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SUBSTITUTION IN THE HYDANTOIN RING—I

AMINOMETHYLATION

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Abstract The behaviour of the hydantoin ring in the aminomethylation reaction was studied in order to determine the orientation of this substitution. It was found that position 3 is the most reactive one and this result is rationalized in terms of influence of structural factors.

Mono-aminomethyl derivatives of hydantoins (I to XV) are described.

CONSIDERING the different positions where an atom or group can be introduced in the hydantoin ring, several papers[1] show that substitution occurs either at the nitrogen in position 1 or in position 3, or at the carbon in position 5. Substitution in N_1 occurs more frequently, for example nitration and formaldehyde in acid medium; the introduction of only one alkyl group results always in substitution at position 3 but these compounds can be further alkylated in position 1;[2] regarding substitution in position 5, it is known that condensation with aldehydes (usually aromatic aldehydes) takes place with the methylene group at C_5.

The simultaneous introduction of two aminomethyl groups was achieved by Bombardieri and Taurins[3] who obtained the 1,3-bis(N-morpholinomethyl)-derivatives by reaction of hydantoin or its 5,5-dimethyl derivatives with formaldehyde and morpholine in yields of 22 and 40 per cent respectively. They also report that the 1,3-bis(N-morpholinomethyl)-derivatives are hydrolysed by acid.

The purpose of this work—by the introduction of the aminomethyl group into only one position of the hydantoin ring - was to determine the orientation of this substitution reaction. The monosubstituted derivatives (I XV) were prepared from equimolecular amounts of the hydantoin, the secondary amine and formaldehyde in yields of 63–100 per cent except for compound V, the yield in this case being only 31 per cent.

The former approach for solving the structure of the mono-aminomethyl-derivatives was by means of the Stuckey's spectroscopic method.[4] According to this method hydantoins with hydrogen on the nitrogen in position 3 show a bathochromic displacement in the ultra-violet region and an increase in intensity of absorption when changing from neutral or acid medium to an alkaline one. Generally, instead of the end absorption that hydantoins present in neutral or acid medium, there is an appearance of a maximum in alkaline solution. Using the 1,5,5-trimethylhydantoin it was shown here that the observed maximum is simply a shift of one already present at

[1] E. Ware, *Chem. Rev.* **46**, 403 (1950).
[2] A. Novelli, Z. M. Lugones and P. Velasco, *Anales asoc. quim. Argentina* **30**, 225 (1942).
[3] C. C. Bombardieri and A. Taurins, *Canad. J. Chem.* **33**, 923 (1955).
[4] R. E. Stuckey, *J. Chem. Soc.* 331 (1947).

lower wavelength that he assumed, but could not observe due to limitations of the experimental procedure (Table 1).

The ultra-violet spectra of compounds VIII and X show a maximum at 221 mμ in alkaline medium and only end absorption in neutral solution. These results should indicate that substitution took place at N_1 but this conclusion is invalidated by the following observations: the 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin (XI) and the 1,3-bis(N-morpholinomethyl)-5,5-dimethylhydantoin (XVI), in which both positions are occupied, show this same type of displacement of their spectra in alkaline medium. In alkaline medium identical spectra are obtained for 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin (XI) and 1,5,5-trimethylhydantoin (literature[4]: λ_{max} 231 mμ; log ε_{max} 3·91), and similarily the spectra for compounds XVI, VIII and X are coincident.

TABLE 1.—ABSORPTION IN THE ULTRAVIOLET REGION[a]

Compound	Neutral medium		Alkaline medium[b]	
	λ_{max}	log ε_{max}	λ_{max}	log ε_{max}
1,5,5-Trimethylhydantoin	214	3·49	229	3·72
X[c]	end absorption		221	3·83
VIII	idem		220	3·82
1,3-Bis(N-morpholinomethyl)-5,5-dimethylhydantoin	idem		221	3·82
3-(N-Piperidinomethyl)-1,5,5-trimethylhydantoin	217	3·50	230	3·73

[a] Solvent: alcohol 50°; λ in mμ
[b] Sodium hydroxide 0·01 N.
[c] In absolute alcohol and alkaline medium with sodium ethoxide the results were coincident.

These facts lead to the definite conclusion that in alkaline solution a fission of the linkage between the hydantoinic nitrogen and the aminomethyl group occurs, thus regenerating the parent hydantoin: 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin giving the 1,5,5-trimethylhydantoin and the substances XVI, VIII and X affording 5,5-dimethylhydantoin. The values here given for the last three aminomethylderivatives in alkaline medium agree with registered values[4] for the 5,5-dimethylhydantoin (λ_{max} 223 mμ; log ε_{max} 3·88).

