Methylenation of the Nitrogen–Halogen Bond of Positive Halogen Compounds [1]

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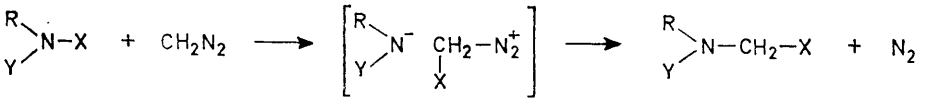
The N–X bond of positive halogen compounds (I) can be readily methylenated at 15° with diazomethane to give the *N*-halogenomethyl derivatives (III), not isolated as such but directly condensed with nucleophiles [sodium *p*-nitrophenoxide, diethyl phthalimido(sodio)malonate, and morpholine]; the parent N–H compounds (VII) are formed as secondary products. This new reaction has been applied to *N*-halogeno-*N*-substituted carboxamides, sulphonamides, phosphoramides, and urethanes. The mechanism of the methylene insertion into the N–X linkage is discussed.

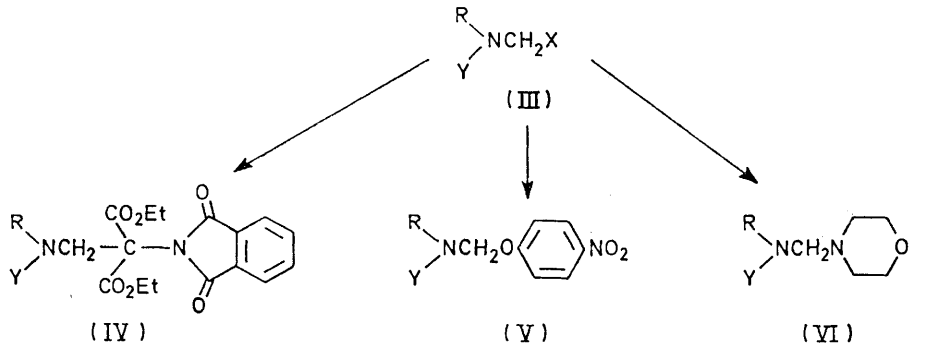
NUMEROUS examples of insertion of a methylene group into the bond between a halogen and another atom by using diazomethane or its derivatives have been described.[2] In some cases the formation of ethylene or polymethylene becomes significant or prevails over the methylene insertion.[3] Prior to our preliminary communications [1] the data on N–X methylenations were limited to those obtained with the non-positive-halogen compounds, nitryl and nitrosyl chlorides.[2]

The reaction in Scheme 1 was performed with 1-chloro-3,5,5-trimethylhydantoin and then applied to some other positive halogen derivatives (I); [1] this paper includes further data on these compounds and the results with some other examples (Table 1). Other authors,[4] following our preliminary communication,[1a] have assumed an analogous diphenylmethylene insertion in the reaction of diphenyldiazomethane with *NN*-dichloroarylsulphonamides.



(I) (II) (III)

SCHEME 1



(IV) (V) (VI)

SCHEME 2

The crude product from 1-chloro-3,5,5-trimethylhydantoin (If') and diazomethane exhibits one sharp n.m.r. signal at δ 5·35 due to the NCH_2Cl or OCH_2Cl group; these two possibilities are considered since the anion component of the assumed intermediate (II) is bidentate. The presence of an *N*-halogenomethyl group in (III) is demonstrated by treatment with morpholine leading to the known *N*(1)-morpholinomethyl derivative (VIf'); the dicarbonyl system of (VIf'), and hence the location of the substituent at N(1), is confirmed by the i.r. absorption [5] [$\nu_{max.}$ (Nujol) 1768 and 1704 cm^{-1}]. Furthermore, the n.m.r. spectrum of 1-hydroxymethyl-3,5,5-trimethylhydantoin shows the methylene resonance [N(1)CH_2OH] as a doublet at δ 4·90 which is replaced by a singlet at 5·35 [N(1)CH_2Cl] on adding thionyl chloride. The same regiospecificity was observed with 1-chloropyrrolidin-2-one (Il).

