N-Chlorination of Dilantin and Sorbinil

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The synthesis, stability, X-ray structural characterization and ^{13}C nmr shifts of *N*-1′, *N*-3′-dichloro and *N*-1′-monochlorohydantoin derivatives of the anticonvulsant dilantin and the aldose reductase inhibitor sorbinil are described. These chlorinated derivatives may be involved in drug induced hypersensitivity reactions.

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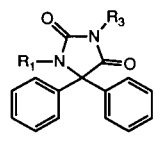
Apparent drug induced hypersensitivity reactions are associated with drugs of the hydantoin class (Figure 1) such as the anticonvulsant dilantin (**1**) and the aldose reductase inhibitor sorbinil (**2**) [1]. Adverse reactions associated with dilantin (also known as phenytoin or diphenylhydantoin) have been summarized [2] as have the similar reactions observed with sorbinil [3]. Furthermore, it has been suggested that dilantin hypersensitivity may be caused by reactive hydantoin ring *N*-chloro metabolites formed by activated neutrophils and monocytes or the combination of myeloperoxidase and hydrogen peroxide [2,4]. The latter is an enzyme system capable of generating reactive species similar to those produced by sodium hypochlorite [5].

Figure 1

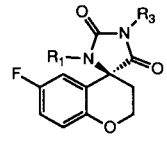


1 R1′ = H R3′ = H

3 R1′ = Cl R3′ = Cl

4 R1′ = Cl R3′ = H

5 R1′ = H R3′ = Cl

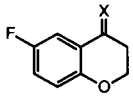


2 R1′ = H R3′ = H

6 R1′ = Cl R3′ = Cl

7 R1′ = Cl R3′ = H

8 R1′ = H R3′ = Cl



9 X = N-Cl

10 X = O

The chlorinated metabolites of dilantin are poorly characterized while those of sorbinil are unknown. Dilantin reacts with basic hypochlorite to give the impure *N*-1′,*N*-3′-dichloro derivative **3** [2] and none of the possible *N*-1′-chloro **4** or *N*-3′-chloro **5** products (Figure 1). In the sorbinil series, corresponding *N*-1′,*N*-3′-dichloro **6** and *N*-1′-chloro **7** and *N*-3′-chloro **8** derivatives are unknown.

In view of the potential importance of *N*-chlorinated metabolites in hypersensitivity reactions we have investigated the reactions of dilantin and sorbinil with hypochlorite and have synthesized the *N*-mono and *N*-dichlorinated hydantoin derivatives of dilantin and sorbinil. Products were characterized by X-ray diffraction and solution stabilities were studied by ^{13}C nmr. Carbon chemical shift assignments are likely to be useful in assigning structures to other *N*-chlorinated hydantoins.

Mechanistic Considerations.

Four factors are important to the syntheses of *N*-chlorohydantoins and to an interpretation of the literature on the chlorination of hydantoins. These factors are: 1) the effect of *p*H on the chlorination rate by hypochlorite; 2) the effect of *p*H on reactivity of hydantoins to give dichlorohydantoins and the more poorly studied and structurally less well defined *N*-monochlorohydantoins; 3) intermolecular chlorine transfer between *N*-chlorinated hydantoins and 4) the effect of *p*H on *N*-chlorohydantoin stability.

*p*H Effect on Hypochlorite Reactivity.

Hypochlorous acid is a much better chlorinating agent at acidic *p*H as opposed to hypochlorite anion which is the species present at basic *p*H. Hypochlorite is a weak acid with -log K_{diss} = 7.18 [6] and therefore the proportion of hypochlorous acid and the rate of chlorination will be greater at *p*H's below 7.18 where the proportion of the neutral hypochlorous acid species is greater. The order of chlorinating ability from best to worst is expected to parallel the stability of the group remaining after delivery of Cl+, *i.e.*, $H_2OCl^+ > Cl_2 > HOCl > OCl^-$ [7].

*p*H Effect on Hydantoin Reactivity. Dichlorohydantoins.

The rate of chlorination of hydantoin anions is expected to be much faster than the rate of chlorination of the neutral hydantoin species. Formation of *N*-1′,*N*-3′-dichloro derivatives from *N*-1′-chlorohydantoins is favored by basic *p*H because above *p*H 6.4, *N*-1′-chlorohydantoins exist largely as the more reactive 3′-anions and are more rapidly chlorinated. The p*K*a's of *N*-1′-monochlorohydantoins in the dilantin and sorbinil series are about 6.4 (8.3-1.86), if one assumes that the p*K*a of 8.3 for the unsubstituted hydantoin will decrease by the same 1.86 p*K*a units upon *N*-1′-chloro substitution as is reported for 5,5-dimethylhydan-

toin (p*K*a-9.03) and its *N*-1'-chloro derivative (p*K*a-7.17) [6].