This cleavage is very fast since the spectrum registered within four minutes after the addition of the base may be exactly reproduced after 24 hours.

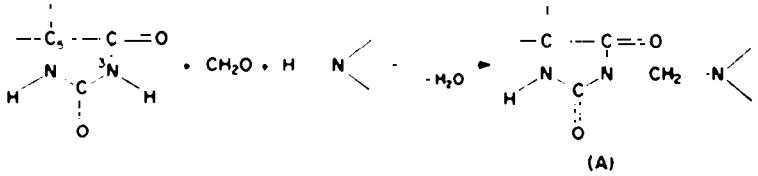
A successful approach to this structural problem is based on comparative methylations of 1,5,5-trimethylhydantoin and 3,5,5-trimethylhydantoin with diazomethane; substitution only being possible at the more acidic N- -H in position 3. This reaction affords a new method for distinguishing substitution at positions 1 or 3 of the hydantoin ring, and depends like others (increase of solubility in water by alkali[5] and electrometric titration[6]) on the difference in acidity of the hydrogens in positions 1 and 3; on account of the behaviour of the aminomethyl-derivatives with bases, it is possible to predict that the two methods[5,6] cannot here be applied.

The methylation of the 1,5,5-trimethylhydantoin with diazomethane appears in the literature[7] and the product m.p. 85° described as 1,3,5,5-tetramethylhydantoin must have been impure since the substance obtained either by methylation in the usual

[5] See for example G. P. Lampson and H. O. Singher, *J. Org. Chem.* **21**, 684 (1956).
[6] L. W. Pickett and M. McLean, *J. Amer. Chem. Soc.* **61**, 423 (1939).
[7] H. Biltz and K. Slotta, *J. Prakt. Chem.* **113**, 233 (1926).

way (methyl iodide in alkaline medium) or with diazomethane melts at 106–106·5°. This compound does not show the N—H band in the infra-red present in the starting hydantoin (KBr: 3·21 μ; Nujol: 3·22 μ) and the methoxyl analysis, being zero, indicates beyond doubt that the compound is the 1,3,5,5-tetramethylhydantoin.

Since VI, VIII, X and XII cannot be methylated with diazomethane it is concluded that *the aminomethyl group in these compounds is situated at* N–3 *position.*



(A)

Further evidence supporting this conclusion is provided by comparison of the easiness of reaction with appropriately substituted hydantoins (Table 2). The 1-methylderivatives of hydantoins (1,5,5-trimethylhydantoin and 1-methyl-5,5-pentamethylenehydantoin), react at 20° with morpholine or piperidine (and formaldehyde) producing in very high yields (74 to 91 per cent) the expected products. Applying the same conditions to the isomers methylated in N_3 (3,5,5-trimethylhydantoin and 3-methyl-5,5-pentamethylenehydantoin) the starting compounds are recovered quantitatively or in good yield.

TABLE 2.—EASE OF FORMING MONO-AMINOMETHYLDERIVATIVES

Starting hydantoin	Morpholine		Piperidine	
	% isolated product	% recovered hydantoin	% isolated product	% recovered hydantoin
3-Methyl-[a]	28	59		
1,5,5-Trimethyl-	79		91	
3,5,5-Trimethyl-		85[b]		45
1-Methyl-5,5-pentamethylene-	74		74	
3-Methyl-5,5-pentamethylene-		100		100
Hydantoin[a] (unsubstituted)	75			
5,5-Dimethyl-	100		67	
5,5-Pentamethylene-	97		83	

[a] in dilute solution; [b] 95% in dilute solution.

The parent hydantoins with no substituent on the nitrogen atoms afford the mono-aminomethylderivatives in good yields and these compounds are, therefore, regarded as N–3-derivatives(A). Comparing hydantoin itself and its 3-methyl-derivative (in more dilute solution than for the preceding comparisons) similar results were obtained (Table 2).

