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Received December 28 1984

The N_1 - and N_3 -cyanohydantoins, a new series of derivatives, were prepared by reaction of the parent hydantoin with a base and a cyanogen halide. Analysis of ir, pmr, and mass spectral data allowed the assignment of ring position-3 to the cyano group in derivatives IIa,b of 1,3-unsubstituted hydantoins. 3-Cyanohydantoins can transfer the cyano substituent to strong nucleophiles *via* an addition-elimination process.

J. Heterocyclic Chem., **22**, 1025 (1985).

Hydantoins (I) represent an important group of compounds from chemical, biological and industrial viewpoints [2,3]. We describe here the preparation and properties of a new series of derivatives, the *N*-cyanohydantoins; two types can be distinguished, N_1 -cyano (III) and N_3 -cyano (II) derivatives.

The general preparative method consists in the reaction of the hydantoin (I), a base and a cyanogen halide (Scheme). The use of cyanogen chloride or bromide led to similar results; however, we preferred the solid bromo to the gas chloro derivative because of the easier preparation, handling and dosage.

In procedure A, the hydantoin is treated in *N,N*-dimethylformamide solution with the strong base sodium hydride which ionizes either the N_3 -H or N_1 -H groups (pK_a ca. 9 and ≥ 14 respectively) [4]; the resulting sodium derivative then reacts with the cyanogen halide. In general, cyanohydantoins of types II and III were successfully prepared by this procedure (Table 1). However, procedure A was inefficient for 3-cyano compounds bearing an acyl group (IIg,h) or a hydrogen atom (IIa,b) at position-1; poor yields

of crude products with a low content of the cyano derivative (ir) were obtained.

In procedure B, the hydantoin and the cyanogen halide react in the presence of a weak base (triethylamine) which ionizes N_3 -H only. As expected, it was ineffective to prepare N_1 -cyano-3,5,5-trisubstituted hydantoins, *e.g.* IIIa. This procedure gave good results for 3-cyano-1,5,5-trisubstituted hydantoins and, more importantly, it furnished 3-cyano derivatives of N_1 -unsubstituted (IIa,b) or N_1 -acylhydantoins (IIg,h), thus complementing procedure A.

The *N*-cyanohydantoins are stable compounds, *e.g.* IIc and IId remained unaltered (mp and ir) after being stored without special precautions for more than one year.

The localization of the cyano group at N_3 in compounds IIa,b is demonstrated by spectroscopic methods. The usual test to distinguish derivatives with an acidic N_3 -H or a neutral N_1 -H group by the increase of the solubility in water by alkali [5] cannot be used here owing to decomposition of IIa,b in aqueous alkaline medium.

The δ value (IIa,b, 6.85 and 6.53 respectively) of the NH pmr signal appears in the range given for the N_1 -H group (δ 6.4-6.9) [6]. Further support comes from the analysis of the ir and ms discussed below. This conclusion shows that the reaction with a pseudohalogen (cyanogen halide) in basic medium introduces a cyano group at position-3 of the hydantoin ring; that group does not rearrange to position-1 in contrast to a halogen atom [7]. Consequently, 1-cyanohydantoins unsubstituted at N_3 cannot be obtained by the procedures A and B.

The ir stretching band of the cyano group in compounds II and III is strong (Table 2). The frequency varies according to the ring position of the cyano group: in the range 2275-2255 for 3-cyano (IIc-h) and 2255-2245 cm^{-1} for 1-cyano (IIIa-d) derivatives. On this basis, position-3 is assigned to the cyano substituent in compounds IIa,b.