Owing to the difficulty in isolating [6] the *N*-halogenomethyl derivatives (III), the methylenation of a variety of *N*-chloro-*N*-substituted-amides and imides [with (Id') the bromo- or iodo-analogues were also used] was followed by condensation with nucleophiles [6,7] (Scheme 2).

[1] Preliminary communications: (*a*) R. A. Corral and O. O. Orazi, *Tetrahedron Letters*, 1964, 1693; (*b*) O. O. Orazi, R. A. Corral, and H. Schuttenberg, *ibid.*, 1969, 2639; this includes the results of the Doctoral Thesis of H. S. (Universidad Nacional de La Plata, 1967).

[2] D. Seyferth, *Chem. Rev.*, 1955, **55**, 1155; B. Eistert, M. Regitz, G. Heck, and H. Schwall, in Houben-Weyl's 'Methoden der Organische Chemie,' ed. E. Müller, vol 10/4, Georg Thieme Verlag, Stuttgart, 1968, p. 692; G. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, **24**, 119.

[3] G. Wittig and K. Schwarzenbach, *Annalen*, 1961, **650**, 1; G. Wittig and F. Wingler, *Chem. Ber.*, 1964, **97**, 2139.

[4] A. Schönberg and E. Singer, *Chem. Ber.*, 1968, **101**, 3445.

[5] O. O. Orazi, R. A. Corral, and H. Schuttenberg, *J.C.S. Perkin I*, 1974, 219, and references cited therein.

[6] N. Kreutzkamp, H. Meerwein, and R. Stroh, in Houben-Weyl's 'Methoden der Organische Chemie,' ed. E. Müller, vol. 5/4, Georg Thieme Verlag, Stuttgart, 1960, p. 694; H. Böhme, A. Dick, and G. Driesen, *Chem. Ber.*, 1961, **94**, 1879.

[7] H. Zahn, R. Dietrich, and W. Gerstner, *Chem. Ber.*, 1955, **88**, 1737; H. Böhme, A. Dick, and G. Driesen, *Arch. Pharm.*, 1961, **294**, 312; H. Gross and E. Höft, *Z. Chem.*, 1964, **4**, 401.