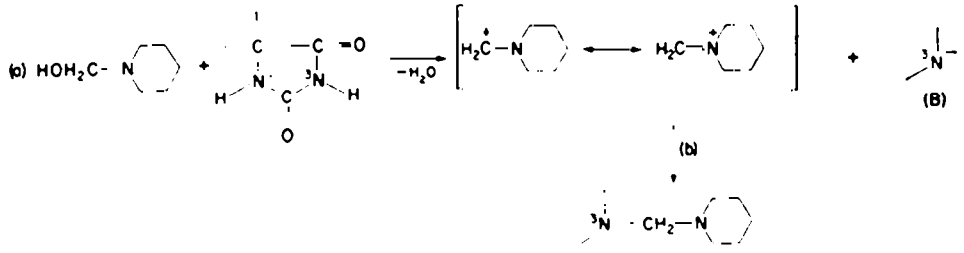
Several attempts at acetylating VIII to transform it into the 1-acetyl-3-(N-morpholinomethyl)-5,5-dimethylhydantoin(IV) and looking for further structural evidence were unsuccessful.

The mechanism of aminomethylation reactions have been extensively discussed by Hellmann and Opitz[8] who assign to the carbonium-immonium ion (originated

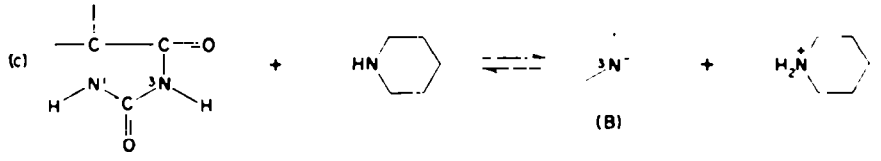
[8] H. Hellmann and G. Opitz, *Angew. Chem.* **68**, 265 (1956).

from formaldehyde, secondary amine and a proton) primordial importance as aminomethylating agent. On the other hand Zinner *et al.*[9] point out that the formation of N-aminomethylderivatives may occur through this same path or by initial reaction between formaldehyde and the "acidic" component N—H, and they give experimental data supporting that the hydroximethylbenzazole is an intermediate in the aminomethylation of benzazoles with secondary amines.

Considering either mechanism it can be explained why the N_3—H is more reactive than the N_1—H under the conditions studied. After the hydroximethylderivative of the secondary amine is formed, the carbonium-immonium ion will be originated (a) reacting N_3—H predominantly because its acid dissociation constant (pK_a 9·12 for the hydantoin[10]) is much higher than that of N_1—H (pK_a 14 or more[6]); the hydantoin anion (B) that leads to the final product according to (b) being formed at the same time.



If instead the reaction starts with nucleophilic attack on the formaldehyde by the "acidic" component N—H, the most reactive part will also be N_3—H since according to the procedure used the equilibrium (c) is first established wherein position 3 will participate prevailing over position 1, and hence the hydantoin anion (B) will be the one added to the formaldehyde.



Considering either reaction mechanism it could be anticipated that in the presence of one mole of acid the aminomethylation would be made difficult by the opposition of the acid to the dissociation of N_3—H and N_1—H (as mentioned above the whole process leading to the carbonium-immonium ion from the amine and formaldehyde requires a proton): in fact aminomethylation of 5,5-dimethylhydantoin using morpholine hydrochloride instead of the free base, under conditions (65°) in which both nitrogens are attacked, yielded only 5 per cent of compound VIII and 92 per cent of the unreacted hydantoin was recovered.

Other experiments show that for hydantoins substituted at C_5, there are reasons of a steric nature, besides the electronic factors, that make position 3 the easier to react.

[9] H. Zinner and B. Spangenberg, *Chem. Ber.* **91**, 1432 (1958), and references therein cited.
[10] J. K. Wood, *J. Chem. Soc.* **89**, 1831 (1906).

From the 3,5,5-trimethylhydantoin it is possible to obtain the 1-(N-morpholinomethyl)-3,5,5-trimethylhydantoin carrying out the reaction at 65°, but under identical conditions the 3-methyl-5,5-pentamethylenehydantoin does not react. Accordingly, the bis-morpholinomethylderivative in positions 1 and 3 of the 5,5-dimethylhydantoin, already described in the literature,[3] is obtained in good yield under conditions wherein the 5,5-pentamethylenehydantoin is only substituted in position 3 (almost quantitative yield of compound XII) even if the heating is much longer.

By comparison of the results obtained in aminomethylation experiments carried out in dilute solution (Table 2) with 3,5,5-trimethylhydantoin and with 3-methylhydantoin (recovering 95 and 59 per cent of unreacted hydantoin respectively), it is concluded that two methyl groups at C_5 render substitution at N_1 more difficult; their influence must be due on the one hand to steric hindrance and on the other hand to the decreased acidity of N_1– H owing to the exerted inductive effect.