Hydantoins show two main ir bands in the carbonyl region at about 1770 and 1700 cm^{-1} ; the assignments were difficult and controversial. Some authors [8] ascribed one band to each individual carbonyl group. Later, those bands were regarded as ν_s and ν_{as} absorptions respectively of a coupling system, either intramolecular ($C_2=O$ and

Scheme

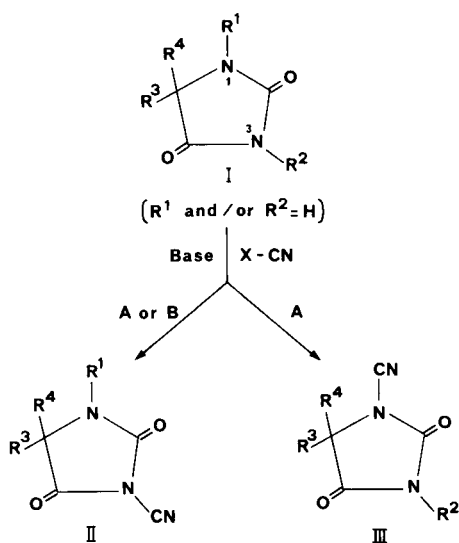


Table 1
Preparation of *N*-Cyanohydantoins

Compound	R ¹	R ²	R ³	R ⁴	Procedure	Yield (%)	Mp [a] (°C)	Calcd. % (Found)		
								C	H	N
IIa	H		Me	<i>i</i> -Bu	B	82	108-109	55.37 (55.58)	6.71 (6.90)	21.53 (21.73)
IIb	H		Et	Et	B	50	107-108	53.03 (53.13)	6.12 (5.93)	23.19 (23.28)
IIc	Me		Me	Me	A	79	158-159	50.29 (50.55)	5.43 (5.55)	25.14 (25.14)
IIId	Me		Me	Et	A	74	119-120	53.03 (53.23)	6.12 (6.40)	23.19 (23.28)
IIe	Me		(CH ₂) ₅		A	79	163-164	57.96 (58.04)	6.32 (6.58)	20.28 (20.38)
IIIf	Me		Me	Ph	A	62	131-132	62.87 (62.90)	4.84 (4.72)	18.33 (18.23)
IIg	MeCO		Me	Me	B	62	154-155	49.23 (49.26)	4.65 (4.89)	21.53 (21.28)
IIh	PhCO		Me	Me	B	56	203-204	60.70 (60.73)	4.31 (4.48)	16.33 (16.14)
IIIa		Me	Me	Me	A	45	102-103	50.29 (50.28)	5.43 (5.63)	25.14 (25.23)
IIIb		Me	Me	Et	A	41	67-68	53.03 (53.25)	6.12 (6.22)	23.19 (23.22)
IIIc		Me	(CH ₂) ₅		A	43	99-100	57.96 (57.78)	6.32 (6.44)	20.28 (20.13)
IIId		Me	Me	Ph	A	55	136-137	62.87 (62.83)	4.84 (4.84)	18.33 (18.05)

[a] Crystallization solvent: alcohol 50% for IIa,b; alcohol for IIc-g, IIIa,b and IIId; methyl ethyl ketone with 5% water v/v for IIh; diisopropyl ether for IIIc.

C₄=O) [9] or intermolecular (two C₂=O) [10] in dimers formed in solid phase or solution by hydrogen bonding through an NH group; the C₄=O band of dimers is overlapped by the very strong ν_{as} band. We have compared the carbonyl absorptions (nujol) of 5,5-pentamethylenehydantoin (I, R¹ = R² = H, R³R⁴ = (CH₂)₅, 1773 and 1730 cm⁻¹) with those of its *N*₁-methyl (1763 and 1710), *N*₃-methyl (1775 and 1707) and *N*₁,*N*₃-dimethyl (1770 and 1713) derivatives. All show the same absorption pattern with small differences in band positions. Analogous similitude appears among 5-methyl-5-phenylhydantoin (I, R¹ = R² = H, R³ = Me, R⁴ = Ph) and its three *N*-alkylated derivatives. The *N*₁,*N*₃-disubstituted compounds cannot form dimers so the above results suggest that intermolecular coupling has little significance on the hydantoin carbonyl absorption.

