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A HIGH-YIELD SELECTIVE N(3)-ALKYLATION PROCESS OF HYDANTOINS USING DIMETHYLFORMAMIDE DIALKYL ACETALS.

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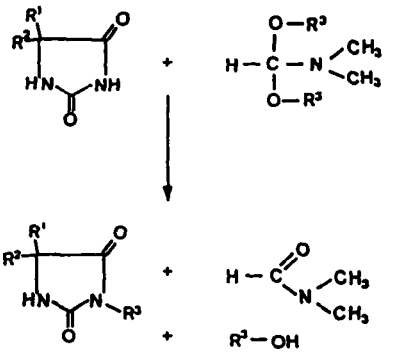
ABSTRACT

A selective N(3)-alkylation process of 5-substituted hydantoins is described. Treatment of hydantoins with excess of dimethylformamide dialkyl acetals at 100°C results in N(3)-alkyl derivatives in 69-90 % yield.

N(3)-Alkylation of 5-substituted hydantoins with short alkyl groups appears to be an effective way to modulate the pharmacological profile of these anticonvulsant drugs[1,2]. The classical N(3)-alkylation is performed by interaction of the sodium or potassium salt of the hydantoin with an alkyl halide or dialkyl sulfate[3]. This process however is not selective and the N(3)-alkyl derivative is contaminated with variable amounts of the N(1),N(3)-dialkyl derivative. As a consequence, the reaction product must be recrystallized and the preparative yield never exceeds 60-70%. In our search for better derivatization methods of phenytoin (5,5-diphenylhydantoin), we became interested in the reactivity of dimethylformamide dialkyl acetals[4]. The rationale behind this approach was based on the reported behaviour of these versatile reagents with barbiturates, where a transacetalization process takes place. In contrast with this situation, we have found out that 5,5-disubstituted hydantoins are selectively and quantitatively alkylated at the N(3)-position (Scheme I).



Scheme I

Typical conditions are reported in the experimental section for two examples. Additional examples are listed in the Table 1. The purity of the materials was checked by GC-MS and the structures were assigned by ^{13}C-NMR, IR, MS and comparison (mixed melting point, GLC) with authentic samples. While dilution of the reaction medium with DMF was found advantageous in certain cases, no beneficial effect was obtained upon addition of trace or stoechiometric amounts of triethylamine.

TABLE 1

Reactivity of various dimethylformamide dialkyl acetals toward different 5-substituted hydantoins.

R^1	R^2	R^3	Yields(%)[a]	Refs.[b]
Ph	H	CH_3	90	(10)
Ph	C_2H_5	CH_3	85	(11)
Ph	Cyclohexyl	CH_3	85	(12)
Ph	Ph	CH_3	90	(13)
Ph	Ph	C_2H_5	87	(8,14)
Ph	Ph	n-C_4H_9	79.5	(15)
Ph	pF-Ph	CH_3	72	(16)
Ph	pCH_3O-Ph	CH_3	69	(17)

[a] Refers to recrystallized material.
[b] See "References and Notes".

In addition to its interest as a preparative method, this method offers interesting potentials in chromatographic applications. As the reaction is fast and quantitative already at 100° C, the present alkylation is particularly well-suited for flash-heater derivatization of phenytoin and related congeners, and we have successfully applied this technique for the assay of phenobarbital-phenytoin mixtures. It is noteworthy however that at 250° C (temperature of the injection port) the monoalkyl compound was contaminated with minor amounts of the dialkyl derivative (0.5-2%). Another chromatographic application for this process was found in HPLC: as asymmetric N(3)-alkylhydantoin enantiomers can be base-line separated on Pirkle's chiral HPLC columns, this technique appears very promising both for preparative resolution and enantiomeric purity determination. An example of such a separation is described in the experimental section.

For pharmacological as well as analytical reasons, we have limited our investigation to dimethylformamide acetals with short alkyl groups (1-4 carbons). Further work will be devoted to exploring the reactivity of other pentacyclic imides (2-thiohydantoins, 2,4-oxazolidinediones, succinimides) of pharmacological interest toward various dimethylformamide dialkyl acetals.

EXPERIMENTAL SECTION

The infrared spectra were recorded with a Perkin-Elmer model 580 spectrometer. ^{13}C NMR spectra were recorded on Brucker WP-80-SY and WM-250-spectrometers operating in the FT mode at 20.105 and 62.86 MHz respectively. The compounds were dissolved in Me_2SO-d_6 to form 0.5 M solutions. The probe temperature was 38° C. The central peak of Me_2SO-d_6 was positioned at 39.60 ppm and was used as reference. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses are indicated only by symbols of the elements and are within 0.4% of theoretical values. HPLC analyses were carried out with a Water Associates (Milford, Ma.) model 6000a solvent delivery system, a Rheodyne (Berkeley, Cal.), model 7125 syringe-loading sample injector, and a Pye Unican (Cambridge, England) model LC3 variable-wavelength UV detector. GC-MS analyses were performed on an LKB model 9000S instrument.