TABLE 1

Methylation of *N*-halogeno-derivatives of *N*-substituted amides and imides

Carboxamides	Y	R	Condensation product [b]	Yield (%)	M.p. (°C)	Cryst. solvent [c]
(Ia)	HCO	Me	(IVa)	64	122—123	A–B
(Ib)	MeCO	Me	(IVb)	53	151·5—152	AA
(Ic)	MeCO	Cyclohexyl	(IVc)	37	165—166	A
(Id)	MeCO	$PhCH_2$	(IVd)	84	129—129·5	A
(Ie)	$ClCH_2CO$	Me	(IVe)	64	140—141	A–B
(If)	Pr^nCO	Me	(IVf)	59	108—109	A–B
(Ig)	Bu^tCO	Me	(IVg)	74	147—148	A
(Ih)	Cyclobutyl·CO	Me	(IVh)	70	146—147	A
(Ii)	Cyclopentyl·CO	Me	(IVi)	72	139—140	A
(Ij)	Cyclohexyl·CO	Me	(IVj)	66	119—120	B
(Ik)	PhCO	Me	(IVk)	80	181·5—182·5	AA
Lactams						
(Il)	$OC[CH_2]_2CH_2$		(IVl)	86	144—145	A
(Im)	$OC[CH_2]_3CH_2$		(IVm)	69	182—183	A
(In)	$OC[CH_2]_4CH_2$		(IVn)	68	140—141	A
Sulphonamides						
(Io)	$MeSO_2$	Me	(IVo)	37	172—173	A
(Ip)	$MeSO_2$	$PhCH_2$	(IVp)	38	221—222	A
(Iq)	*p*-$MeC_6H_4SO_2$	Me	(IVq)	51	159—159·5	AA
			(Vq)	58 [d]	162—162·5	C
			(VIq) [e]	42	83—84	E–D
(Ir) [f]	*p*-$MeC_6H_4SO_2$	Et	(IVr)	68	161—161·5	A
(Is)	*p*-$MeC_6H_4SO_2$	Pr^i	(IVs)	70	171—172	A
(It)	*p*-$MeC_6H_4SO_2$	Bu^t	(IVt)	22	146·5—147·5	A
			(Vt)	35	155·5—156·5	A
(Iu)	*p*-$MeC_6H_4SO_2$	Cyclohexyl	(IVu)	60	165—166	A
(Iv)	*p*-$MeC_6H_4SO_2$	$PhCH_2$	(IVv)	57	149—150·5	A
Phosphoric amides						
(Iw)	$(PhO)_2PO$	Me	(IVw)	70	129—130	A
(Ix)	$(PhO)_2PO$	Bu^n	(IVx)	60	126—127	A
(Iy)	$(PhO)_2PO$	$PhCH_2$	(IVy)	57	121—122	A
Urethanes						
(Iz)	EtOCO	Me	(IVz)	63	93—94	A
(Ia′)	EtOCO	Et	(IVa′)	60	82—83	A
(Ib′)	EtOCO	Bu^n	(IVb′)	59	79—80	B–D
(Ic′)	EtOCO	$PhCH_2$	(IVc′)	63	127—128	A–B
Imides and hydantoins [g]						
(Id′)	$OC[CH_2]_2CO$		(VId′) [h]	84	184—185 (decomp.)	F
(Id′) (X = Br)	$OC[CH_2]_2CO$		(VId′)	55		
(Id′) (X = I)	$OC[CH_2]_2CO$		(VId′)	52		
(Ie′)	3-Chloro-1,5,5-trimethylhydantoin		(VIe′) [i]	76	76—78	D
(If′)	1-Chloro-3,5,5-trimethylhydantoin		(VIf′) [i]	75	75—76	D

[a] Unless noted otherwise, X = Cl. [b] Known compounds (VI) were identified by m.p. and mixed m.p. New compounds, (IV) and (V), were analysed for all elements except oxygen and gave results within ±0·3% of the calculated values, except the P data for (IVw) (Required: 5·35. Found: 4·75 and 6·2%). Mass spectral measurements on (IVw) by Dr. D. H. Hunneman (Varian-MAT; Bremen, West Germany) with a CH7 instrument [Found: M^+, 580·155; intensity ratio of $M^+ : (M + 1)^+ : (M + 2)^+$, 100 : 34 : 9. $C_{29}H_{29}N_2O_9P$ requires *M*, 580·161; $M^+ : (M + 1)^+ : (M + 2)^+$, 100 : 33 : 7]. [c] A = 95% EtOH; AA = abs. EtOH; B = di-isopropyl ether; C = acetone; D = hexane; E = benzene; F = dioxan. [d] Replacement of dioxan by other solvents gave the following yields (%) of (Vq): Et_2O, 51; benzene, 53; DMF, 10; $PhNO_2$, 3. [e] H. Hellmann and K. Teichmann, *Chem. Ber.*, 1958, **91**, 2432. [f] With benzoyldiazomethane (prepared according to P. Yates and B. L. Shapiro, *J. Amer. Chem. Soc.*, 1959, **81**, 212) instead of diazomethane, the consumption of positive chlorine was 8% after 2 h. [g] (Id′; X = Cl, Br, or I) (2 mmol) in dioxan (7 ml); for further details see ref. 1*a*. [h] As the picrate salt: W. I. Weaver, J. K. Simons, and W. E. Baldwin, *J. Amer. Chem. Soc.*, 1944, **66**, 222. [i] O. O. Orazi and R. A. Corral, *Tetrahedron*, 1961, **15**, 93.

The results of Table 1 demonstrate the wide scope of the methylenation reaction and illustrate its preparative usefulness. The products (IV) and (V) are new and their structures are supported by analytical and n.m.r. data. The overall yields are higher than 50% in 31 out of the 37 examples studied.

