Hydantoin Formation from Alaninamide Derivatives. Reactions with 5-Amino-5-methylhydantoin

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The influence of the α-substitution on hydantoin formation from urethan protected alaninamide derivatives is investigated. Several 5-methyl-5-substituted hydantoins, obtained from 5-amino-5-methylhydantoin, are described.

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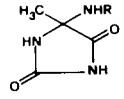
The chemistry of 2-substituted-2-amino acids, of 2,3-dehydroamino acids and of the corresponding peptides is receiving increasing attention (1). Several observations have been made in this field concerning side reactions leading to cyclic derivatives such as diketopiperazines and hydantoins (2). Hydantoin formation however does not generally occur or is very limited in the mild conditions usually adopted for the alkaline hydrolysis of *N*-benzyloxycarbonylpeptide esters.

In a previous work (3) we reported on the facile formation of 5-amino-5-methylhydantoin derivatives during mild aqueous alkaline treatment of peptides containing 2,2-dibenzyloxycarbonylamidopropionic acid as *N*-terminal residue. In this paper we wish to report some results concerning (i) the effect of α-substitution and of the nature of the urethan protecting group on hydantoin formation and (ii) the chemical properties of 5-amino-5-methylhydantoin and of related 5-methylenehydantoin. In order to test hydantoin formation, the model compounds reported in Table I were prepared. Benzyloxycarbonyl, ethyloxycarbonyl and *t*-butyloxycarbonyl were used as urethane-type protecting groups to acylate substrates such as alaninamide (compounds **1-3**), 2-methyl-2-acylamidoalaninamide (compounds **4-6** and **7-9**, respectively) and 2,3-dehydroalaninamide **10**.

These products (1.0 mmole) were treated at room temperature for 1.5 hours in methanol (15 ml) with 2*N* sodium hydroxide (1.5 ml). The results reported in Table II show that the substitution of the α-hydrogen with methyl or acylamido groups greatly enhances hydantoin formation. All the examined 2,2-disubstituted derivatives in fact, excepting 2-methyl-2-*t*-butyloxycarbonlyalaninamide **6** were completely transformed into the corresponding hydantoins. The nature of the urethane group also affects the course of the reaction; in the series of 2-unsubstituted alaninamides (**1-3**) a significant yield of 5-methylhydantoin **11** was obtained only from ethyloxycarbonyl derivative **2**, whereas in the series of 2-methylalaninamide (**4-6**) only the *t*-butyloxycarbonyl derivative **6** gave, as already mentioned, a comparatively low yield of 5,5-dimethylhydantoin **12**. In case of compound **9** possessing two different urethane groups at position 2, a mixture of 5-benzyloxycarbonylamido-5-methylhydantoin **13** and of 5-ethyloxycarbonylamido-5-methylhydantoin **15** was obtained in nearly quantitative overall yield; the two hydantoins **13** and **15** were formed in comparable yields (40% and 55% respectively). By comparing this result with those relative to compounds **1**, **2** and **4**, **5** it is evident how in the adopted conditions only the less reactive monosubstituted compounds show a higher reactivity of the ethyloxycarbonylamido group in respect to benzyloxycarbonylamido.

In the cyclization conditions adopted here, 2,3-dehydro-*N*-benzyloxycarbonylalaninamide **10** was found to be stable and 5-methylenehydantoin **17** was not detected. This finding is in accordance with a recent report (2d) in which non-*N*-methylated-*t*-butyloxycarbonyldehydrophenylalanyl peptides are shown not to undergo hydantoin formation when treated with sodium hydroxide or methanolic ammonia. It is interesting to note, however, that dehydroalaninamide derivative **10** was almost completely converted to 5-methylenehydantoin **17** when treated at room temperature with alcoholic sodium ethoxide.

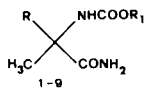
5-Amino-5-methylhydantoin **16**, obtained in two steps from 2,2-dibenzyloxycarbonylamidopropionamide **7**, could be easily reacylated to give 5-acylamido-5-methylhydantoins **18-21**. Acylation was accomplished by using both acid chlorides in dry pyridine or dicyclohexylcarbodiimide.



