Substitution in the Hydantoin Ring. Part VIII.[1] Alkylation

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N(3)-Substituted hydantoins bearing a variety of substituents at position 5 have been *N*(1)-alkylated at room temperature by treatment with several types of alkyl halide or tosylate in anhydrous *NN*-dimethylformamide containing sodium hydride. The method shows a wide applicability, giving good yields with or without activating groups at position 5.

In a preliminary communication [2] we described the formation of *N*(1)-alkyl derivatives of *N*(3)-unsubstituted hydantoins from the pre-formed hydantoin system. This route involves three steps: (1) introduction of an aminomethyl group to protect position 3; (2) alkylation at position 1 with an alkyl halide in *NN*-dimethylformamide (DMF) containing sodium hydride at room temperature; and (3) hydrolytic elimination of the protecting group at room temperature. Step (1) has been studied previously;[3] under appropriate conditions selective aminomethylation at the more reactive position 3 can be accomplished in high yield. However, little information is available with regard to the subsequent steps. The present paper deals with the scope of the *N*(1)-alkylation method [step (2)].

It has been stated [4] that hydantoins can generally be alkylated in basic medium at position 3 but not at position 1. However, when C-5 is part of an ethylenic bond [5a] conjugated with an aromatic system, the adjacent N(1) proton becomes more acidic and *N*(1)-alkylation then occurs satisfactorily; aryl groups at C-5 also activate this substitution reaction [5b,c] but with lower efficiency. Although it is reported [4] that *N*(1)-alkylation fails when C-5 bears only hydrogen atoms and/or alkyl-type substituents, a 60% yield has been claimed [5c] in the methylation of 2′-isopropyl-3,5′-dimethylhydantoin-5-spirocyclopentane with dimethyl sulphate.

The sodium hydride method [2] has been applied to a few intramolecular alkylations, furnishing bicyclic hydantoins: attack at N(1) or the 2-carbonyl oxygen atom occurs when the alkylating system is attached at C(5) or N(3), respectively.[6] Another alkylation method,[7] operating at 110°, uses as intermediate the magnesium chelate of a 5-carboxyhydantoin; according

[1] Part VII, O. O. Orazi, R. A. Corral, and (in part) A. O. Sánchez, *Synthesis*, 1972, 205.

[2] O. O. Orazi and R. A. Corral, *Experientia*, 1965, **21**, 508. Another route based on formation of the 1,3-dianion of the hydantoin followed by selective alkylation at position 1 is under study.

[3] O. O. Orazi and R. A. Corral, *Tetrahedron*, 1961, **15**, 93.

[4] E. Ware, *Chem. Rev.*, 1950, **46**, 403.

[5] (*a*) T. B. Johnson and B. H. Nicolet, *Amer. Chem. J.*, 1910, **47**, 459; D. A. Hahn and E. Dyer, *J. Amer. Chem. Soc.*, 1930, **52**, 2494 and references cited therein; (*b*) H. Biltz and O. Behrens, *Ber.*, 1910, **43**, 1984; (*c*) A. Novelli, Z. M. Lugones, and P. Velasco, *Anales Assoc. quim. Argentina*, 1942, **39**, 225.

[6] (*a*) E. E. Smissman, P. L. Chien, and R. A. Robinson, *J. Org. Chem.*, 1970, **35**, 3818; (*b*) V. E. Márquez, L. Twanmoh, H. B. Wood, and J. S. Driscoll, *ibid.*, 1972, **37**, 2558.

[7] H. Finkbeiner, *J. Org. Chem.*, 1965, **30**, 3414.

to the proportion of the alkylating agent the 5-mono- or the 1,5-di-alkyl derivative is formed but no mono-alkylation at position 1 occurs. The reaction of 3-benzyl-5-methoxyhydantoin with vinylic ethers is reported to lead to *N*(1)-alkyl derivatives (oily; constants are not given).[8]

N-Alkylations with sodium hydride and alkylating agents under various conditions have been applied to other classes of compound containing an amide system: *N*-monosubstituted amides in non-polar solvents[9a] or in DMF;[9b] lactams in benzene, toluene,[10a] or DMF;[10b] and *N*-acylamino-acids and peptides[11] in several solvents (DMF, dimethyl sulphoxide, *etc.*). We have studied the applicability of this method[2] to a number of *N*(3)-substituted hydantoins with a variety of groups at position 5; furthermore, some structural variations in the alkyl (R^4) and leaving (Y) groups of the alkylating agent have also been tested (see Table 1).