The low yields from (Io), (Ip), and (Iq) [the latter only giving (VIq)] are ascribed to isolation losses, since the analyses for labile halogen [roughly proportional to the amount of compound (III) formed] gave values higher than 70%; furthermore, (Iq) furnishes higher yields with other nucleophiles [to give (IVq) and (Vq)]. With (Ic) and (It) the amount of labile halogen was lower (*ca.* 40%) indicating that another reaction predominates. The n.m.r. spectra of the crude mixtures from the methylenation of (If), (Ig), (Il), (It), and (If') either by attack on the substrate by free (under irradiation) or complexed (with Cu^{I}) carbene or by co-ordination of the donor diazomethane molecule with the halogen-supporting atom. These alternatives are excluded for the methylenation described here by the reaction conditions used and by the inability of the nitrogen atom in (I) to accept an electron pair, respectively.

The reaction occurs very rapidly without initiator and does not show an induction period. The methylenation of *N*-chloro-*N*-methylbutyramide (If) does not take place in the non-polar solvent pentane,[10] whilst it is complete after 15 min in dioxan–benzene. These data favour a polar mechanism.

It is suggested [1a] that the reaction starts with abstraction of the positive halogen by diazomethane

TABLE 2

New *N*-chloro-amides (I) [a]

	Y	R	Preparation procedure *	Yield (%)	B.p. (°C) (*p*/Torr)	M.p. (°C)
(Ia)	HCO	Me	B	45	51—52 (40)	
(Id)	MeCO	$PhCH_2$	A	90		23—24 [b]
(Ie)	$ClCH_2CO$	Me	B	92	82—83 (9)	
(If)	Pr^nCO	Me	B	71	64—66 (20)	
(Ih)	Cyclobutyl·CO	Me	B	65	68—70 (5)	
(Ii)	Cyclopentyl·CO	Me	B	54	79—82 (5)	
(Ij)	Cyclohexyl·CO	Me	B	77	91—94 (5)	17—18
(Im)	$OC[CH_2]_3CH_2$		B	83	97—98 (3)	33—34 [c]
(Ip)	$MeSO_2$	$PhCH_2$	C	88		65—66 [c]
(Ib')	EtOCO	Bu^n	B	83	67—68 (4)	
(Ic')	EtOCO	$PhCH_2$	B	53	98—99 (0·6)	

* See Experimental section.

[a] All were analysed for positive chlorine giving results within ±0·4% of the calculated values. [b] From hexane. [c] From chloroform–hexane.

indicate the general formation of the parent N–H compound (VII) which is the more abundant product with (It).

The methylenation of the N–X bond fails with *N*-monohalogeno-derivatives of unsubstituted amides (*N*-chloro-benzamide and -toluene-*p*-sulphonamide) owing to the occurrence of other reactions as described previously.[1b]

Three *N*-monosubstituted amides (*N*-methylacetamide, *N*-methylbenzamide, and *N*-ethyltoluene-*p*-sulphonamide) were subjected to the classical methylene insertion method [6,8] using paraformaldehyde and phosphorus pentachloride to give the *N*-chloromethyl derivative (III) which was then converted without isolation into (IV). The yields largely favour the diazomethane route [(Ib), (Ik), and (Ir)] but the classical method has the advantage that it can also be applied to *N*-unsubstituted amides.

Previous methylenations of the bond between a halogen and another atom using diazomethane [2,9] occur (Scheme 1). This is in agreement with the 'positive' character [11] of the halogen atom and with the low reactivity of the less nucleophilic benzoyldiazomethane [see Table 1 under (Ir)]. The N–X bond polarity is of significance since (I) and organic hypohalites [12] are rapidly methylenated while *N*-chloroamines [12] do not react. The formation of the ion-pair (II) is consistent with the yields given by *N*-chloro-*N*-methyltoluene-*p*-sulphonamide (Iq) in solvents of different ion-pairing ability: [13] addition of a strong ion-pair separating solvent (*NN*-dimethylformamide or nitrobenzene) affords negligible results.