5,5-Diphenyl-3-ethylhydantoin. N,N-Dimethylformamide diethyl acetal (1,19 g, 10 mmol) and phenytoin (500 mg, 2 mmol) were placed in a dry snap-cap vial and heated at 100° C for 1 h in an oven. An orange fluorescence soon developped. The reaction mixture was then diluted with 50 ml of water, filtered, washed with water and dried to give the title compound in 92% yield. m.p.143-145°C. Recrystallization from n-heptane-toluene (85:15, v/v) raised the mp up to 155-156°C[8,14] (85%). ^{13}C-NMR 173.26 (C=O 4), 157.06 (C=O 2) 139.34 (i), 128.71 (m), 128.40 (p), 126.80 (o), 70.04 (C 5), 33.98 (CH_2), 13.39 (CH_3) ppm. IR (KBr) 3280 (N-H), 3030 (aromatic C-H), 2990, 2930 (aliphatic C-H), 1765, 1695 (coupled carbonyl vibrators). MS (m/z) 280, 265, 251, 223. The same compound was obtained in the following way: phenytoin (1 g, 3.97 mmol), ethyl bromide (1 g, 9.18 mmol), anhydrous potassium carbonate (3 g, 21.7 mmol) and 3 ml of DMF were stirred at room temperature for 72 h. The heterogeneous mixture was diluted with 100 ml of water, filtered, washed with distilled water, dried, and recrystallized from n-heptane-toluene (85:15, v/v) to yield a compound similar (mixed mp , GC-MS, ^{13}C-NMR) to that obtained above. GC-MS indicated the presence of trace amounts of dialkylated material. This material had to be recrystallized from absolute ethanol with important loss (yield: 64%).

(R,S)5-(4-Fluorophenyl)-5-phenyl-3-methylhydantoin. N,N-Dimethylformamide dimethyl acetal (1.19 g, 10 mmol) and (R,S)5-(4-fluorophenyl)-5-phenylhydantoin[9] (540 mg, 2 mmol) were dissolved in 1 ml of dry DMF. The mixture protected from moisture was heated at 100° C for 1 h in a oven and the solvent was removed in vacuo to yield a residue which was then taken up in warm ethanol and precipitated by adding water. The precipitate was filtered, washed with cold water and dried to yield the title compound (87%). mp.165-166°C. The material was recrystallized from 95% ethanol without improvement of the mp (72%). Anal.($C_{16}H_{13}FN_2O_2$) C,H,N.[9] This material was also synthesized from 5-(4-fluorophenyl)-5-phenylhydantoin[9], methyl iodide and anhydrous potassium carbonate in DMF in 64 % yield.
^{13}C-NMR 173.31 (C=O 4), 155.52 (C=O 2), 139.68, 128.62, 128.24, 126.66 (i, m, p, o of the unsubstituted phenyl group, respectively), 167.93, 155.75 (p), 135.95, 135.78 (i), 129.17, 128.75 (o), 115.90, 114.82 (m), 68.83 (C 5), 24.54 (CH_3). IR (KBr) 1770, 1705 cm^{-1}. HPLC was carried out on BAKERBOND^{cm} Chiral Phase (DNBPG) column (25 cm x 4.6 mm) containing (L)-N-(3,5-dinitrobenzoyl) phenylglycine as chiral ligand. The flow rate of the mobile phase (n-hexane: 2-propanol, 95:5, v/v) was 1 ml/min and UV detection was performed at 240 nm. Typical k' values were 4.6 and 5.0. (Resolution factor R: 1.49).

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(12) m.p.204-205°C. IR (CH_2Cl_2) 1777, 1716 cm^{-1}. This material was also obtained by interaction of 5-cyclohexyl-5-phenylhydantoin (J. H. Poupaert, R. Cavalier, M. Claesen, and P. A. Dumont, J. Med. Chem., **18**, 1268 (1975)), methyl iodide and anhydrous potassium carbonate in DMF in 65 % yield.
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(15) m.p.122-123°C. MS (m/z) 308 (m^+), 280, 223
(16) see Experimental Section
(17) m.p.165-166°C. MS 296, 268, 253. IR (CH_2Cl_2) 1782, 1720 cm^{-1}. This compound was also prepared from 5-(4-methoxyphenyl)-5-phenylhydantoin (H. R. Henze and A. F. Isbell, J. Am. Chem. Soc., **76**, 4152 (1954)), methyl iodide and anhydrous potassium carbonate in DMF in 68 % yield.