From the results obtained with ethyl iodide we concluded that alkylation at position 1 occurs in high yield in the presence or in the absence of alkyl or aryl substituents at position 5. Even bulky groups at C-5 do not prevent the alkylation; this is a significant difference from the case of aminomethylation[3] at position 1. The effects of variations in the alkyl and leaving groups of R^4X are interdependent. With appropriate choice of the leaving group Y, R^4 can be primary alkyl or allylic or benzylic; high yields are obtained in the numerous examples shown in Table 1. Moreover, R^4 may bear a variety of functional groups as illustrated by examples XXII—XXIV; compounds of this sort are difficult to obtain or not accessible by previous methods. The introduction of the simplest secondary alkyl group (example XX) gave poor yields; this discouraged the examination of further examples of the same type and of tertiary alkyl systems.

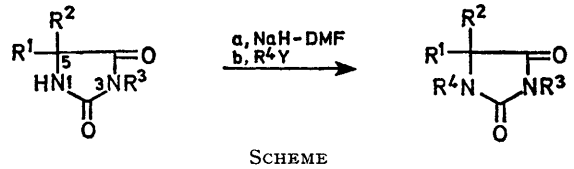
Alkyl tosylates showed wider applicability as alkylating agents as demonstrated by examples XVIII—XX; this is due to their low tendency[12] to participate in

TABLE 1

N(1)-Alkylation of *N*(3)-substituted hydantoins (see Scheme) [a]

	R^1	R^2	R^3	R^4	Y [b]	M.p. (°C); cryst. solvent [b.p.]	Yield (%)
I	H	H	$PhCH_2$	Et	I	[151—152 at 0·3 Torr]	76
II	Me	H	$PhCH_2$	Et	I	[143—144 at 0·3 Torr]	80
III	Me	Me	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	Et	I	89—90; EtOH	75
IV	Et	Et	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	Et	I	72—73; EtOH	64
V	$CH_2{\cdot}[CH_2]_3{\cdot}CH_2$		Me	Et	I	60—61; Pr^i_2O	55
					TsO		85
VI	Me	Pr^i	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	Et	I	62—63; EtOH	78
VII	Pr^i	Pr^i	Me	Et	I	69—70; C_6H_{14}	82
VIII	Me	Bu^t	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	Et	I	86—87; AcOEt [c]	70
IX	Me	Ph	Me	Et	I	79—80; C_6H_{14}	87
X	Ph	Ph	Me	Et	I	118—119; EtOH	96
XI	Ph	Ph	Me	n-C_5H_{11}	Br	64—65; EtOH	91
XII	Ph	Ph	Me	iso-C_5H_{11}	Br	80—81; Pr^i_2O	68
XIII	Me	Ph	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	iso-C_5H_{11}	Br	95—96; EtOH	50
					Cl		6
XIV	Me	Ph	Me	$CH_2{:}CH{\cdot}CH_2$	Cl	52—53; C_6H_{14}	71
XV	Me	Ph	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	$CH_2{:}CH{\cdot}CH_2$	Cl	96—97; EtOH	81
XVI	Me	Me	Me	$PhCH_2$	Cl	48—49; Pr^i_2O	78
XVII	Me	Ph	Me	$PhCH_2$	Cl	107—108; EtOH	92
XVIII	Ph	Ph	Me	Bu^t	TsO	154—155; EtOH	82
					Br		25 [d]
XIX	Ph	Ph	Me	$PhCH_2{\cdot}CH_2$	TsO	134—135; EtOH	68
					Br		10 [d]
XX	Ph	Ph	Me	Pr^i	TsO	152—153; EtOH	31
					Br		13 [d]
XXI	Ph	Ph	Me	$NC{\cdot}CH_2$	Cl	153—154; Me_2CO	94
XXII	Me	Ph	Me	$EtO_2C{\cdot}CH_2$	Cl	96—97; EtOH	68
XXIII	Me	Ph	Me	DMAB [e]	Cl	135—136; EtOH	98
XXIV	$CH_2{\cdot}[CH_2]_3{\cdot}CH_2$		Me	DMAB [e]	Cl	96—97; Pr^i_2O	72