The formation of the secondary product (VII) can be rationalized by assuming a proton transfer in (II) [Scheme 3(a)]; the halogenodiazomethane (VIII) also formed is unstable [14] at the temperature used. The reaction of 1-chloro-3,5,5-trimethylhydantoin (If') with diazomethane at −60° displays an orange-red colour which vanishes at −15° suggesting [14] the formation and

[8] H. Hellmann, in 'Neuere Methoden der Präparativen Organischen Chemie,' ed. W. Foerst, vol. II, Verlag Chemie, Weinheim, 1960, p. 190.

[9] D. Bethell, *Adv. Phys. Org. Chem.*, 1969, **7**, 153; W. Kirmse, 'Carbene, Carbenoide und Carbenanaloge,' Verlag Chemie, Weinheim, 1969.

[10] *Cf.* K. Kramer and N. Wright, *Chem. Ber.*, 1963, **96**, 1877, and references cited therein.

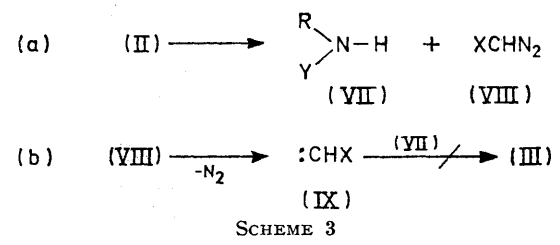
[11] S. S. Novikov, V. V. Sevost'yanova, and A. A. Frainzyl'-berg, *Russian Chem. Rev.*, 1962, **31**, 671.

[12] R. A. Corral, O. O. Orazi, and L. Trippetta, *Anales Asoc. Quim. Argentina*, 1966, **54**, 221.

[13] See, for example, M. Pánková, M. Svoboda, and J. Závada, *Tetrahedron Letters*, 1972, 2465, and references cited therein.

[14] G. L. Closs and J. J. Coyle, *J. Amer. Chem. Soc.*, 1965, **87**, 4270; R. J. Bussey and R. C. Neuman, *J. Org. Chem.*, 1969, **34**, 1323.

subsequent decomposition of (VIII; X = Cl); the n.m.r. spectrum shows that (IIIf') is formed in very low yield.



SCHEME 3

The alternative pathway to (III) through the halogenocarbene (IX) [Scheme 3(b)] was ruled out by two experiments: addition of cyclohexene as a carbene-trapping agent has a small effect on the yield given by 1-chloro-3,5,5-trimethylhydantoin (If'); thermolysis of (VIII; X = Cl) at −15° [known [14] to give the carbene (IX)] in the presence of *N*-methylbutyramide or 3,5,5-trimethylhydantoin leaves the latter compounds unchanged.

EXPERIMENTAL

Analytical and n.m.r. data for the new compounds referred to in Table 1, and analytical data for those in Table 2, are available as Supplementary Publication No. SUP 21065 (5 pp.).*

M.p.s were determined in sealed capillary tubes. Stirring was done magnetically and evaporations were performed under reduced pressure. N.m.r. spectra were measured at 60 MHz (Varian A-60 instrument) with tetramethylsilane as internal standard. Positive halogen was analysed iodometrically in sodium acetate–acetic acid buffer; [15] labile halogen was determined by treatment with anhydrous sodium acetate in boiling absolute ethanol [16] (3 h) followed by titration of the halide ion. Microanalyses were performed in the Dr. A. Bernhardt Laboratory (Germany) and by Dr. B. B. de Deferrari (University of Buenos Aires, Argentina).

Diazomethane, Solvents, and Nucleophiles.—Diazomethane, used in solution in benzene, ether, or pentane, was prepared from *N*-nitroso-*N*-methylurea or (co-distilled with ether) *N*-nitroso-*N*-methyltoluene-*p*-sulphonamide; the solutions were dried with potassium hydroxide at 0—5° for 24 h and titrated just before use.

Reaction solvents were purified and carefully dried by usual procedures. The known diethyl phthalimido(sodio)-malonate and sodium *p*-nitrophenoxide were dried at 140° (0·01 Torr).