EXPERIMENTAL*

Monoaminomethyl derivatives. The following procedure was generally used. The secondary amine (0·001 mole) was added to a solution of the hydantoin (0·001 mole) in methanol (1 ml) cooled in a water bath (heat is evolved) and to the solution thus obtained formaldehyde (40% aqueous solution, 0·001 mole) was added. After standing 2 hr at room temp the solution was evaporated to dryness in vacuum and benzene was added several times to ensure the removal of all the water from the crude product.

Direct crystallization of the latter furnished the desired derivative except for II and V whose isolation was done as follows.

3-(N-*Piperidinomethyl*)-5-*methyl*-5-*ethylhydantoin*(II). The partly oily crude product was dissolved in benzene and chromatographed† in a column of neutral Woelm alumina (2·5 g) activity II, eluting with the same solvent and taking fractions of 5 ml each. Practically all the product was collected in the first fraction (partly oily) and only a few mg more were obtained from the next fractions using the same solvent, benzene chloroform and chloroform. Crystallization of the first fraction gave compound II.

1-(N-*Morpholinomethyl*)-3,5,5-*trimethylhydantoin*(V). The crude product was chromatographed (5 g of alumina Woelm, neutral, activity II) using successively benzene, benzene with gradual addition of chloroform and finally chloroform for elution. The benzene eluted fraction after recrystallization afforded compound V; the eluate from benzene chloroform (9:1 to 1:1) furnished 27 mg of the starting 3,5,5-trimethylhydantoin identified by m.p. and mixed m.p.

In Table 3 data about purification, analysis, etc. of the aminomethylderivatives are given.

Comparisons of reactivities. Hydantoins and their 1 and 3-methyl derivatives were compared in reactions with morpholine and piperidine maintaining the solution in a thermostat and following the general procedure above described; reaction conditions and results are indicated in Tables 2 and 3.

The comparison of the pentamethylenehydantoin derivatives were performed at 65° because at 20° it is not possible to obtain a homogeneous medium since the 5,5-pentamethylenehydantoin and its 3-methyl derivative do not dissolve completely and with the former, the reaction product soon begins to separate.

From the experiments with 3-methyl-5,5-pentamethylenehydantoin and morpholine or piperidine (65°; 6 hr) washing the crude product with hexane, the unreacted hydantoin was recovered quantitatively (m.p. and mixed m.p.) The 3-methyl-5,5-pentametilenehydantoin was prepared by methylation of the parent hydantoin with methyl iodide in alkaline medium working as for the 1,3,5,5-tetramethylhydantoin (see below); yield 60%, m.p. 210 211° (methanol) (literature:[11] m.p. 212 213°).

* The m.p., taken in sealed capillaries, are not corrected; the ultraviolet and infra-red spectra were measured in Cary (Model 11 MS) and Perkin-Elmer (model 21) recording spectrophotometers respectively. The microanalyses were carried out by Dr. A. Bernhardt (Mülheim, Germany).

† The elution of the aminomethyl derivatives should be done quickly to avoid a long contact with the alumina since otherwise with some of these substances considerable decomposition was observed.

[11] H. C. Carrington and W. S. Waring, *J. Chem. Soc.* 354 (1950).