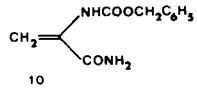
18 R = $-OCOCH_2C_6H_5$
19 R = $-COCH_2C_6H_5$
20 R = $-SO_2C_6H_4-CH_3$ (p)
21 R = $-C(CH_2CH_3)_2COOCH_2CH_3$

In order to examine the possibility of obtaining bicyclo derivatives with potential pharmaceutical acitivity, 5-amino-5-methylhydantoin **16** was treated with 2,2-di-

Table I



1-9

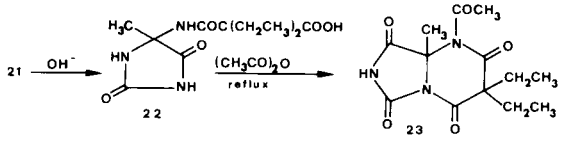


10

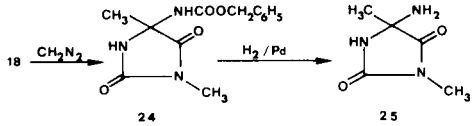
Compound No.	R	R_1	Yield % (a)	Mp °C	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found C	H	N	IR ν max (potassium bromide)
1	H	$C_6H_5CH_2$	83	132	ethyl acetate	$C_{11}H_{14}N_2O_3$	59.45 59.37	6.35 6.36	12.60 12.74	3380, 3300, 3180, 1680, 1650, 1530
2	H	CH_3CH_2	85	138	ethyl acetate	$C_6H_{12}N_2O_3$	44.99 45.07	7.55 7.54	17.49 17.51	3380, 3240, 3200, 1700, 1660, 1625 1550
3	H	$(CH_3)_3C$	65	126	ethyl acetate/ light petroleum	$C_8H_{16}N_2O_3$	51.05 51.19	8.57 8.56	14.88 14.81	3380, 3340, 3290, 1675, 1635, 1520
4	CH_3	$C_6H_5CH_2$	55	118	ethyl acetate	$C_{12}H_{16}N_2O_3$	61.00 60.92	6.83 6.89	11.86 11.89	3410, 3310-3275, 1690, 1650, 1530
5	CH_3	CH_3CH_2	70	118	ethyl acetate	$C_7H_{14}N_2O_3$	48.26 48.30	8.10 8.09	16.08 16.03	3420, 3320-3200, 1720, 1680, 1650, 1610, 1520
6	CH_3	$(CH_3)_3C$	80	175	ethyl acetate	$C_9H_{18}N_2O_3$	53.45 53.43	8.97 8.87	13.85 13.84	3410, 3300, 3210, 1680, 1650, 1525
7 (b)	$C_6H_5CH_2OCONH$	$C_6H_5CH_2$	63							
8	CH_3CONH	$C_6H_5CH_2$	60	140	ethyl acetate	$C_{13}H_{17}N_3O_4$	55.91 55.82	6.14 6.20	15.04 14.98	3435, 3410, 3330, 3240, 1720, 1685-1650, 1600
9	CH_3CH_2OCONH	$C_6H_5CH_2$	69	114	ether	$C_{14}H_{19}N_3O_5$	54.36 54.22	6.19 6.20	13.58 13.51	3420, 3280, 3080, 1750, 1700, 1670, 1550, 1500
10			74	126	ether	$C_{11}H_{12}N_2O_3$	59.99 60.15	5.49 5.56	12.72 12.81	3360-3340, 3330, 3170, 1720, 1690, 1550, 1500

(a) Yields are of isolated, analitically pure materials. (b) See lit (3).

ethylmalonyl chloride monoethyl ester to give the 5-acylamido derivative **21**; subsequent hydrolysis of **21** and cyclization with acetic anhydride of the 5-acylamido derivative **22** gave the bicyclo derivative imidazo[1,5-*a*]-pyrimidine-1-acetyl-3,3-diethyl-8*a*-methyloctahydro-2,4,6,8-tetraone (**23**).



Treatment of **18** with diazomethane afforded 3,5-dimethyl-5-benzyloxycarbonylamidohydantoin **24** from which 3,5-dimethyl-5-aminohydantoin **25** could be obtained by hydrogenolysis.

