m, Ar)
3b	2251 (C≡N), 1750 (C=O)	1.70 (3H, s, CH_3); 2.42 (4H, m, CH_2-α); 3.12 (2H, t, *J* = 7.0, CH_2-α); 3.80 (1H, dt, *J* = 13.0, *J* = 7.0, CH_2-β); 4.05 (1H, dt, *J* = 13.0, *J* = 7.0, CH_2-β); 4.20 (2H, dt, *J* = 5.6, *J* = 1.0, N–CH_2); 5.03 (2H, t, *J* = 10.4, =CH_2); 5.75 (1H, ddt, *J* = 15.5, *J* = 10.4, *J* = 5.6, =CH–)
4a	3753 (NH), 3480 (OH), 1755 (C=O), 1630 (C=O), 1080, 1210 (C=S), 3050 (s, C_6H_5)	1.68 (3H, s, CH_3); 2.32 (1H, m, CH_2-α); 2.48 (1H, CH_2-α); 2.55 (1H, m, CH_2-β); 2.62 (1H, m, CH_2-β); 7.45 (2H, m, Ar); 7.65 (3H, m, Ar)
4b	3750 (NH), 3480 (OH), 1765 (C=O), 1630 (C=O), 1080-1210 (C=S)	1.75 (3H, s, CH_3); 2.32 (1H, m, CH_2-α); 2.48 (1H, m, CH_2-α); 2.55 (1H, m, CH_2-β); 2.62 (1H, m, CH_2-β); 4.40 (2H, dt, *J* = 5.6, *J* = 1.0, N–CH_2); 5.03 (2H, t, *J* = 10.4, =CH_2); 5.75 (1H, ddt, *J* = 15.5, *J* = 10.4, *J* = 5.6, =CH–)

* UV spectrum, λ_{max}, nm (log ε): **2a** 246 (3.21), 268 (4.01); **2b** 248 (3.25), 278 (4.01); **3a** 246 (3.25), 278 (4.01); **3b** 248 (3.17), 178 (4.01).

signals of the substituents for all compounds **2-5** were in agreement with the proposed structures. There were peaks in the mass spectra of compounds **2-4** of medium intensity for the molecular ions, the character of the breakdown of which confirms the structures of these products.

EXPERIMENTAL

The IR spectra (KBr disks) were obtained on a Perkin-Elmer 2000 Fourier spectrometer, the mass spectra on a MX 1303 instrument, and the ^1H NMR spectra on a INM 4-100 instrument in $CDCl_3$, internal standard was HMDS (δ 0.05 ppm). The UV spectra of solutions in ethanol were taken on a Hitachi EPS 3T spectrometer. The purity of the products and the progress of reactions was checked by TLC on Silufol UV 254 plates in the system methanol–benzene, visualizing with iodine vapor.

Interaction of 3-R-5-methyl-2-thiohydantoins 1a,b with Acrylonitrile. Thiohydantoin **1a** (1.03 g, 0.005 mol) and a catalytic quantity of sodium hydroxide were added to a solution of acrylonitrile (1.98 g, 0.015 mole) in alcohol (20 ml). The mixture obtained was stirred for 1 h forming a transparent solution, from which a copious white precipitate began to precipitate. The reaction mixture was maintained at room temperature for 1 h, the solid was filtered off, and recrystallized from alcohol. 5-(β-Cyanoethyl)-2-(β-cyanoethylthio)-5-methyl-3-phenylhydantoin (**3a**) (0.78 g) was obtained. The filtrate was evaporated, the residue, oily crystals of a light yellow color, was treated with 5% sodium hydroxide solution, and further (0.1 g) product **3a** was filtered off. The alkaline mother liquor was neutralized with dilute hydrochloric acid, the precipitated solid was filtered off, and recrystallized from benzene. 2-(β-Cyanoethylthio)-5-methyl-3-

phenylhydantoin (**2a**) (0.19 g) was obtained. The neutral mother liquor was acidified with dilute hydrochloric acid to pH 3, the precipitated solid was filtered off, and recrystallized from alcohol. 5-(β-Carboxyethyl)-5-methyl-3-phenyl-2-thiohydantoin (**4a**) (0.35 g) was obtained. The mother liquor after isolating compound **4a** was acidified with hydrochloric acid to pH 1, the precipitated solid was recrystallized from alcohol (to remove contamination by starting material **1a**), and 5-methyl-3-phenylhydantoin (**5a**) (0.095 g) was obtained.

The interaction of acrylonitrile with thiohydantoin **1b** was carried out analogously and 3-allyl-2-(β-cyanoethylthio)-5-methylhydantoin (**2b**), 3-allyl-5-(β-cyanoethyl)-2-(β-cyanoethylthio)-5-methylhydantoin (**3b**), 3-allyl-5-(β-carboxyethyl)-5-methyl-2-thiohydantoin (**4b**), and 3-allyl-5-methylhydantoin (**5b**) respectively, were isolated.

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