Amides, Imides, and their N-Halogeno-derivatives.—Most of the amides and imides were prepared by literature methods while a few were commercial samples.

N-*Methylcyclobutanecarboxamide* was obtained by dropwise addition of 40% aqueous methylamine (0·1 mol) to a stirred solution of cyclobutanecarbonyl chloride [17] (0·05 mol) in anhydrous ether (25 ml) at 0°. After stirring for 2 h at room temperature the solvents were removed and the residue was extracted with benzene. Distillation of the extract gave the water-soluble *amide* (56%), b.p. 124—125° at 10 Torr, n_D^{20} 1·4754 (Found: C, 63·4; H, 9·9; N, 12·6. $C_6H_{11}NO$ requires C, 63·7; H, 9·8; N, 12·4%).

N-Halogeno-derivatives (I) were prepared according to literature methods or essentially by the following procedures used for analogous examples: A [18] for carboxamides and sulphonamides; B [19] for carboxamides and urethanes; C (as B but using sodium hydroxide as base) for sulphonic and phosphoric amides; D [20] for phosphoric amides.

Only some of the compounds (I) were amenable to purification by vacuum distillation (preheated short column) and/or crystallization. Preparation and characterization data of the new examples are given in Table 2.

Frequently, crude compounds (I) with a positive halogen content higher than 90% of the calculated value were directly employed in the methylenation reactions; the amount used was based on the halogen content. All the samples of (I) were stored at 0—5°, protected from moisture.

Methylenation Reactions.—All the operations were performed excluding moisture. Some variations of the general procedure described here are indicated in Table 1.

To a stirred solution of the *N*-halogeno-compound (I) (2 mmol) in dioxan (2 ml) at 15°, diazomethane (2·2 mmol) in benzene (*ca.* 5 ml) was added dropwise through a septum with a syringe. During this addition, gas evolution (N_2) and rapid disappearance of the yellow diazomethane colour were generally observed; finally the solution remained pale yellow (slight excess of diazomethane). After 15 min, benzene was added to 10 ml.

Duplicate analyses of positive and labile halogen were performed on aliquot portions. The former was null or negligible indicating total consumption of the starting compound (I); *N*-chloro-*N*-t-butyltoluene-*p*-sulphonamide (It) in the usual solvent (dioxan) and *N*-chloro-*N*-methyltoluene-*p*-sulphonamide (Iq) in *NN*-dimethylformamide (DMF) or nitrobenzene were exceptions requiring 50—100% excess of diazomethane. The labile halogen content, used as a rough estimate of the NCH_2X derivative (III) formed, was usually 70—85% of the calculated value.

Condensations of N-Halogenomethyl Derivatives (III) *with Nucleophiles* (*Table* 1).—Diethyl phthalimido(sodio)malonate or sodium *p*-nitrophenoxide (1 mmol) and DMF (5 ml) were added to the diluted solution [5 ml; equivalent to 1 mmol of (I)] from the foregoing methylenation reaction and the mixture was stirred 12 h at room temperature under exclusion of moisture. After evaporation to dryness, the residue was extracted with boiling benzene (3 × 5 ml); removal of the solvent gave the crude product (IV) or (V) which was crystallized to constant m.p.

Condensation with anhydrous morpholine (2 mmol) was performed as above but omitting the addition of DMF. The crystalline precipitate was identified by m.p. and mixed m.p. with an authentic sample of morpholine hydrochloride [21] or hydrobromide. The latter hygroscopic *salt* was prepared by addition of morpholine and hydrobromic acid in DMF followed by precipitation with benzene and recrystallization from the same solvent mixture, m.p.

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue (items less than 10 pp. are sent as full-size copies).

[15] E. D. Hughes, H. B. Watson, and E. D. Yates, *J. Chem. Soc.*, 1931, 3323.

[16] J. Sampey, F. Fawceett, and B. Morehead, *J. Amer. Chem. Soc.*, 1940, **62**, 1839.