Formation of 1',3'-dichloro derivatives by hypochlorite reaction on 3'-chlorohydantoins is favored at very basic *p*H values because 3'-chlorohydantoins exist in the more reactive *N*-1'-anionic form only at basic *p*H's of greater than 11. The p*K*a of the *N*-1'-hydrogen in a hydantoin ring is > 14 [6]. Although *N*-3'-chloro substitution in the hydantoin ring increases the acidity of the remaining *N*-1'-hydrogen it remains only very weakly acidic with a p*K*a greater than 11.

*p*H Effect on Hydantoin Reactivity. *N*-Monochlorohydantoins.

There is discrepancy between predictions extrapolated from chlorination experiments on *N*-methyl substituted hydantoins and the actual *N*-chloro species isolated from chlorination of *N*-unsubstituted hydantoins. On the basis of competitive halogenation of *N*-methyl substituted hydantoins, Corral and Orazi concluded that *N*-3'-chlorination is kinetically preferred over *N*-1'-chlorination under both acidic and basic conditions. However no *N*-3'-monochlorinated hydantoins having a free hydantoin *N*-1'-hydrogen were isolated from chlorination experiments on *N*-unsubstituted hydantoins [6].

These results are at variance from those predicted from the faster ionic chlorination of the more nucleophilic *N*-3'-hydantoin anion over that of the free hydantoin. Sorbinil has an *N*-3' H p*K*a in water at 23° of 8.30, a value similar to that of 8.31 reported for dilantin [8]. Therefore considering only ionic chlorination rates, sorbinil and dilantin should be *N*-3'-chlorinated at *p*H's more basic than 8.3, a *p*H region where these compounds largely exist as the more reactive 3'-anions. Clearly another factor must be considered to explain the failure to isolate *N*-3'-chlorohydantoins.

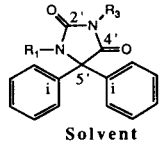
Intermolecular Chlorine Transfer.

Intermolecular transfer of chlorine from *N*-3' to *N*-1', in part, accounts for the failure to isolate *N*-3'-chlorohydantoins. For example, a 1:1 molar mixture of hydantoin and *N*-1',*N*-3'-dichlorohydantoin under a variety of conditions disproportionates to give only *N*-1'-chlorohydantoin [6].

Literature reports on preparation of *N*-3'-chlorohydantoins are without experimental support. Mono-chlorinated dilantin analogs have been assigned as *N*-3'-chloro isomers based on extrapolation from kinetic work on chlorination of monomethylhydantoins without proof of structure [9]. The ir N-Cl stretching bands for 1'-Cl and 3'-Cl-5,5-dimethylhydantoin have been reported without experimental details for compound preparation or independent confirmation of structure [10].

TABLE 1

Carbon-13 NMR Chemical Shifts for Hydantoin and Ipso Carbons in Dilantin Derivatives

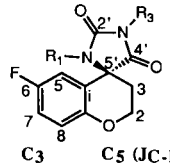


R1	R3	C2'	C4'	C5'	Ci	Solvent
H	H	156.0	174.8	70.3	139.8	DMSO d-6 [1]
		156.13	175.0	72.13	140.60	CD_3CN
Cl	Cl	151.52	168.52	79.88	135.56	CD_3CN
H	Cl	152.09	170.58	72.18	139.54	CD_3CN
Cl	H	154.41	172.26	79.40	136.61	CD_3CN

TABLE 2

C-13 NMR Chemical Shifts for Sorbinil and Derivatives

Solvents: a= DMSO d-6; b= CD_3CN; c= $CDCl_3$



R1	R3	C2'	C4'	C5'	C2	C3	C5 (JC-F)
H [a,19]	H	156.30	176.63	59.37	62.35	31.50	117.14 (23.3)
Cl [b]	Cl	151.67	169.17	68.25	63.61	29.48	119.43 (23.4)
Cl [c]	Cl	150.43	167.51	67.55	62.46	29.14	119.48 (23.3)
Cl [c]	H	150.30	167.45	67.49	62.41	29.08	119.42 (23.2)

R1	R3	C6 (JC-F)	C7 (JC-F)	C8 (JC-F)	C9	Ci (JC-F)
H [a,1]	H	156.26 (238.4)	112.82 (23.3)	118.74 (8.1)	151.35	121.60 (7.2)
Cl [b]	Cl	157.94 (239.0)	112.05 (24.6)	120.67 (8.2)	154.21	116.82 (7.5)
Cl [c]	Cl	157.12 (241.5)	112.11 (25.2)	120.65 (8.2)	153.01	114.84 (7.5)
Cl [c]	H	157.05 (242.1)	112.07 (24.6)	120.01 (7.6)	152.91	114.5

Table 3. Single Crystal X-Ray Crystallographic Parameters for Dilantin Derivatives