TABLE 3. MONOAMINOMETHYL DERIVATIVES OF HYDANTOINS

	Hydantoin derivative	Reaction conditions[a] ml CH_2O; T°; hr	Purification solvent; m.p.; (yield %)	Analytical sample: m.p.	C	H	N	O
					required %			
					found			
(I)[b]	3-(N-Morpholinomethyl)-5-methyl-5-ethyl $C_{11}H_{19}N_3O_3$		benzene; 146–147° (73)	147–148°	54·75	7·94	17·42	19·89
					55·01	7·91	17·33	19·99
(II)[a]	3-(N-Piperidinomethyl)-5-methyl-5-ethyl $C_{12}H_{21}N_3O_2$		benzene–hexane; 127·5–128·5° (63)	130–131°	60·22	8·85	17·56	
					60·11	8·47	17·33	
(III)	3-(N-Morpholinomethyl)-5-methyl-5-isopropyl $C_{12}H_{21}N_3O_3$		dioxane–hexane; 155·5–156·5° (88)	156–157°	56·44	8·30	16·46	18·80
					56·55	8·34	16·32	18·99
(IV)[d]	1-Acetyl-3-(N-morpholinomethyl)-5,5-dimethyl $C_{12}H_{19}N_3O_4$		benzene–hexane; 91–93° (84)	94–96°	53·52	7·11	15·61	23·76
					53·59	7·14	15·59	24·05
(V)[c,e]	1-(N-Morpholinomethyl)-3,5,5-trimethyl $C_{11}H_{19}N_3O_3$	65°; 12	benzene–hexane; 76–78° (31)	78–79°	54·75	7·94	17·42	
					54·83	7·84	17·57	
(VI)	3-(N-Morpholinomethyl) $C_8H_{13}N_3O_3$	6·5; 20°; 1	ethyl acetate; 128–130° (75)	132–133°	48·23	6·58	21·09	24·10
					47·91	6·53	21·20	24·44
(VII)[c,e]	1-(N-Morpholinomethyl)-3-methyl $C_9H_{15}N_3O_3$	idem	ethyl acetate–hexane; 101–102° (28)	102–103°	50·69	7·09	19·71	22·51
					50·27	7·29	19·62	22·70
(VIII)[h]	3-(N-Morpholinomethyl)-5,5-dimethyl $C_{10}H_{17}N_3O_3$	1; 20°; 1	141–142° (100)	148–149° (benzene)	52·85	7·54	18·49	21·12
					53·10	7·59	18·42	21·30
(IX)	3-(N-Morpholinomethyl)-1,5,5-trimethyl $C_{11}H_{19}N_3O_3$	idem	hexane; 73–76° (79)	76–78°	54·75	7·94	17·42	19·89
					54·81	7·92	17·37	20·13
(X)	3-(N-Piperidinomethyl)-5,5-dimethyl $C_{11}H_{19}N_3O_2$	idem	hexane; 93–95° (67)	96–98° (dioxane–hexane)	58·64	8·50	18·65	14·21
					58·57	8·65	18·20	14·04
(XI)	3-(N-Piperidinomethyl)-1,5,5-trimethyl $C_{12}H_{21}N_3O_2$	idem	hexane; 90·5–94° (91)	94·5–95·5° (AcOEt)	60·22	8·85	17·56	13·37
					59·72	8·84	17·41	13·29
(XII)[f]	3-(N-Morpholinomethyl)-5,5-pentamethylene $C_{12}H_{21}N_3O_3$	3; 65°; 1	178–179° (97)	181–182° (dioxane–hexane)	58·40	7·92	15·72	17·96
					58·26	7·96	15·73	18·33
(XIII)	3-(N-Morpholinomethyl)-1-methyl-5,5-pentamethylene $C_{14}H_{23}N_3O_3$	idem	hexane; 76–78° (74)	77–78° (AcOEt–hexane)	59·76	8·24	14·94	17·06
					59·75	8·36	15·01	17·06
(XIV)	3-(N-Piperidinomethyl)-5,5-pentamethylene $C_{14}H_{23}N_3O_2$	idem	dioxane; 189–193° (84)	191–193° (alcohol)	63·36	8·74	15·84	12·06
					63·42	8·66	16·05	12·23
(XV)	3-(N-Piperidinomethyl)-1-methyl-5,5-pentamethylene $C_{13}H_{23}N_3O_2$	idem	hexane; 80–81° (74)	81–81·5°	64·48	9·02	15·04	11·46
					64·52	8·78	15·28	11·70

[a] Deviations from the general procedure are specified.
[b] During the reaction crystallized from the solution.
[c] For isolation see text.
[d] Due to the low solubility of the 1-acetyl-5,5-dimethylhydantoin double volume of methanol was used and even so only after addition of formaldehyde a complete solution was obtained.
[e] With 3,5,5-trimethylhydantoin working as for VII, VIII and X, the starting hydantoin (m.p. and mixed m.p.) was recovered in 95, 85 and 45% respectively washing the crude product with hexane; aminomethylderivatives not isolated.
[f] Recrystallization of crude product from 3·5 ml benzene gave 59% of the starting hydantoin identified by m.p. and mixed m.p.; compound VII was obtained after evaporating the mother liquor.
[g] By heating 12 hr at 65° (as for compound V) the same derivative VII was obtained, m.p. 101·5–103° (yield 72%).
[h] Washed with hexane.
[i] Quantitative yield was also obtained using 6 ml methanol, room temperature and stirring.

Aminomethylation using morpholine hydrochloride. To a solution of 5,5-dimethylhydantoin (0·001 mole) and morpholine hydrochloride (0·001 mole) in methanol (1 ml), formaldehyde (solution 40%, 0·001 mole) was added and heated for 12 hr in a bath at 65°. After evaporation to dryness in vacuum, the residue was dissolved in a solution of sodium bicarbonate (0·001 mole) in water (2·5 ml) and then evaporated again under diminished pressure (benzene was added to remove water completely).