[17] S. Skraup and O. Binder, *Ber.*, 1929, **62**, 1130.

[18] R. Hügel and A. Pasetti, It. P. 579,122/1959 (*Chem. Abs.*, 1960, **54**, 1310*c*).

[19] R. B. Krauss and E. Crede, *J. Amer. Chem. Soc.*, 1917, **39**, 2720.

[20] J. S. Chalsty and S. S. Israelstam, *J. S. African Chem. Inst.*, 1956, **9**, 33.

[21] J. Sand, *Ber.*, 1901, **34**, 2908.

208—209° (Found: Br, 47·0. C_4H_9NO,HBr requires Br, 47·6%).

The liquid phase was evaporated, adding benzene to remove any excess of morpholine; the crude (VI) was purified by direct crystallization or through the picrate salt prepared with picric acid in benzene.

Other Methylenation Experiments.—These were run with exclusion of moisture and employing purified samples of the *N*-halogeno-derivatives (I).

(a) N-*Chloro*-N-*methylbutanamide* (If) *in dioxan–benzene or pentane.* A solution of diazomethane (*ca.* 4 ml; 1·1 mmol) in benzene (or pentane) at 18·0° was added to (If) (1 mmol) dissolved in dioxan (or pentane) (1 ml); analyses at intervals showed that after 15 min the positive chlorine content in dioxan–benzene was practically nil whilst that in pentane remained unchanged.

(b) *Crude products examined by n.m.r.* Only one example is detailed. To 1-chloro-3,5,5-trimethylhydantoin (If') (0·5 mmol) dissolved in dioxan (1·6 ml), a benzene solution of diazomethane (1·4 ml; 0·55 mmol) was added dropwise at 15° with stirring until a yellow colour persisted. After 15 min, the solution was almost colourless and analysis for positive chlorine gave a null value. The solution was evaporated at room temperature, adding carbon tetrachloride to ensure the removal of the reaction solvents.

The residue showed δ ($CDCl_3$) 1·45 (*gem*-Me_2 of 3,5,5-trimethylhydantoin and its 1-hydroxymethyl derivative), 1·53 [*gem*-Me_2 of (IIIf')], 3·00 (NMe of 3,5,5-trimethylhydantoin and its 1-hydroxymethyl derivative), 3·07 [NMe of (IIIf')], and 5·35 [N(1)CH_2Cl of (IIIf')]. The methylenation yield, including the hydroxymethyl derivative formed from (IIIf') and traces of water, was 89%. Addition of thionyl chloride (0·1 ml) followed by standing 1 h at room temperature caused the disappearance of the small absorption at δ 4·90 (NCH_2OH group) and increased the area at 5·35; the signals at δ 1·53 and 3·07 were intensified at the expense of those at 1·45 and 3·00 respectively. The assignments for 3,5,5-trimethylhydantoin and its 1-hydroxymethyl derivative were supported by addition of pure samples in a duplicate n.m.r. measurement; the NCH_2 protons of the latter gave a singlet at δ 4·90 due to traces of acid formed by hydrolysis of (IIIf').

1-Hydroxymethyl-3,5,5-trimethylhydantoin was prepared by the method described for 1-hydroxymethylpyrrolidin-2-one.[22] Several crystallizations from ethyl acetate–di-isopropyl ether gave a *sample*, m.p. 91—92° (25% yield), $\nu_{max.}$ (Nujol) 3438 (OH), 1770 (split), and 1708 cm^{-1} (hydantoin dicarbonyl system [5]), δ ($CDCl_3$) 1·48 (6H, s, *gem*-Me_2), 3·02 (3H, s, NMe), 4·13 (1H, t, *J* 7 Hz, OH, displaced to higher field by dilution or heating), and 4·90 (2H, d, *J* 7 Hz, NCH_2) [after shaking with D_2O or addition of CF_3CO_2H (5 μl), the triplet disappears and the doublet coalesces to a singlet at δ 4·90. Another measurement with thionyl chloride (0·1 ml; 1 h at room temperature) showed δ 1·53 (6H, s, *gem*-Me_2), 3·07 (3H, s, NMe), 5·35 (2H, s, NCH_2Cl), and a small signal (impurity) at 1·95] (Found: C, 48·85; H, 7·05; N, 16·5. $C_7H_{12}N_2O_3$ requires C, 48·8; H, 7·05; N, 16·25%).