The introduction of a cyano group at positions *N*₃ or *N*₁ of hydantoins bearing a substituent at *N*₁ or *N*₃ respectively (IIc-h and IIIa-d) increases the frequency of the ν_c and ν_{as} carbonyl bands (Table 2). The former appears at 1825-1800 cm⁻¹ in both types of cyano compounds. Comparing with the parent hydantoin, the *N*₃-cyano substituent causes a ν_{as} shift (30-70 cm⁻¹) larger than that of the

*N*₁-cyano (10-25 cm⁻¹); the resulting ranges for the ν_{as} band are 1785-1745 and 1730-1720 cm⁻¹ respectively. On this basis position-3 is assigned to the cyano group in IIa,b.

Electron-impact fragmentations of some representative 1- and 3-cyanohydantoins (Table 2) follow essentially the same patterns found earlier [11] for the corresponding parent hydantoins. Ring position-3 for the cyano group in IIb is established by the peak at *m/z* 56 (90%, Et-C≡N⁺H, with the *N*₁-H group of the molecule) which also appears (52%) in the fragmentation of the parent 5,5-diethylhydantoin.

The halogen of *N*-bromo and *N*-chlorohydantoins reacts as a positive or a neutral species in heterolytic or homolytic reactions respectively; the iodo analogues participate in the former type of reactions only [12]. We have found that the cyano substituent of 3-cyanohydantoins can be transferred as a positive group to strong nucleophiles (Table 3) *via* a reaction visualized as an addition-elimination process by analogy with related transfer reactions [13]. With *N*₁-anions of 3,5,5-trisubstituted hydantoins as nucleophiles, the corresponding 1-cyano derivatives were obtained in fair yields; these could not be improved by varying reaction temperature and time, with tetrahydrofuran as

Table 2
Spectral Data of N-Cyanohydantoins

Compound	IR (nujol) cm^{-1} [a]			PMR δ [b]	MS m/z (Relative intensity %) [c]
	$\text{C}\equiv\text{N}$	$\nu_{\text{C}}-\text{C}=\text{O}$	$\nu_{\text{ar}}-\text{C}=\text{O}$		
IIa	2260	1810 (1770)	1760 [d] (1715)	0.68-1.17 (m, 6H, gem-Me ₂), 1.52 (s, 3H, 5-Me), 1.65-2.15 (m, 3H, CH ₂ CH), 6.85 (s, 1H, NH)	
IIb	2265	1815 (1730)	1775 [d] (1710)	0.97 (t, 6H, two Me), 1.60-2.18 (m, 4H, two CH ₂), 6.53 (s, 1H, NH)	181 (3, M*), 153 (60), 152 (100), 151 (26), 138 (8), 97 (10), 70 (7), 56 (90)
IIc	2260	1805 (1765)	1750 (1700)	1.52 (s, 6H, gem-Me ₂), 2.95 (s, 3H, NMe)	167 (26, M*), 152 (100), 56 (49)
IIId	2255	1800 (1765)	1745 (1710)	0.83 (t, 3H, Me), 1.50 (s, 3H, 5-Me), 1.60-2.30 (m, 2H, CH ₂), 2.92 (s, 3H, NMe)	
IIe	2255	1800 (1765)	1780 (1710)	1.73 (s with broad base, 10H, five CH ₂), 2.93 (s, 3H, NMe)	
IIf	2260	1800 (1770)	1760 (1725)	1.95 (s, 3H, Me), 2.90 (s, 3H, NMe), 7.18-7.78 (m, 5H, Ph)	229 (67, M*), 215 (10), 214 (100), 201 (10), 200 (33), 152 (9), 132 (11), 118 (87), 77 (17), 56 (33)
IIg	2275	1815 (1795)	1765 [e] (1735)	1.75 (s, 6H, gem-Me ₂), 2.57 (s, 3H, MeCO)	
IIh	2270	1825 (1800)	1785 [e] (1740)	1.78 (s, 6H, gem-Me ₂), 7.47-8.00 (m, 5H, Ph)	
IIIa	2250	1810 (1760)	1730 (1720)	1.63 (s, 6H, gem-Me ₂), 3.13 (s, 3H, NMe)	167 (65, M*), 152 (42), 110 (48), 82 (91), 67 (100), 41 (9)
IIIb	2255	1810 (1780)	1720 (1705)	0.92 (t, 3H, Me), 1.62 (s, 3H, 5-Me), 1.73-2.25 (m, 2H, CH ₂), 3.13 (s, 3H, NMe)	
IIIc	2250	1800 (1770)	1725 (1700)	1.90 (s with broad base, 10H, five CH ₂)	
IIId	2245	1815 (1780)	1730 (1710)	2.03 (s, 3H, Me), 3.17 (s, 3H, NMe), 7.50 (s, 5H, Ph)	229 (69, M*), 214 (87), 172 (9), 144 (37), 129 (100), 104 (41), 103 (16), 77 (19)