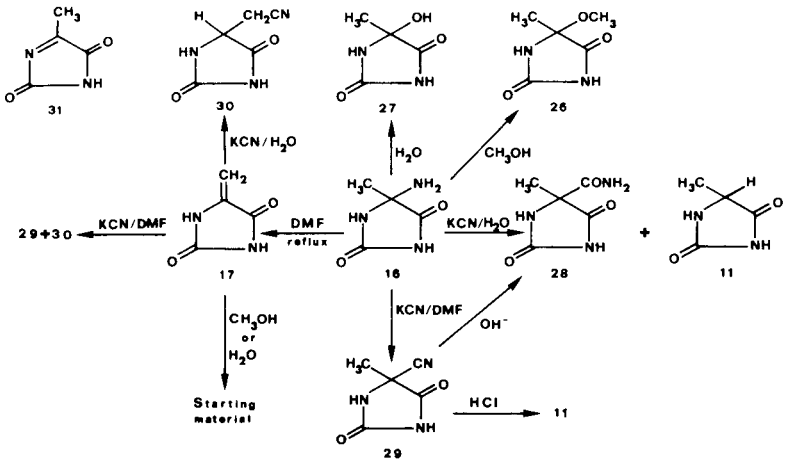


Heating of 5-amino-5-methylhydantoin **16** in methanol resulted in elimination of ammonia and rapid formation of 5-methyl-5-methoxyhydantoin **26**. This reaction parallels the already reported (3) formation of 5-hydroxy derivative **27** by treating **16** with water and confirms the utility of 5-alkyl-5-aminohydantoins as versatile intermediate to obtain 5-alkyl-5-substituted derivatives.

An interesting example of the reactivity of **16** is given by its reaction with potassium cyanide (see Scheme I). Treatment of **16** with potassium cyanide in water gave a mixture of 5-methyl-5-carboxyamidohydantoin **28** and of 5-methylhydantoin **11**. When the reaction was carried out in non aqueous medium using potassium cyanide in dimethylformamide, 5-methyl-5-cyanohydantoin **29** was obtained as the sole product.

Compounds **28** and **11** could be obtained by treating **29** with aqueous sodium hydroxide. Hydrolysis of **29**, with concentrated hydrochloric acid gave on the other hand 5-methylhydantoin **11**. By refluxing **16** in an aprotic solvent such as dimethylformamide, elimination of ammonia took place and 5-methylenehydantoin **17** was isolated in high yield. Despite its easy formation, 5-methylenehydan-

SCHEME I



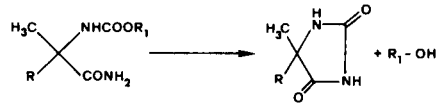
toin **17** is not an intermediate in the formation of 5-substituted derivatives obtained from 5-amino-5-methylhydantoin **16**. 5-methylenehydantoin **17** in fact was not found to react with water or methanol and the reaction with potassium cyanide in water gave exclusively 5-cyanomethylhydantoin **30**, a product of 1,4 nucleophylic addition.

It is interesting to note, however, that a mixture of 5-cyano-5-methylhydantoin **29** and 5-cyanomethylhydantoin **30** was obtained when 5-methylenehydantoin **17** was refluxed with potassium cyanide in dry dimethylformamide. A possible explanation of these results is as follows: heating of 5-methyl-5-aminohydantoin **16** leads to initial formation of unstable 5-methyl-5-dehydrohydantoin **31**; this reactive cyclic *N*-acylimine (4) reacts rapidly with nucleophiles to give exclusively 5-substituted-5-methyl derivatives. In absence of nucleophiles, **31** isomerizes to give the more stable 5-exomethylene isomer **17**. This latter compound does not react with water or alcohols but in aqueous medium undergoes conjugate addition of the soft nucleophile CN^- to give **30**. When the treatment of **17** with potassium cyanide is carried out in an aprotic solvent, higher temperature is necessary to bring about the reaction. In this condition an equilibrium between 5-methylenehydantoin **17** and its acylimino isomer **31** seems to take place; accordingly both 5-cyanomethylhydantoin **30** and 5-cyano-5-methylhydantoin **29** can be formed.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are not corrected. A Perkin Elmer 521 spectrometer was used to obtain infrared spectra in potassium bromide discs. A Varian A 60 instrument was used to record ^{1}H-nmr spectra in dimethylsulfoxide with TMS as internal standard. An AEI/MS 12 instrument was used to obtain mass spectra. Preparative layer chromatography was carried out with Merck silica gel (layers 0.5 mm thick); anhydrous sodium sulfate was used throughout as drying agent. Evaporations were under reduced pressure.