Crystal Parameters	N-1', N-3' Dichloro Dilantin(3)	N-1' Chloro Dilantin(4)
formula (MW)	$C_{15}H_{10}N_2O_2Cl_2$ (321.2)	$C_{15}H_{11}N_2O_2Cl$ •CH_3CN(327.8)
crystallization medium	chloroform	acetonitrile
crystal size, mm	0.42 x 0.46 x 0.61	0.19 x 0.34 x 0.40
cell dimensions	a = 8.862(2)Å	a = 12.925(3)Å
	b = 20.890(5)Å	b = 12.925(3)Å
	c = 8.893(3)Å	c = 12.925(3)Å
	α = 90.00°	α = 94.01(1)°
	β = 118.06(2)°	β = 94.01(1)°
	γ = 90.00°	γ = 94.01(1)°
	V = 1452.8(6)Å^3	V = 2143(1)Å^3
space group	$P2_1/n$	$R\bar{3}$
molecules/unit cell	4	6
density calcd, g/cm^3	1.47	1.52
linear absorption factor, cm-1	41.42	24.13
B. Refinement Parameters		
no. of reflections	1499	1475
nonzero reflections (I>3.0s)	1262	1349
R-index	0.048	0.101
GOF	1.51	2.01
scale factor	1.516(4)	1.756(9)
secondary extinction factor	30(8) x 10-4	3(1) x 10-4

N-Chlorohydantoin Stability.

Isolation of *N*-1',*N*-3'-dichlorohydantoins is difficult since these species are unstable to base. For example, the *p*H optimum for ring cleavage of *N*-1',*N*-3'-dichloro-5,5-dimethylhydantoin is about *p*H 9 [11] and this is also the usual *p*H range for sodium hypochlorite chlorinations. We have employed chlorinations at slightly neutral to acid *p*H to prepare dichlorosorbinil, a molecule whose structural features lead to pronounced base instability.

Discussion - Chlorination Studies.

We studied the formation of dichlorohydantoins from sorbinil and dilantin in two *p*H regions. At *p*H's of about 8 to 10 chlorination is fast through the intermediacy of the initially formed *N*-3'-chloro species but, depending on the substrate, instability to base and intermolecular chlorine transfer can lead to very poor results. Dichlorination at *p*H 6.5 to 7.2, while very slow, can be synthetically useful and occurs through the intermediacy of the *N*-1'-chloro species which forms by intermolecular chlorine transfer.

Table 4. Single Crystal X-Ray Parameters of Chloro Sorbinil Derivatives

Crystal Parameters	N-1', N-3' Dichloro Sorbinil (6)	N-1' Chloro Sorbinil (7)
formula (MW)	$C_{11}H_7N_2O_3Cl_2F$ (305.1)	$C_{11}H_8N_2O_3ClF \cdot 1/6\ CHCl_3$(290.6)
crystallization medium	chloroform	chloroform
crystal size, mm	0.44 x 0.52 x 0.64	0.12 x 0.12 x 0.16
cell dimensions	a = 7.674(3)Å	a = 18.607(5)Å
	b = 16.364(6)Å	b = 18.607(5)Å
	c = 19.625(7)Å	c = 7.333(3)Å
	α = 90.00°	α = 90.00°
	β = 90.00°	β = 90.00°
	γ = 90.00°	γ = 90.00°
	V = 2464(1)Å^3	V = 2539(1)Å^3
space group	$P2_12_12_1$	I4
molecules/unit cell	8 (z=2)	8
density calcd, g/cm^3	1.62	1.52
linear absorption factor, cm-1	50.3	38.4
B. Refinement Parameters		
no. of reflections	1434	727
nonzero reflections (I>3.0s)	1128	652
R-index	0.058	0.098
GOF	1.31	5.64
scale factor	0.784(1)	1.131(8)
secondary extinction factor	none	none

N-1',*N*-3'-Dichlorosorbinil is prepared by acidic chlorination as the minor product; the major product isolated in moderate yield, is the *N*-1'-monochloro isomer. Basic chlorination of sorbinil is not synthetically useful because the dichloro product is very unstable under basic reaction conditions and is contaminated by hydantoin ring cleaved by-products.

Dilantin and sorbinil show a marked difference in chlorination rates with basic sodium hypochlorite. Sorbinil chlorination at basic *p*H, even at 0°, gives gummy mixtures of *N*-chlorinated hydantoin products as well as 6-fluorochromanone (**9**) and 6-fluoro-4-iminochlorochromane (**10**). The latter product has previously been isolated from *N*-chlorosuccinimide degradation of the 6-fluoro-4-aminochromane-4-carboxylic acid derived from base hydrolysis of sorbinil [12].

The isolation of hydantoin ring opened products when sorbinil was chlorinated at basic *p*H led us to explore sorbinil chlorination in the *p*H range 6.5 to 6.9. The major product isolated at 0° was *N*-1'-chlorosorbinil (**7**) accompanied by unreacted sorbinil and a small amount of *N*-1',*N*-3'-dichlorosorbinil (**6**). Products were separated based on solubilities (see Experimental). The temperature of 0° for the *p*H 6.5 sorbinil chlorination is important to synthetic success. At 25°, 6-fluoro-4-iminochlorochromane (**9**) was formed while none of this material was formed at 0°. No 6-fluoro-4-chromanone (**10**) was formed in acidic *p*H 6.5 chlorination experiments in contrast to chlorinations at basic *p*H where both **9** and **10** were formed.