[a] All the alkylated products are new and were analysed for C, H, and N giving results within ±0·3% of the calculated values; they do not show NH absorption in the i.r. spectra. [b] Leaving group of R^4Y. [c] Prior to crystallization the product was sublimed at 100—140° and 10^{-3} Torr. [d] The amount of bromide ion found in the benzene-insoluble fraction was >80% of the theoretical value. [e] 5-Acetyl-2,4-dimethylbenzyl.



SCHEME

[8] D. Ben-Ishai and G. Ben-Et, *Chem. Comm.*, 1969, 1399; see also D. Ben-Ishai and E. Goldstein, *Tetrahedron*, 1971, **27**, 3119.

[9] (*a*) W. S. Fones, *J. Org. Chem.*, 1949, **14**, 1099; (*b*) A. P. Martínez, W. W. Lee, and L. Goodman, *Tetrahedron*, 1964, **20**, 2763; G. Schill, H. Neubauer, K. Rotmaier, and H. Zollenkopf, *Synthesis*, 1971, 436.

[10] (*a*) R. M. Moriarty, *J. Org. Chem.*, 1964, **29**, 2748; V. A. Snieckus, T. Onouchi, and V. Boekelheide, *ibid.*, 1972, **37**, 2845; (*b*) L. A. Paquette and W. C. Farley, *ibid.*, 1967, **32**, 2725.

[11] G. Marino, L. Valente, R. A. W. Johnstone, and F. Mohammedi-Tabrizi, *J.C.S. Chem. Comm.*, 1972, 357 and references cited therein; J. R. Coggins and N. L. Benoiton, *Canad. J. Chem.*, 1971, **49**, 1968.

[12] J. March, 'Advanced Organic Chemistry,' McGraw-Hill, New York, 1968, p. 746.

elimination reactions leading to alkenes. For alkyl groups (R^4) that are not prone to elimination, the more easily available bromides or iodides afforded similar results (*e.g.* V and XI). Only activated chlorides worked well (*e.g.* XIV and XXI); in cases such as XIII the reaction was incomplete (less than 10%), as indicated by the amount of chloride anion in the benzene-insoluble fraction.

Similar results, concerning the behaviour of the foregoing alkylating agents with other substrates, have already appeared.[13]

Ambident anions are formed from the starting hydantoin and sodium hydride but the products isolated are alkylated at N(1) and not at the 2-carbonyl oxygen atom. The dicarbonyl structures of the products are firmly supported by their i.r. spectra, which show two carbonyl absorptions, at 1722—1701 and 1774—1758 cm^{-1}.[14] Bands within these ranges are exhibited by 1,3,5,5-tetramethylhydantoin [3] and 1,3-dimethylhydantoin-5-spirocyclopentane,[15] which cannot exist as enolic tautomers. The isomeric *O*-alkyl derivatives would be expected to show one carbonyl and one C=N absorption (below 1700 cm^{-1}).[6b,16]

The structures of the hydantoin ring substituents in the products were confirmed by n.m.r. spectroscopy.[17]

EXPERIMENTAL

Analytical, i.r., and n.m.r. data for the products referred to in Table 1, and analytical data for those in Table 2, are available as Supplementary Publication No. 20857 (5 pp.).*

M.p.s were determined for samples in sealed capillary tubes. I.r. spectra (Nujol mulls) were measured with a Perkin-Elmer 337B grating spectrophotometer. N.m.r. spectra were recorded at 60 MHz with a Varian A60 instrument for solutions in carbon tetrachloride, except for the less soluble compounds (examples VIII, XXI, and XXIII) which were dissolved in deuteriochloroform. Microanalyses were carried out in the Dr. A. Bernhardt Laboratory (Germany) and by Dr. B. B. de Deferrari (University of Buenos Aires, Argentina).