[a] Values in parentheses refer to parent hydantoins. [b] Measured in deuteriochloroform; IIh in DMSO-*d*₆. Signals assigned to NH groups (IIa,b) disappear after shaking with deuterium oxide. [c] Peaks \leq 6% (except M*) and satellites are not included. [d] Shows three bands in the range 3260-3120 cm^{-1} (NH). [e] Acetyl C=O (IIg) and benzoyl C=O (IIh) appear at 1725 and 1690 cm^{-1} respectively; in the parent hydantoins, at 1675 and 1645 cm^{-1} respectively.

Table 3
Transfer Reactions of Cyano Group

Substrate I				Cyanating agent	Product	Yield (%)
R ¹	R ²	R ³	R ⁴			
H	Me	Me	Me	IIc	IIIa [a]	55
				IIg	IIIa	52
				IIh	IIIa	54
H	Me	Me	Et	IIc	IIIb [a]	50
H	Me	Me	Ph	IIc	IIIId	55

[a] After elution of this compound from the alumina column, the secondary product (1,5,5-trimethylhydantoin, 65% yield) was eluted (benzene-ethyl acetate mixtures and ethyl acetate) and identified by mp, mixed mp and ir.

solvent instead of *N,N*-dimethylformamide, by inverse addition of the reactants or with either of these in 100% excess. The results of Table 3 show that the crystalline and stable 3-cyanohydantoins are useful reagents for synthetic work.

Compound IIc failed to produce homolytic side-chain cyanation of toluene in experiments performed at boiling temperature of the solvent (carbon tetrachloride or 1,2-dichloroethane) with dibenzoyl peroxide or uv irradiation

(with or without benzophenone). It was recovered 80-90% of the starting IIc.

EXPERIMENTAL

Melting points, taken in capillaries, are uncorrected. The following instruments were used: ir (nujol), Perkin-Elmer 337E; pmr (60 MHz, δ from tetramethylsilane as internal standard), Varian EM-360A; ms (70 eV, direct inlet), Varian-MAT 112S. The pmr and ms were obtained from LEA, University of San Luis or UMYMFOR, University of Buenos Aires (Argentina). Elementary analyses were performed by UMYMFOR or Dr. A. Bernhardt Laboratory (Germany).

Distilled *N,N*-dimethylformamide (DMF) was dried [14] by azeotropic removal of water with benzene and then over 4 Å molecular sieves. The oil dispersion of sodium hydride was freshly titrated (45-47%) measuring the volume of hydrogen from reaction with alcohol in DMF. For column chromatography it was used alumina pH 6, activity II, in an amount of 50:1 w/w.

Cyanogen bromide was prepared as described [15]; after reaction completion, the product was distilled drying the vapors through Drierite (85% yield). It was stored in a Teflon stoppered flask at -15° in a desiccator thus avoiding volatilization losses and decomposition. Cyanogen chloride [16], stored likewise, was used as titrated carbon tetrachloride solution.

Preparation of Hydantoins (I).

Most of the known hydantoins were synthesized by classical methods [2]. For 1,5-dimethyl-5-phenylhydantoin the method [17] of 1-alkylation of

the hydantoin blocked at position-3 was used; the crude product was purified by column chromatography (silicagel, 230-400 mesh, activity II; chloroform-absolute ethanol 49:1) and crystallization from alcohol (44% yield).