Dichlorodilantin is prepared in better yields by chlorination at basic rather than acidic *p*H because this dichloro product is reasonably base stable and the alternative acidic chlorination rate is very slow. No monochlorodilantins were isolated from basic chlorinations. However *N*-1'-monochlorodilantin could be prepared by intermolecular halogen exchange.

Dilantin chlorination at basic *p*H at 25° using hypochlorite for short reaction times followed by extraction of crude product with ethyl acetate, as described by Uetrecht [2] gave a good mass recovery of material which, even after recrystallization, analyzed poorly for dichlorinated product (also as described by Uetrecht). When products were extracted with chloroform rather than ethyl acetate, material recovery was much lower. A control experiment showed that, in contrast to chloroform, extraction with ethyl acetate dramatically changed the *p*H of a solution of sodium hypochlorite towards neutrality. This behaviour is unusual. Possible ethyl acetate hydrolysis contributes.

In preparation of dichlorodilantin, the parent dilantin and *N*-1'-chlorodilantin are likely contaminants. These materials are base soluble and will not extract at basic *p*H (as when chloroform is used in a workup), but will extract at neutral *p*H (as in an ethyl acetate workup) leading to a product mixture. When dilantin was allowed to react with basic sodium hypochlorite for an optimum period of 24 hours and product was isolated with a chloroform extraction, reproducible yields of analytically pure *N*-1',*N*-3'-dichlorodilantin were obtained. This material was characterized by a single crystal X-ray structure determination.

A mixture of dilantin and *N*-1',*N*-3'-dichlorodilantin could be equilibrated in acetonitrile solution to a mixture of the isomeric monochlorodilantins. The two monochlorodilantins could be partially separated into the more solu-

ble *N*-3′-chloro and less soluble *N*-1′-chloro isomers. Based on firm nmr ^{13}C assignments in deuteriochloroform for *N*-1′-chlorosorbinil and ^{13}C assignments for the stable dichloro species in both the sorbinil and the dilantin series we were able to partially assign the hydantoin ^{13}C shifts in deuterioacetonitrile for both the *N*-1′- and *N*-3′-monochlorodilantin isomers.

Intermolecular chlorine transfer in the sorbinil series, in initial experiments, did not appear promising and was not pursued since the expected *N*-1′-monochlorinated product could be more easily prepared by acidic chlorination.

Solid State X-Ray Structure Assignments.

Structure proof for *N*-1′,*N*-3′-dichlorodilantin rests on a single crystal X-ray structure determination and C, H, N, Cl analytical data. *N*-1′-Chlorodilantin was isolated in analytically pure form by a slurry procedure from chloroform. An X-ray structure on crystals of the same substance obtained from rapid evaporation of an acetonitrile solution at reduced pressure clearly showed an *N*-1′-chlorine location but failed to refine well because of disordered acetonitrile solvent.

Structure proof for *N*-1′,*N*-3′-dichlorosorbinil relies on a single crystal X-ray structure determination and C, H, N, Cl analytical data while that for *N*-1′-chlorosorbinil also relies on a single crystal X-ray structure and C, H, N, Cl analytical data. The latter X-ray study clearly shows enhanced electron density corresponding to chlorine at *N*-1′ but does not refine well due to disordered chloroform. Satisfactory C, H, N, Cl analyses were obtained on a dried sample of *N*-1′-monochlorosorbinil. However the X-ray sample recrystallized from chloroform did not analyze satisfactorily because of disordered solvate. Differential scanning calorimetry (DSC) curves of the X-ray lot before drying show an endotherm at 110° to 130° corresponding to loss of very tightly bound solvent. Drying at high vacuum at 25° does not remove this solvent while drying at high vacuum at 80° effectively removes solvent but also fractures the crystals.

Solid state X-ray structure proofs coupled with analytical data for both *N*-1′,*N*-3′-dichlorodilantin and dichlorosorbinil and both *N*-1′-chlorosorbinil and *N*-1′-chlorodilantin allowed us to assign nmr ^{13}C shift assignments for the hydantoin C2, C4 and C5 carbons and aromatic *ipso* carbons (Table 1) [13]. We were also able to assign all the carbon resonances in sorbinil (**2**) and most of the resonances in dichlorosorbinil (**6**) and *N*-1′-chlorosorbinil (**7**).

With firm solid state structures as a reference point, we discovered that the stabilities of *N*-chlorinated species depended on solvent and structure. *N*-1′-Chlorosorbinil is stable in deuteriochloroform in contrast to deuterioacetonitrile and this allowed a comparison of ^{13}C shift assignments for the *N*-1′-monochloro and *N*-1′,*N*-3′-dichloro species in deuteriochloroform. *N*-1′-Chlorodilantin unfortunately was too insoluble in deuteriochloroform to obtain a spectrum.