Table II



Starting Material No.	Product (b) No.	Yield (a) %
1	**11**, R = H	10
2	**11**, R = H (c)	55
3	**11**, R = H	10
4	**12**, R = CH_3	90
5	**12**, R = CH_3	95
6	**12**, R = CH_3	40
7	**13**, R = $C_6H_5CH_2OCONH$	95
8	**14**, R = CH_3CONH (d)	95
9	**13**, R = $C_6H_5CH_2OCONH$	40
9	**15**, R = CH_3CH_2OCONH (e)	55

(a) Obtained through tlc determination on the crude reaction mixture. (b) Spectroscopic data for compounds **11**, **12**, **13** are in agreement with literature. For **11** and **12** see lit (5a, 5b, 5c), for **13** see lit (3). (c) $[\alpha]_D$ = -40° (c, 2, Ethanol), lit (6),$[\alpha]_D$ = -48° (c, 2, ethanol). (d) **14**: mp 134° (from ethanol); ir: ν max 3430, 3260, 3060, 1780, 1720, 1650, 1565 cm^{-1}; *Anal.* Calcd. for $C_6H_9N_3O_3 \cdot H_2O$: C, 38.10; H, 5.86; N, 22.21. Found: C, 38.12; H, 5.85; N, 22.21. (e) **15**: mp 175° (from methanol); ir: ν max 3320-3290, 3150, 3090, 1780, 1720, 1690, 1515 cm^{-1}; *Anal.* Calcd. for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.71; H, 5.46; N, 20.89.

(±) 2-Benzyloxycarbonylamido-2-ethyloxycarbonylamidopropionic Acid.

To a stirred solution of 2.0 g of 2-benzyloxycarbonylamido-2-aminopropionic acid (3) in 25 ml of 0.5*N* sodium carbonate, were added at 0° 3.6 g of ethylchloroformate. The reaction mixture was stirred for 30 minutes at 0° and for 3 hours at room temperature; solid material was filtered, the solution acidified and extracted with ethyl acetate. Evaporation of the dried extracts gave 1.5 g of 2-benzyloxycarbonylamide-2-ethyloxycarbonylamidopropionic acid, mp 111° (from ether/light petroleum).

Anal. Calcd. for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.22; H, 5.87; N, 8.98.

General Procedure for the Preparation of the Amides **2-10**.

To a stirred solution of 1.0 mmole of carboxylic acid in 10 ml of dry tetrahydrofuran, was added 1.0 mmole of triethylamine. The solution was chilled at -8° and 1.0 mmole of ethyl chloroformate was added. The flask

was kept at -8° for 10 minutes, during which time some triethylamine hydrochloride was separated. A dry solution of 1.0 mmole of ammonia in 10 ml of tetrahydrofuran was then added and the mixture kept for 3 hours at room temperature. The solvent was evaporated, the residue taken up in ethyl acetate and washed with 1*N* hydrochloric acid, 5% sodium bicarbonate and water. The residue of the evaporation of the dried extracts was recrystallized (see Table I). Compounds **1-3** were prepared from the corresponding derivatives of L-alanine; **1**, $[\alpha]_D$ = -4.7° (*c*, 2, methanol); **2**, $[\alpha]$ = -8° (*c*, 3, methanol); **3**, $[\alpha]_D$ = -3.75° (*c*, 4, methanol). Compounds **8** and **9** were prepared from racemic carboxylic acids. For the preparation of the acids corresponding to amides **7** and **8** see references (3) and (7).

General Procedure of the Cyclization to Hydantoins.

A solution of 1.0 mmole of amide derivative in 15 ml of methanol was treated with 1.5 ml of 2*N* aqueous sodium hydroxide and left for 1.5 hours at room temperature. Then 10 ml of water was added and methanol was evaporated under reduced pressure. The aqueous solution was filtered through a Dowex A1 column, the residue evaporated, purified by preparative tlc and recrystallized.