(c) 1-*Chloro*-3,5,5-*trimethylhydantoin* (If') *at* −60°. A solution of diazomethane in ether (0·36 mmol; 0·5 ml) was added dropwise to a stirred solution of (If') (0·33 mmol) in dichloromethane (1 ml) at −60°; after 30 min the solution was orange-red. The mixture was allowed to warm in 15 min to −15°; after 15 min the solution was pale yellow. The bath was allowed to reach ambient temperature and the solution was worked up as detailed above under (b); the yield of the methylenation product was 10%. A parallel, control experiment run at 15° gave 90% yield.

(d) 1-*Chloro*-3,5,5-*trimethylhydantoin* (If') *in the presence of cyclohexene.* Commercial cyclohexene (10 ml) was washed with 10% aqueous iron(II) sulphate (2 × 5 ml) and water (3 × 5 ml); after drying ($CaCl_2$), the fraction b.p. 82—82·5° was collected and kept in the dark over Drierite and then over molecular sieves (24 h).

A dioxan solution (1·6 ml) of (If') (0·5 mmol) and cyclohexene (5 mmol) was stirred at 15° while a benzene solution of diazomethane (1·4 ml; 0·55 mmol) was added dropwise until there was a persistent yellow colour and a null positive-chlorine value. Operating as in (b), the methylenation yield was 72%. A parallel reaction without cyclohexene gave an 80% yield.

(e) N–H *Compounds* (VII) *and chlorocarbene.* The preparation of chloro(diazo)methane and its thermolysis to chlorocarbene were essentially carried out as described.[14]

To a stirred solution of diazomethane (1 mmol) in ether (1·5 ml) at −100°, redistilled t-butyl hypochlorite (0·8 mmol) in trichlorofluoromethane (2 ml) was added in 15 min. After a further 15 min the orange-red solution was warmed to −80° and then 3,5,5-trimethylhydantoin (0·8 mmol) in dichloromethane (2·5 ml) was added over 15 min. The temperature was then slowly raised and the mixture left 1 h at −15°; the resulting yellow solution was allowed to reach room temperature and was worked up as in (b). The n.m.r. spectrum showed signals due to 3,5,5-trimethylhydantoin, minor impurities, and the absence of NCH_2Cl absorption. Analogous results were obtained in similar experiments using *N*-methylbutyramide.

N-*Chloromethylamides by using the Paraformaldehyde–Phosphorus Pentachloride Method.*[6,8]—A mixture of the anhydrous amide (2 mmol) and paraformaldehyde (dried at 40° and 5 Torr; 60 mg) was heated in a sealed tube for 2 h at 120° and then 2 h at 145°. The oily product from *N*-methylacetamide contained 70% of the *N*-hydroxymethyl derivative as measured by n.m.r.[23] in a parallel experiment.

Under exclusion of moisture, a solution of the crude *N*-hydroxymethylamide in dioxan (1 ml) was added dropwise to a stirred suspension of phosphorus pentachloride (2·2 mmol) in dioxan (1 ml) at 0°; stirring was continued for 30 min at 40°. The solvent was removed and the residue maintained at 0·01 Torr (room temperature) until of constant weight; the crude *N*-chloromethylamide (III) was dissolved in dioxan (2 ml) and benzene (to 10 ml) and analysed for labile chlorine. The condensation with diethyl phthalimido(sodio)malonate was carried out as detailed above.

Reaction with *N*-methylacetamide, *N*-methylbenzamide, and *N*-ethyltoluene-*p*-sulphonamide gave 74, 52, and 34% of labile halogen respectively; the yields of (IV) were 38, 15, and 19% respectively. Compounds (IV) were identified by m.p. and mixed m.p.

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