1-Benzoyl-5,5-dimethylhydantoin(I, $R^1 = \text{PhCO}$, $R^2 = \text{H}$, $R^3 = R^4 = \text{Me}$).

It was prepared by reaction [5] of 5,5-dimethylhydantoin with benzoyl chloride in anhydrous pyridine. The crude product was extracted at 0° with aqueous sodium hydroxide (0.25 M); acidification of the alkaline extract furnished 30% yield of the 1-benzoyl derivative, constant mp 200-202° (from alcohol); ir: 3160, 3090 (NH), 1800, 1740 (hydantoin carbonyls), 1645 (benzoyl C=O) cm^{-1} ; pmr (deuteriochloroform): δ 1.75 (s, 6H, *gem*-Me₂), 7.43 (s broad in the base, 5H, Ph), 8.63 (broad, 1H, removed by deuterium oxide, N₃-H) [6].

Anal. Calcd. for C₁₂H₁₂N₂O₃: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.79; H, 5.27; N, 12.27.

Preparation of *N*-Cyanohydantoin (II and III).

All the preparations (Tables 1 and 2) were performed with exclusion of moisture; magnetic stirring was used and the extracts were dried over anhydrous sodium sulphate and evaporated *in vacuo*. Similar yields were obtained when cyanogen chloride in carbon tetrachloride was used [18] instead of the cyanogen bromide solution indicated in the procedures.

General Procedure A.

A solution of the hydantoin (1 mmole) in DMF (2 ml) was cooled in an ice bath and oil dispersion of sodium hydride (1 mmole) was added; the mixture was stirred for 30 minutes at 0° and then at room temperature until gas evolution ceased (*ca.* 30 minutes). While stirring at 0°, a solution of cyanogen bromide (117 mg, 1.1 mmole) in anhydrous benzene (0.6 ml) was added dropwise; the reaction mixture was maintained 3 hours at 0°. After addition of acetic acid (1 mmole), the solvent was stripped off (< 50°) and the residue was sequentially washed with hexane (3 × 1 ml), 3% aqueous acetic acid (1 ml, 0°) and water (2 × 1 ml) and then it was taken up in chloroform (5 ml). The solution was washed with water (1 ml), dried and evaporated to give the crude product which was purified by crystallization directly or, for compounds IIIc,d, after fast column chromatography (alumina, hexane-benzene 1:9).

General Procedure B.

Anhydrous triethylamine (101 mg, 1 mmole) was added to a solution or suspension of the hydantoin (1 mmole) in acetone (1 ml, dried over Drierite); the mixture was cooled at 0° and, while stirring, cyanogen bromide (117 mg, 1.1 mmoles) in anhydrous carbon tetrachloride (2 ml) was added in 30 minutes. After 2 hours at 0° and 1 hour at 20°, the insoluble triethylamine hydrobromide (80-90% yield, identified by ir with an authentic sample) was filtered off. The filtrate was evaporated and the residue was crystallized to constant mp.

Cyano Group Transfer Reactions.

Under exclusion of moisture, oil dispersion of sodium hydride (1 mmole) was added at 0° to a solution of the substrate (1 mmole) in DMF (2 ml). The mixture was magnetically stirred for 15 minutes at 0° and

then for 45 minutes at room temperature. After addition of the cyanating agent (1 mmole) in one portion, the solution was kept at 35° for 2 hours; the mixture was acidified with acetic acid and evaporated to dryness (< 50°). The residue was partitioned between chloroform (10 ml) and water (4 ml); the dried (anhydrous sodium sulphate) organic phase was evaporated leaving a residue which was washed with hexane (2 × 2 ml) and rapidly chromatographed through alumina with hexane-benzene 1:9 as eluant. The resulting 1-cyanohydantoin (Table 3) were identified by mp and mixed mp with samples obtained above by the general procedure A.

Acknowledgement.

For financial support the authors thank the Consejo Nacional de Investigaciones Científicas y Técnicas (Argentina).

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