5-Methylenehydantoin **17** from **10**.

A solution of 0.2 g of benzyloxycarbonyldehydroalaninamide (**10**) in 10 ml of methanol was treated at room temperature for 2 hours with 1.5 ml of 2*N* alcoholic sodium ethoxide. The solvent was removed and the residue purified by preparative tlc (2:1 benzene/ethyl acetate) to give 0.08 g of **17**, mp 214° (from ethyl acetate), lit (8).

5-Methyl-5-benzyloxycarbonylamidohydantoin (**18**).

A solution of 0.1 g of 5-amino-5-methylhydantoin **16** in 5 ml of dry pyridine was treated for 6 hours at room temperature with 0.134 g of benzyloxycarbonyl chloride. The residue of the evaporation was purified by preparative tlc (7:3 ether/ethyl acetate) to give 0.04 g of **18**, mp 170° (from ethyl acetate), lit (3).

5-Methyl-5-phenylacetamidohydantoin (**19**).

Procedure A.

A solution of 0.1 g of 5-amino-5-methylhydantoin **16** in 5 ml of dry pyridine was treated for 6 hours at room temperature with 0.131 g of phenylacetylchloride. After evaporation of the solvent, the residue was recrystallized from ethyl acetate to give 0.08 g of **19**, mp 214°; ir: ν max 3340, 3240, 3050, 1770, 1730, 1710, 1695, 1660, 1530 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.13; H, 5.39; N, 16.81.

Procedure B.

A mixture of 0.026 g of 5-amino-5-methylhydantoin **16**, 0.041 g of dicyclohexylcarbodiimide and 0.027 g of phenylacetic acid in 5 ml of dioxane was stirred overnight at room temperature, solid material was filtered and the solvent removed. The residue purified by preparative tlc (8:2 ethyl acetate/ether) gave 0.020 g of **19**, mp 217° (from ethyl acetate).

5-Methyl-5-tosylhydantoin **20**.

A solution of 0.1 g of 5-amino-5-methylhydantoin **16** in 5 ml of dry pyridine was treated for 10 hours at room temperature with 0.161 g of tosyl chloride. The solvent was removed and the residue purified by preparative tlc (6:4 ethyl acetate/ether) to give 0.04 g of **20**, mp 230° (from methanol/ether/light petroleum); ir: ν max 3350, 3270, 3120, 1780, 1740, 1720, 1590 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.64; H, 4.62; N, 14.83; S, 11.32. Found: C, 46.56; H, 4.65; N, 14.67; S, 11.31.

5-Methyl-5-(2,2-diethyl-2-carboethoxy)butyramidohydantoin (**21**).

A solution of 0.4 g of 5-amino-5-methylhydantoin **16** in 20 ml of dry pyridine was treated for 20 hours at room temperature with 0.7 g of 2,2-diethylmalonyl chloride monoethyl ester. After evaporation of the solvent, the residue was taken up in chloroform and washed with 1*N* hydrochloric acid and water. Evaporation of the dried extracts gave 1 g of neutral fraction. Crystallization from ethyl acetate gave 0.920 g of **21**, mp 164°; ir: ν max 3390, 3260, 3200, 3060, 1780, 1740, 1720, 1660, 1520 cm^{-1}.

Anal. Calcd. for $C_{13}H_{21}N_3O_5$: C, 52.16; H, 7.07; N, 14.04. Found: C, 52.16; H, 7.00; N, 14.02.

Alkaline Hydrolysis of **21**.

Compound **21** (0.929 g) was treated for 18 hours at room temperature with 30 ml of 2*N* sodium hydroxide, 50 ml of water was added and the solution extracted with ethyl acetate. Acidification of the aqueous phase (*p*H 3) with concentrated hydrochloric acid and extraction with ethyl acetate gave 0.720 g of **22**, mp 230° (from methanol/ethyl acetate); ir: ν max 3310, 3270, 3160, 3060, 1770, 1720, 1700, 1625, 1530 cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}N_3O_5$: C, 48.70, H, 6.32; N, 15.49. Found: C, 48.70; H, 6.31; N, 15.34.