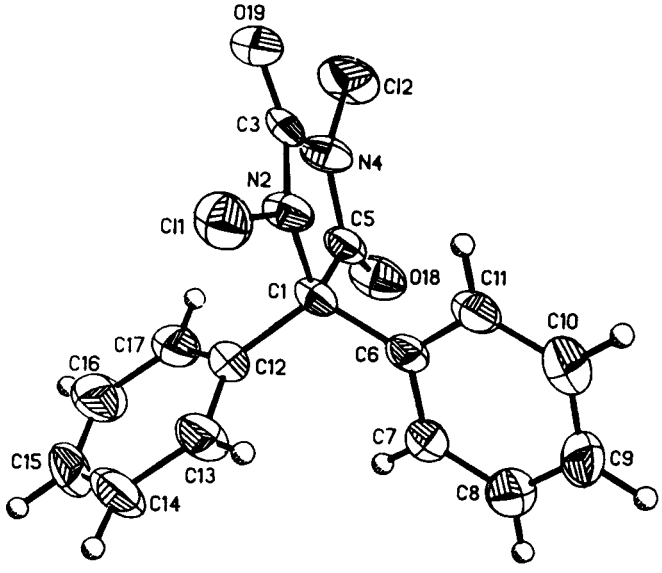
N-1′-Monochloro species in both sorbinil and dilantin series are unstable in deuterioacetonitrile. The dilantin derivative is the more stable and decomposes significantly over several hours at room temperature while the sorbinil derivative is even more unstable. However, we were able to obtain partial ^{13}C shift assignments in deuterioacetonitrile for *N*-1′-monochloro and partially purified *N*-3′-monochlorodilantin, species by comparing deuterioacetonitrile spectra at short and long time intervals and correlating shifts with those of the far more stable dichloro species in deuterioacetonitrile and with those of *N*-1′-chlorosorbinil which was stable and soluble in deuteriochloroform (Table 1).

Great care needs to be taken in interpreting ^{13}C spectra of *N*-1′-chlorohydantoins in any solvent other than deuteriochloroform since compound stability can be structure dependent. Analytically pure *N*-1′-chlorodilantin disproportionated in deuterioacetonitrile solution to a mixture of dilantin and *N*-1′- and *N*-3′-chlorodilantins over the course of 1-2 hours at room temperature. Analytically pure *N*-1′-chlorosorbinil gave a satisfactory spectrum in deuteriochloroform but the same lot in deuterioacetonitrile gave a spectrum within 10-15 minutes indicative of decomposition.

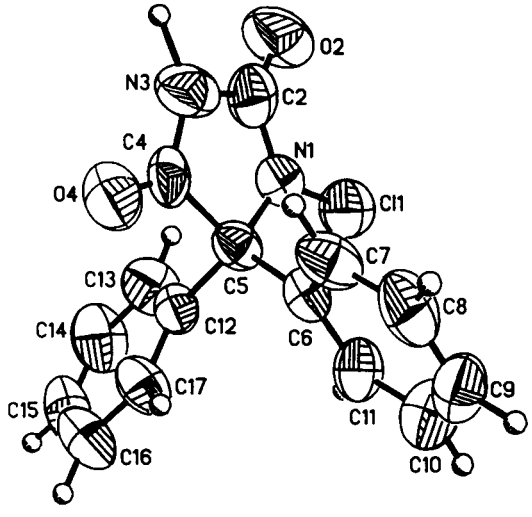
Both dichlorosorbinil and *N*-1′-chlorosorbinil decompose in dimethyl sulfoxide-d_6 solutions to give ^1H nmr spectra of the parent sorbinil but with different rates. Dichlorosorbinil generates a proton spectrum of the parent as soon as a spectrum can be taken after solution. The ^1H

N-1', N-3' Dichloro Dilantin

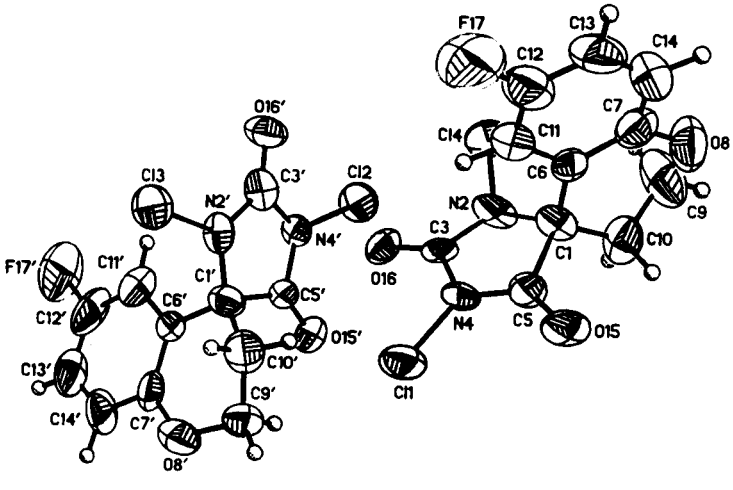
X-Ray (3)



N-1' Chloro Dilantin X-Ray (4)



