New Route for 1-Substituted Hydantoins[1]

Alkylation reactions on hydantoins (I) lead smoothly to 3-alkyl derivatives; more rigorous conditions allow further substitution at position 1 provided the N_1–H group is activated by an aryl group or an ethylenic bond attached to the adjacent C_5[2,3]. All the hitherto available methods for the not readily accessible 3-unsubstituted-1-alkylhydantoins (IV) require placing the substituent at the appropriate nitrogen atom prior to the complete formation of the hydantoin system[2,4,5].

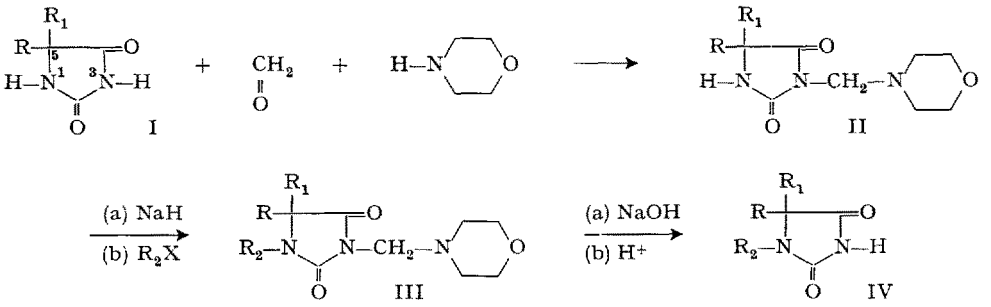
We are reporting here a new route that furnishes compounds IV through the alkylation at position 1 of the preformed hydantoin ring. This synthesis involves the following steps: (1) blockage of the more reactive position 3 by aminomethylation[6]; (2) alkylation at position 1 using a new procedure that operates under mild conditions and does not require the presence of activating groups at C_5; (3) removal of the blocking group by controlled base or acid-catalysed hydrolysis.

The entire process can be run in one operation as illustrated by the following example. Crude 3-(N-morpholinomethyl)-5,5-dimethylhydantoin (II; $R = R_1 = CH_3$), prepared from I ($R = R_1 = CH_3$; 0.001 *M*) as described earlier[6], was dried to constant weight at 56°/10^{-1} Torr and dissolved in anhydrous N,N-dimethylformamide (1.5 ml). To the solution protected from humidity, sodium hydride (0.001 *M*) as oil dispersion was added and the mixture stirred magnetically at room temperature until hydrogen evolution ceased; after addition of benzyl chloride (0.0011 *M*), the mixture was left for 24 h under the same conditions.

The solvent was evaporated under reduced pressure and the residue containing III ($R = R_1 = CH_3$; $R_2 = PhCH_2$) was washed with hexane (2 · 1 ml), dried in vacuum and then stirred 1 h at room temperature with 2 ml 3*N* aqueous sodium hydroxide. From the centrifuged solution, 1-benzyl-5,5-dimethylhydantoin (IV; $R = R_1 = CH_3$; $R_2 = PhCH_2$) was precipitated by acidification with concentrated hydrochloric acid; 45% yield, m.p. 128–129°, after recrystallization from benzene-hexane.

Alternatively, the aminomethylation step was carried out in anhydrous N,N-dimethylformamide using the calculated amount of paraformaldehyde (stirring 24 h at room temperature) instead of aqueous formaldehyde; the resulting solution was then treated directly with sodium hydride and the process followed as above. The overall yield was practically coincident.

Similar results were obtained in other experiments.



Zusammenfassung. 1,3-unsubstituierte Hydantoine (I) werden in einem 3-Stufenprozess in 1-substituierte Abkömmlinge (IV) übergeführt: Blockierung der Stellung 3 durch Aminomethylierung, gefolgt von N_1-Alkylierung mit anschliessender Entfernung der Schutzgruppe durch Hydrolyse.

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[1] This paper represents Part V of the series *Substitution in the Hydantoin Ring*; preceding Part, L. TRIPPETTA, O. O. ORAZI, and R. A. CORRAL, An. Asoc. quím. argent., in press.

[2] E. WARE, Chem. Rev. *46*, 403 (1950).

[3] However, A. NOVELLI, Z. M. LUGONES, and P. VELASCO [An. Asoc. quím. argent. *30*, 225 (1942)] converted (60% yield) the 3-methyl-5,5-(2'-isopropyl-5'-methyl-pentamethylene)hydantoin into its 1-methyl derivative by means of dimethyl sulphate and sodium hydroxide in ethanol.

[4] E. CATTELAIN and P. CHABRIER, Bull. Soc. chim. Fr. *1947*, 639, reported the preparation of 1-methyl-5,5-diphenylhydantoin (and other 1-alkyl derivatives) from 5,5-diphenyl-2-thiohydantoin, but other workers[5] identified the product as the 3-methyl-5,5-diphenylhydantoin.

[5] H. C. CARRINGTON and W. S. WARING, J. chem. Soc. *1950*, 354, transformed 5,5-diphenylhydantoin into 2-keto-4-methylthio-5,5-diphenyl-2,5-dihydro-glyoxaline, which by methylation and subsequent hydrolysis of the product led to 1-methyl-5,5-diphenylhydantoin.

[6] O. O. ORAZI and R. A. CORRAL, Tetrahedron *15*, 93 (1961).

A Uniform Numbering System for Indole Alkaloids[1]

It is a remarkable fact that the occurrence of complex alkaloids (some 350 of known structure[2]) containing indole or equivalent moieties is largely restricted to a few plant families, viz. *Apocynaceae*, *Loganiaceae*, and *Rubiaceae*. It is worth remembering that these families stand close together in the phylogenetic charts of the taxonimists[3].

On the chemical side there has been discerned an apparent uniformity in the building blocks of these substances which is not always obvious upon casual examination[4]. For a number of alkaloids tryptophan or its equivalent has been proved to be one of the precursors; but the source of the remaining portion, a ten (or nine)