Cyclization of **22** to 1-Acetyl-3,3-diethyl-8a-methyloctahydroimidazo-[1,5-*a*]pyrimidino-2,4,6,8-tetrone (**23**).

Compound **22** (0.3 g) was refluxed for 4 hours in 10 ml of acetic anhydride. The mixture was evaporated under vacuum and the residue purified by preparative tlc (9:1 chloroform/ether) to give 0.1 g of **23**, mp 162° (from ether); ir: ν max 3310, 3100, 1800, 1760, 1740, 1670 cm^{-1}; ms: m/e 268 (M^+), 267, 256, 252, 224, 209, 196, 183, 176, 160, 141 (base peak); ^{1}H-nmr: δ 0.85 (t, 6H), 1.68 (q, 4H), 2.0 (s, 3H), 2.4 (s, 3H).

Anal. Calcd. for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.58; H, 5.80; N, 14.50.

3,5-Dimethyl-5-benzyloxycarbonylamidohydantoin (**24**).

To a solution of 0.2 g of 5-methyl-5-benzyloxycarbonylamidohydantoin **18** in 5 ml of methanol a slight excess of diazomethane in ether was added (9); after 3 hours at 0° the solvent was removed and the residue recrystallized from methylene chloride to give 0.17 g of **24**, mp 159°; ir: ν max, 3290, 3180, 1775, 1730, 1690 cm^{-1}; ^{1}H-nmr: δ 1.4 (s, 3H), 2.8 (s, 3H), 5 (s, 5H), 8.5 (s, 1H).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.19; H, 5.44; N, 14.88.

3,5-Dimethyl-5-aminohydantoin (**25**).

3,5-Dimethyl-5-benzyloxycarbonylamidohydantoin (**24**) (0.2 g) in 10 ml of methanol was hydrogenated for 2 hours at room temperature in the presence of 0.1 g of palladium on aluminium oxide (5% palladium). The mixture was filtered from the catalyst and evaporated to a small volume to give 0.07 g of crystals of **25**. This compound decomposes by heating with loss of ammonia, without melting; ir: ν max 3340-3300, 3100, 1780, 1750, 1700 cm^{-1}; ms: m/e 143 (M^+), 129, 114, 84; ^{1}H-nmr: δ 1.25 (s, 3H), 2.75 (s, 3H), 8 (s, 1H).

Anal. Calcd. for $C_5H_9N_3O_2$: C, 41.95; H, 6.34; N, 29.35. Found: C, 42.02; H, 6.31; N, 29.34.

5-Methyl-5-methoxyhydantoin (**26**).

5-Amino-5-methylhydantoin (**16**) (0.1 g) in 10 ml of methanol was refluxed for 2.5 hours. The solvent was evaporated and the residue purified by preparative tlc (1:1 ethyl acetate/ether) to give 0.44 g of **26**, mp 136° (from ethyl acetate/light petroleum); ir: ν max 3280-3220, 3100, 1780, 1750, 1700 cm^{-1}; ms: m/e 144 (M^+), 129, 116, 113, 101, 83; ^{1}H-nmr: δ 1.4 (s, 3H), 3.08 (s, 3H), 8.3 (s, 1H), 10.8 (s, 1H).

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.67; H, 5.59; N, 19.44. Found: C, 41.69; H, 5.41; N, 19.84.

5-Methyl-5-cyanohydantoin (**29**).

A mixture of 0.26 g of 5-amino-5-methylhydantoin (**16**) and 0.65 g of potassium cyanide in 5 ml of dimethylformamide was refluxed for 30 minutes. Solid material was filtered off and the residue from the evaporation taken up in water. Continuous extraction with ethyl acetate for 12 hours gave 0.33 g of a residue which was purified by preparative tlc (8:2 ethyl acetate/ether) to give 0.1 g of **29**, mp 124° (from ether/light

petroleum); ir: ν max 3380, 3310, 3210, 3100, 2240, 1785, 1730, 1620 cm^{-1}; ms: m/e 139 (M^+), 124, 112, 96, 68, 53 (base peak); ^{1}H-nmr: δ 1.7 (s, 3H), 9 (s, 1H), 11.5 (s, 1H).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.13; H, 3.65; N, 30.23.