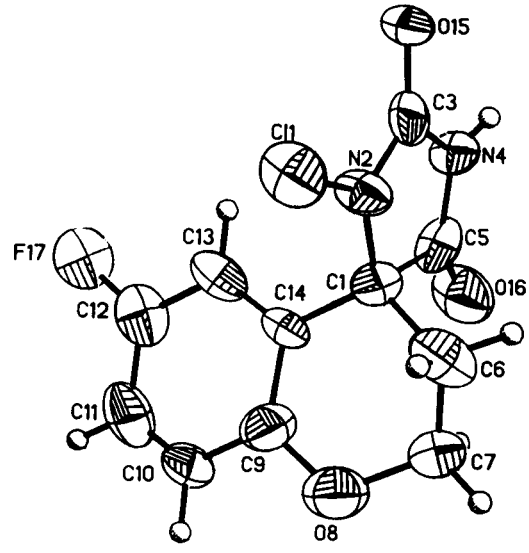
N-1', N-3' Dichloro Sorbinil X-Ray (6)



spectrum of dichlorodilantin in dimethyl sulfoxide-d_6 is that of the parent dilantin indicating a similar rapid *N*-chloro loss. By way of contrast, *N*-1'-chlorosorbinil reverts to sorbinil in dimethyl sulfoxide-d_6 at an appreciably slower rate with half life of about 10 minutes at room temperature. This behavior implies that in this solvent dichlorosorbinil does not decompose to *N*-1'-chlorosorbinil.

In summary, we have prepared pure samples of *N*-1'-monochlorosorbinil and dilantin an *N*-1',*N*-3'-dichlorosorbinil and dilantin. These materials are potential toxic metabolites in hydantoin hypersensitivity reactions. The species are stable enough to purify by slurrying techniques and differential solubility but not by crystallization and were characterized in the solid state by X-ray and analytical data. Solution stability is good in chloroform but not

N-1' Chloro Sorbinil X-Ray (7)



in acetonitrile or dimethyl sulfoxide. Analyzing a hydantoin chlorination mixture in deuteriochloroform by ^{13}C nmr using our shift assignments is feasible for soluble samples but should be approached with extreme caution in other solvents. Our studies emphasize the solution instability of *N*-chlorohydantoins. Having a single pure compound in the solid state does not guarantee the same species in solution.

EXPERIMENTAL

Chlorination of Dilantin.

N-1',*N*-3'-Dichlorodilantin (**3**). Basic Chlorination Procedure.

To 300 ml of 5% sodium hypochlorite (Chlorox bleach) (200 mmoles) was added 25.2 g (100 mmoles) of dilantin. The reaction was stirred mechanically overnight at room temperature and was extracted with chloroform. The *p*H of the aqueous following extraction was 11.65. The chloroform layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 12.8 g of white solid, mp 144-147°. This material was washed repeatedly with carbon tetrachloride and dried at 23° to give 10.1 g (31%) of product mp (capillary) 158-165°; see Table 1 for ^{13}C nmr parameters.

Anal. Calcd. for $C_{15}H_{10}N_2O_2Cl_2$: C, 56.10; H, 3.14; N, 8.72; Cl, 22.08. Found: C, 56.34; H, 3.06; N, 8.59; Cl, 22.16.

N-1',*N*-3'-Dichlorodilantin (**3**). Acidic Chlorination Procedure.

To 95 ml (63.4 mmoles) of 5% sodium hypochlorite adjusted to *p*H 6.5 with 6*N* hydrochloric acid at room temperature was added 10.0 g (39.6 mmoles) of dilantin. Over a 4 hour period an additional 32 ml (13.3 mmoles) of 5% sodium hypochlorite was added to maintain the *p*H at 6.5. After stirring vigorously for 4 hours the reaction slurry was filtered and the solid was washed with chloroform. The chloroform washes were concentrated *in vacuo* to give 2.43 g crude solid. This solid was washed with carbon tetrachloride and the insoluble material was collected by filtration to give 600 mg (4.7%), mp (capillary) 150-156°. The sample

was dissolved in chloroform and the clear solution was slowly evaporated in a vacuum desiccator to deposit prisms; DSC (20°/minute scan rate) peak from 134.04° to 172.91°; onset of endotherm 162.45°; maximum 166.97°; cal/gram 24.72; ir (potassium bromide): 3530, 2960, 1800, 1730 cm^{-1}; see Table 1 for ^{13}C nmr parameters.

Anal. Calcd. for $C_{15}H_{10}N_2O_2Cl_2$: C, 56.10; H, 3.14; N, 8.72; Cl, 22.08. Found: C, 56.39; H, 3.03; N, 8.51; Cl, 21.68.

N-1′,*N*-3′-Dichlorodilantin (**3**) X-Ray.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.048. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL [14] plotting package.

Monochlorodilantins.