N(1)-*Unsubstituted* N(3)-*Alkylhydantoins*.—The starting *N*(1),*N*(3)-unsubstituted hydantoins were synthesized according to literature directions or by known general methods.[4]

For *N*(3)-alkylation, the hydantoin (0·01 mol) was dissolved with stirring in ethanolic potassium hydroxide (15—20 ml; 0·01 mol). With methyl iodide (0·011 mol) as alkylating agent, the mixture was heated in an Erlenmeyer flask with sealed ground-glass joint and a Teflon stopper (3 h at 65°); with benzyl chloride or *p*-nitrobenzyl bromide as reagent the mixture was refluxed for 1·5 h. Products were isolated (A) by filtration to separate the potassium halide and evaporation of the filtrate; (B) by evaporation to dryness followed by extraction with benzene; or (C) by evaporation and washing the residue with water or aqueous sodium hydroxide. The crude products were recrystallized; known compounds gave values in agreement with those reported. Data for the new ones are collected in Table 2.

N(1)-*Alkylations*.—Alkylating agents, of commercial origin or prepared by known procedures, were dried before use. The commercial DMF was kept for 3 days over potassium hydroxide pellets, decanted, rectified, and stored over calcium hydride. The operations described were carried out with exclusion of moisture.

First, the DMF (7 ml) was redistilled; after a forerun (2 ml) it was collected directly (2—3 ml) in the reaction tube containing the *N*(3)-substituted hydantoin (2 mmol), previously dried under vacuum. After cooling to 15°, sodium hydride (2·2 mmol; oil dispersion) was added, and the mixture was stirred until gas evolution ceased (*ca.* 15 min). The alkylating agent (2·2 mmol) was then added, and stirring was continued for 12 h at room temperature. The DMF was removed under reduced pressure and the residue was heated with hexane (2 × 0·5 ml); the mixture was then cooled to −10° before removal of the hexane phase containing the paraffin oil. The insoluble material was extracted with boiling benzene (3 × 5 ml). When the leaving group (X) was halide, the extent of reaction was determined from the halide content of the residue. Evaporation of the benzene extract gave the crude product, which was recrystallized or purified by vacuum distillation through a preheated short column.

The *N*(1)-alkyl derivatives (Table 1) were characterized by elemental analyses and n.m.r. and i.r. spectra.

TABLE 2

New *N*(1)-Unsubstituted *N*(3)-alkylhydantoins [a]

R^1	R^2	R^3	Isolation procedure	M.p. (°C); cryst. solvent	Yield (%)
H	H	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	219—220; AcOH	66 [b]
H	Me	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	160—161; Me_2CO	50 [b]
Me	Me	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	164—165; EtOH	59
Et	Et	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	127—128; EtOH	78
Me	Pr^i	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	140—141; EtOH	63
Pr^i	Pr^i	Me	B	132—133; EtOH–H_2O	89
Me	Bu^t	Me	B	135—136; EtOH	82 [b]
Me	Bu^t	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	B	161—162; EtOH	82
Me	Ph	*p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	A	134—135; EtOH	77

[a] All were analysed for C, H, and N giving results within ±0·3% of the calculated values. [b] This compound was tried as substrate but subsequently replaced by an analogous one since the *N*(1)-alkylated product was easier to isolate.

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* For details of Supplementary Publications, see *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (Notice to Authors No. 7).

[13] See, for example, F. P. Hauck and J. T. Fan, *J. Org. Chem.*, 1969, **34**, 1703; A. I. Meyers and N. Nagarenko, *J. Amer. Chem. Soc.*, 1972, **94**, 3243; A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, 1973, **38**, 36.

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[16] L. J. Bellamy, ' The Infrared Spectra of Complex Molecules,' Methuen, London, 2nd edn., 1958, p. 267.

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