5-Methylhydantoin (**11**) from **29**.

5-Methyl-5-cyanohydantoin **29** (0.03 g) in 1 ml of hydrochloric acid was refluxed for 2.5 hours. The residue of the evaporation was taken up in water. Continuous extraction of the aqueous solution with ethyl acetate for 5 hours gave a residue which was crystallized from ethyl acetate/light petroleum to yield 0.01 g of **11**, mp 151°.

Anal. Calcd. for $C_4H_6N_2O_2$: C, 42.12; H, 5.30; N, 24.55. Found: C, 42.12; H, 5.29; N, 24.58. Literature (8).

5-Methyl-5-carboxyamidohydantoin (**28**).

Procedure A. From 5-Amino-5-methylhydantoin (**16**).

A mixture of 0.16 g of 5-amino-5-methylhydantoin **16** and 0.1 g of potassium cyanide in 5 ml of water was refluxed for 1.5 hours. The residue from the evaporation was taken up in methanol and solid material filtered off. The solvent was removed and the residue purified by preparative tlc (8:3 ethyl acetate/ether) to give 0.3 g of 5-methylhydantoin (**11**) and 0.02 g of 5-methyl-5-carboxyamidohydantoin (**28**). Compound **28** was recrystallized from ethyl acetate/light petroleum, mp 223°; ir: ν max 3380, 3260, 3180, 3100, 3000, 1775, 1730, 1650, 1580 cm^{-1}; ms: m/e 157 (M^+), 114 (base peak), 112, 86, 71.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 37.94; H, 4.56; N, 26.48.

Procedure B. From 5-Methyl-5-cyanohydantoin (**29**).

To a solution of 0.1 g of 5-methyl-5-cyanohydantoin (**29**) in 10 ml of water, 1*N* sodium hydroxide was added (0.5 ml). The solution was refluxed for 1 hour, neutralized with 1*N* hydrochloric acid and evaporated. After working up as in the above described procedure A, the same reaction products were isolated.

5-Methylenehydantoin (**17**) from 5-Amino-5-methylhydantoin (**16**).

5-Amino-5-methylhydantoin **16** (0.1 g) in 5 ml of dimethylformamide was refluxed for 1 hour. During the reaction ammonia evolution was observed. The solvent was removed and the residue purified by preparative tlc (8:2 ethyl acetate/ether) to give 0.03 g of **17**, mp 214° (from ethyl acetate); ir: ν max 3210-3100, 3050, 3010, 1770, 1735, 1715, 1660, 1620 cm^{-1}; ms: m/e 112 (M^+, base peak), 84, 69, 60, 52; ^{1}H-nmr: δ 4.7 (d, 1H), 5.03 (d, 1H), 10.2 (s, 1H), 11 (s, 1H), Literature (8).

Anal. Calcd. for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.86; H, 3.66; N, 25.00.

5-Cyanomethylhydantoin (**30**) from 5-methylenehydantoin (**17**).

A mixture of 0.1 g of 5-methylenehydantoin (**17**) and 0.2 g of potassium cyanide in 8 ml of water was refluxed for 1.5 hours. The residue from the evaporation was taken up in methanol, solid material filtered and the solvent removed. The residue purified by tlc (8:2 ethyl acetate/ether) gave 0.04 g of **30**, mp 147° (from ethyl acetate/light petroleum); ir: ν max 3230, 3180, 3120, 3050, 2240, 1775, 1715 cm^{-1}; ms: m/e 139 (M^+), 99 (base peak) 86, 68; ^{1}H-nmr: δ 2.92 (d, 2H), 4.38 (t, 1H), 8.12 (s, 1H), 10.9 (s, 1H).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.16; H, 3.70; N, 30.29.

5-Methyl-5-cyanohydantoin (**29**) and 5-Cyanomethylhydantoin (**30**) from 5-Methylenehydantoin (**17**).

A mixture of 0.3 g of 5-methylenehydantoin (**17**) and 0.6 g of potassium cyanide in 20 ml of dimethylformamide was refluxed for 1 hour. Solid material was filtered off and the residue from the evaporation purified by preparative tlc (8:2 ethyl acetate/ether) to give 0.06 g of **29** and 0.04 g of **30**.

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