The dry residue was extracted with hot benzene (1 ml) which by concentration to a small volume afforded 11 mg (5%) of a compound m.p. 143–147° proved to be identical with compound VIII by mixed m.p.

The material unextracted by benzene was re-extracted with several portions of hot absolute ethanol and upon evaporation of the combined alcoholic extract yielded 0·118 g (92%) of 5,5-dimethylhydantoin, identified by its m.p. and mixed m.p.

Methylations with diazomethane. For these reaction excess of diazomethane in ethereal solution was used (prepared from 0·003 mole of Diazald[12]) and directly distilled into a dioxane solution of 0·001 mole of the substance to be methylated; the final solution was allowed to stand 24 hr in a refrigerator and then evaporated under reduced pressure.

Compounds VI, VIII, X, XII and 3,5,5-trimethylhydantoin were recovered quantitatively and identified by m.p. and mixed m.p.; attempts to methylate X and the 3,5,5-trimethylhydantoin using dichloromethane as solvent and adding 0·0012 mole of the boron trifluoride–ethyl ether complex were also unsuccessful.

Under the conditions indicated formerly, 1,5,5-trimethylhydantoin furnished[7] after recrystallization of the crude product from ethyl ether–hexane 0·110 g (71%) of 1,3,5,5-*tetramethylhydantoin*, m.p. 101–106°, which recrystallized again from ethyl ether provided 68 mg, m.p. 105–106°. (Found: C, 53·84; H, 7·58; N, 17·71; O, 20·31; —OCH_3, 0·00. $C_7H_{12}N_2O_2$ requires: C, 53·81; H, 7·75; N, 17·93; O, 20·48%).

The same substance was obtained by methylation with methyl iodide: a solution of 1,5,5-trimethylhydantoin (0·01 mole) in alcohol (6 ml) containing sodium hydroxide (0·01 mole) was mixed with methyl iodide (0·011 mole) and heated 3 hr at 60° followed by evaporation in vacuum. Extractions of the solid with ethyl ether and concentration gave 0·530 g (34%) of 1,3,5,5-tetramethylhydantoin, m.p. 103–105° which after further recrystallizations from acetone–ethyl ether remained constant at 106–106·5°; there was no depression in the m.p. when mixed with the sample obtained with diazomethane.

Acetylation attempts. The acetylation of VIII following several procedures was unsuccessful. Acetyl chloride in pyridine (at 25° or 65°); in excess of acetic anhydride at 80° or 130°; acetic anhydride and pyridine at 110°; sodium hydride in benzene and subsequent addition of acetyl chloride; ketene in presence of anhydrous sodium acetate,[13] and silver perchlorate and acetyl chloride in nitromethane. It was not possible to obtain the acetylated product and the starting substance (VIII) could be recovered only in some cases and in low yields.

Attempt to obtain the 1,3-*bis*(N-*morpholinomethyl*)-5,5-*pentamethylenehydantoin.* To a solution of 5,5-pentamethylenehydantoin (0·002 mole) in methanol (6 ml) morpholine (0·004 mole) and formaldehyde (solution 40%, 0·004 mole) were added and maintained at 65° during 15 hr (homogeneous medium throughout the heating period). The solvent was removed in vacuum and the residue after washing with 2 ml warm hexane gave 3-(N-morpholinomethyl)-5,5-pentamethylenehydantoin (0·500 g; 94%), m.p. 175–178°, and gave no depression when mixed with the above described specimen XII.

Under identical conditions but using 5,5-dimethylhydantoin and heating 2 hr with subsequent removal of the solvent (in vacuum) a solid was obtained which after recrystallization twice from cyclohexane yielded 0·340 g (52%) of 1,3-bis(N-morpholinomethyl)-5,5-dimethylhydantoin (XVI), m.p. 129–132° which was raised to 134–136° (literature:[8] m.p. 134–134·5°) by recrystallization from hexane. (Found: C, 55·14; H, 7·64. Calc. for $C_{16}H_{28}N_4O_4$: C, 55·19; H, 8·03%).

[12] Th. J. DeBoer and H. J. Backer, *Rec. Trav. Chim.* **73**, 229 (1954).
[13] R. E. Dunbar and W. M. Swenson, *J. Org. Chem.* **23**, 1793 (1958).