To 75 ml of acetonitrile was added 5.0 g (15.6 mmoles) *N*-1′,*N*-3′-dichlorodilantin and 2.61 g (10.4 mmoles) of dilantin and the reaction was stirred at room temperature for 3 days. The reaction was concentrated *in vacuo* to give 7.4 g of white solid. The ^{13}C nmr (deuterioacetonitrile - 512 scans) (6 minutes scan time) showed carbon resonances assigned to a mixture of dichloro and 1′-chloro and 3′-chlorodilantins. The same sample was run for 7200 scans (84 minutes run time) and now showed the same resonances with altered relative intensity and new resonances attributable to the parent dilantin.

The 7.4 g of material was slurried in chloroform to give 5.40 g of insoluble material. This was slurried in acetonitrile to give 3.05 g insoluble material. The ^{13}C nmr (deuterioacetonitrile - 512 scans) showed a major *ipso* carbon resonance at 136.6 and minor at 139.5. The CHN analysis excludes significant content of the dichloro species and hence the sample was assigned as a 2:1 mixture of 1′-chloro to 3′-chloro species. The same was run for 6144 scans (72 minutes run time) and now showed a 1:1 mixture of 1′-Cl and 3′-Cl species along with a small amount of dilantin.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C 62.84; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 62.83; H, 3.84; N, 10.23; Cl, 12.08.

The mother liquors from acetonitrile slurry of the 5.40 g of chloroform insoluble material were concentrated *in vacuo* to give 2.2 g of a gum. The ^{13}C nmr analysis of this material in deuterioacetonitrile (4800 scans) showed *N*-3′-Cl, *N*-1′-Cl and parent dilantins in approximate ratios of 3:1:1. The *N*-3′-chlorodilantin appears to be the more soluble monochlorohydantoin. No peaks attributable to dichloro species were observed.

N-1′-Chlorodilantin (**4**).

A 2.5 g sample of the chloroform insoluble 3.05 g material was washed with 100 ml of chloroform and dried to give 966 mg of white solid; DSC (20°/minute scan rate): single endotherm, max 148.47° peak from 122.63° to 157.36°, onset 140.29°, maximum 148.47°. The ir (potassium bromide) of this non-solvated material was identical to that of dried prisms deposited from acetonitrile. The proof that this is *N*-1′-chlorodilantin (**4**) and a single material rests on: 1) the identity of the ir spectrum of this 966 mg sample obtained by a slurry from chloroform with the ir (potassium bromide) spectrum of a dried X-ray sample (obtained by deposition from acetonitrile); 2) the single DSC endotherm for the 966 mg sample which was slurried in chloroform and 3) the correct C, H, N analysis for the 966 mg sample; see Table 1 for ^{13}C nmr parameters.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.49; H, 3.90; N, 10.10.

A 255 mg sample of the chloroform-insoluble 3.05 g material was dissolved in acetonitrile at 23° and placed in a shallow dish in a vacuum dessicator at reduced pressure and evaporated over an hour to give large prisms; ir (potassium bromide): 3160, 3070, 2720, 1780, 1730 cm^{-1}. The sample was too insoluble for ^{13}C nmr in deuterioacetonitrile. A single crystal X-ray structure study showed that this material was *N*-1′-chlorinated and contained disordered acetonitrile.

N-1′-Chlorodiphenylhydantoin (**4**) X-Ray.

A trial structure was obtained by direct methods. This trial structure refined routinely. A difference map revealed an acetonitrile molecule of crystallization. Subsequent refinement indicated that this molecule of crystallization was located on a three fold axis and was disordered. The two primary positions for the acetonitrile molecule could be generated by turning the molecule end to end. Unfortunately this type of disorder does not lend itself to least squares refinement, because the atomic centers are very nearly the same. The acetonitrile was fit using difference maps, and the knowledge of the bond lengths in acetonitrile. Hydrogen positions were calculated wherever possible. The hydrogen on nitrogen was located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.101. This larger than normal R-index was attributed to the inability to fit the disordered acetonitrile of crystallization by least squares refinement. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package.

Chlorination of Sorbinil.

N-1′,*N*-3′-Dichlorosorbinil (**6**).

The carbon tetrachloride ml from the slurry used to isolate 16.7 g of crude *N*-1′-chlorosorbinil was concentrated *in vacuo* to give 3.5 g (9.9%). A small sample of this material was dissolved in warm chloroform and the clear solution was slowly evaporated in a vacuum desiccator to deposit plates; DSC-broad endotherm centered at 124.39 with shoulder at 115°; ir (potassium bromide): 3420, 1800, 1755; see Table 2 for ^{13}C nmr parameters.

Anal. Calcd. for $C_{11}H_7N_2O_3Cl_2F$: C, 43.31; H, 2.31; N, 9.18; Cl, 23.24. Found: C, 43.55; H, 2.28; N, 8.97; Cl, 23.01.

N-1′,*N*-3′-Dichlorosorbinil (**6**) X-Ray.

A trial structure was obtained by direct methods and contained two molecules in the asymmetric unit. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.058. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. The absolute configuration was determined

by the method of Ibers and Hamilton [15,16]. The difference between the two molecules in the asymmetric unit involves the conformation of the oxygen containing six membered ring.

N-1'-Chlorosorbinil (7).

A solution of 200 ml of 5% sodium hypochlorite (0.134 mole) was cooled to 0° and the *p*H was brought to 6.5 with 6*N* hydrochloric acid. To the well stirred solution was added in one portion 25 g (0.11 mole) of sorbinil. The solution was stirred well at 0° with periodic addition of a total of 50 ml (0.0336 mole) of 5% sodium hypochlorite to keep the *p*H in the range 6.0 to 6.6. After 5 hours at 0° the suspended white solid was collected by filtration and dried under a rubber dam overnight. The crude solid was slurried in chloroform and filtered to remove 7.4 g of unreacted sorbinil. The mother liquors were stripped to dryness to give 20 g of a crude mixture of mono and dichlorosorbinil products. This was slurried in carbon tetrachloride and filtered to give 16.7 g (56%) of *N*-1'-chlorosorbinil; DSC-broad endotherm centered at 124.93°, sharp endotherm at 170.8°. Calcd. for $C_{11}H_8N_2O_3ClF$ + 0.304 $CHCl_3$: C, 44.23; H, 2.73; N, 9.13; Cl, 22.08. Found C, 43.60; H, 2.59; N, 8.59; Cl, 22.09. A sample was dried at high vacuum at 80° for 20 hours; DSC-sharp endotherm at 172.18°; see Table 2 for ^{13}C nmr parameters.

Anal. Calcd. for $C_{11}H_8N_2O_3ClF$: C, 48.82; H, 2.98; N, 10.35; Cl, 13.10. Found: C, 48.69; H, 2.93; N, 10.28; Cl, 13.39.

A sample of this material was dissolved in warm chloroform and the clear solution was slowly evaporated in a vacuum desiccator to deposit long needles suitable for X-ray study; DSC-broad endotherm centered at 115.77°, sharp endotherm at 170.99°; ir (potassium bromide): 3450, 3220, 1790, 1725 cm^{-1}.

N-1'-Chlorosorbinil (7) X-Ray.

A representative crystal was surveyed and a 1 Å data set (maximum sin $\theta/\lambda = 0.5$) was collected on a Nicolet R3m/μ diffractometer. During data collection it was noticed that the unprotected crystal was turning white and losing check reflection intensity. A new crystal was mounted and encased in epoxy cement. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [17]. All crystallographic calculations were facilitated by the SHELXTL system. All diffractometer data were collected at room temperature.

A trial structure was obtained by direct methods. This trial structure refined routinely up to a point. A difference map revealed a molecule of crystallization located at a four fold center. Because none of the molecules used in the reaction or crystallization contained a four fold axis of symmetry, this result posed a problem. The difference map indicated bond distances of approximately 1.8 Angstroms. This suggested a disordered chloroform molecule. The intensities in the difference map also indicated that the occupancy of the molecule was 1/6.

Four chloroform molecules were fit to the difference map to explain the observed density. However, refinement of this model was not successful, tending to show an average of the disorder. Refinement did produce a very good R-index and goodness-of-fit. However, the geometry of the resulting "chloroform molecule" was chemically impossible. Therefore, the refined model was abandoned in favor of the chemically correct molecules seen in the difference maps. This led to higher than usual agreement indicies. The possibility of this crystal belonging to space group I4 was investigated but did not prove more satisfactory.

Hydrogen positions were calculated wherever possible. The hydrogen on nitrogen was located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.3 of their corresponding standard deviations. The final R-index was 0.098. A final difference Fourier revealed no missing or misplaced electron density. A difference map did reveal residual density around the disordered chloroform molecule, but no further efforts were made to better fit the disorder. The refined structure was plotted using the SHELXTL plotting package.

In conclusion, we have developed synthetic procedures to prepare analytically pure *N*-1',*N*-3'-dichloro and *N*-1'-monochloro species in both dilantin and sorbinil series. Carbon-13 nmr shift assignments allow an estimation of monochloro and dichloro ratio's in solution and likely will be useful to structure assignment of other *N*-chlorinated hydantoins. The disproportionation chemistry of the chloro hydantoins in deuterioacetonitrile solution suggests a CAVEAT for both chemical and biological studies. Well characterized species in the solid state may not exist as such in solution and solution species need to be verified by nmr in deuteriochloroform. The availability of standards and knowledge of their solution stabilities should facilitate the study of chlorinated species formed *in vitro* by activated neutrophils, monocytes or myeloperoxidase and should assist in studying the role of *N*-1'-chlorinated hydantoins in experimental models of hypersensitivity reactions.

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[19] Ms Diane Rescek's assistance in running **13C** nmr spectra is gratefully acknowledged. The C_5 and C_7 shifts in sorbinil are uncertain. Based on chlorinated derivatives, C_7 is assigned as the upper field carbon based on its shift being unaffected by *N*-1'-chlorination. By contrast C_5 would be expected (and is) shifted downfield by *N*-1'-chlorination.