REACTION OF 1-METHYLPYRROLE WITH 1,3-DICHLORO-5,5-DISUBSTITUTED HYDANTOINS: PRODUCTS AND AM1 STUDY OF INTERMEDIATES

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Abstract-The reaction of 1-methylpyrrole with 1,3-dichloro-5,5-dimethylhydantoin gave 3-(1-methyl-1H-pyrrol-2-yl)-5,5-dimethylhydantoin and 1,3-di-(1-methyl-1H-pyrrol-2-yl)-5,5-dimethylhydantoin as products. In contrast reaction with 1,3-dichloro-5-methyl-5-phenylhydantoin (3) or 1,3-dichloro-5,5-diphenylhydantoin (4) gave only the monopyrroylhydantoin derivatives. This difference was attributed to a steric interaction between the substituents on C-5 and N_1.

Pyrrole and its derivatives generally undergo electrophilic aromatic substitution in typical ArS_E2 fashion.[3] In 1986 we reported the first example of electrophilic substitution in pyrroles by addition-elimination in pyrrole chemistry.[4] It was found that in the reaction of 1-methylpyrrole with N-chloroacetanilide the acetanilide moiety was incorporated into the pyrrole ring by a process of addition-elimination. Subsequent studies were on the effect of halogen [5], the 1-substituent[6] and the structure of the N-chloro derivative[6,7] on the addition-elimination reaction. Evidence was obtained that addition-elimination was observed when the N-chloro derivative contained a good leaving group and a qualitative relationship was found between the pK_a *of the parent nitrogen compound and the observation of addition-elimination.*[6]

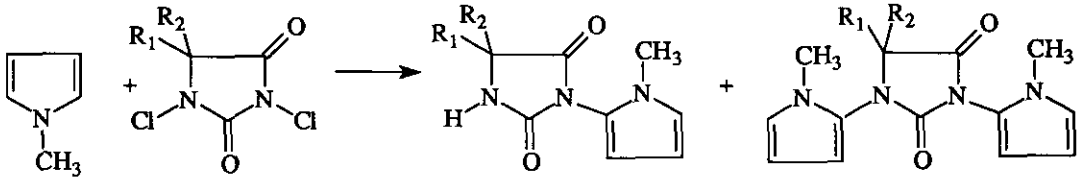
In this study the reaction of 1,3-dichloro-5,5-disubstituted hydantoins with 1-methylpyrrole was examined. A 1,3-dichlorohydantoin formally contains both N-chloroamide (N_1-Cl) and N-chloroimide (N_3-Cl) groups. The acidity constants of N_1-H and N_3-H are >14 and ca. 9 respectively for the types of hydantoins used to make the 1,3-dichloro derivatives used in this study.[8] It should therefore be possible to study the intramolecular competition between these two positions. In contrast previous studies have examined the effect of changes in structure[6] or of the *para* substituent[7] on addition-elimination in pyrroles.

RESULTS

1-Methylpyrrole (**1**) was reacted with the 1,3-dichloro derivatives of 5,5-dimethylhydantoin (**2**), 5-methyl-5-phenylhydantoin (**3**) and 5,5-diphenylhydantoin (**4**) in chloroform containing sodium bicarbonate. 1,3-Dichlorohydantoins (**3**) and (**4**) were prepared by reacting the appropriate hydantoin with sodium hypochlorite (Clorox^{R}).[8c] 1,3-Dichlorohydantoin (**2**) was commercially available. Reactions were followed until the reaction mixture gave a negative test with KI/ethanol/acetic acid. It took 57 h for the reaction between **1** and 1,3-dichloro-5,5-dimethylhydantoin (**2**) to go to completion. Solvent and any chloropyrroles formed were removed by rotary evaporation and the residue separated by flash chromatography to give a 70 % yield (based on available $\underline{N}_3$-Cl) of 3-(1-methyl-1$\underline{H}$-pyrrol-2-yl)-5,5-dimethylhydantoin (**5**) and a 28 % yield (based on available $\underline{N}_1$-Cl) of 1,3-di-(1-methyl-1$\underline{H}$-pyrrol-2-yl)-5,5-dimethylhydantoin (**8**).

The reaction time was varied and it was found that after 5 min 80% of the species capable of oxidizing iodide ion had disappeared. The reaction was quenched at this point and the ^{1}H nmr of the crude reaction mixture indicated that monopyrroylhydantoin (**5**) was the sole addition-elimination product present. Monopyrroylhydantoin (**5**) was isolated in 60 % yield.

Reactions between **1** and 1,3-dichlorohydantoins (**3**) and (**4**) were carried out and in both cases only their respective monopyrroylhydantoin derivatives (**6**) and (**7**) were formed (Scheme 1). Yields of **6** and **7** were 61% and 74% respectively and the yields were not influenced by reaction time (5 min or 57 h).



2, $R_1 = R_2 = CH_3$
3, $R_1 = CH_3$; $R_2 = C_6H_5$
4, $R_1 = R_2 = C_6H_5$

5, $R_1 = R_2 = CH_3$
6, $R_1 = CH_3$; $R_2 = C_6H_5$
7, $R_1 = R_2 = C_6H_5$

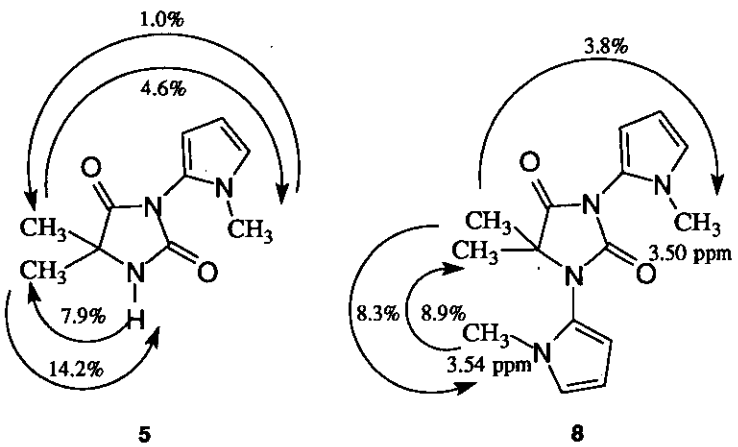
8, $R_1 = R_2 = CH_3$

Scheme 1

The structure of **8** was elucidated on the basis of ms and nmr spectra. Chemical shift differences could not be used to unambiguously assign the position of the pyrroyl substituent in **5**. The nuclear Overhauser effect (NOE) can be used to determine the proximity of groups in a molecule.[9] A search of the literature indicated

that in the hydantoins NOE, NOED AND NOESY spectra have been used to study conformation[10] in solution, to identify rotamers[11] and to establish absolute configuration[12] respectively. NOE spectra have not been used to determine the nitrogen substitution pattern in hydantoins.

In the following figure (Scheme 2) are summarized the results of the NOE difference spectra of pyrroylhydantoins (**5**) and (**8**). These results clearly demonstrated that the pyrroyl substituent was found on N_3 of monopyrroylhydantoin (**5**). Similar results were obtained for monopyrroylhydantoin (**6**) but in the case of monopyrroylhydantoin (**7**) the N_1-H signal overlapped with those of the pyrrole ring protons and it was not possible to obtain the NOE for the interaction between the N_1-H group and the substituents at C-5. Its structure is proposed by analogy with **5** and **6**.



5 **8**

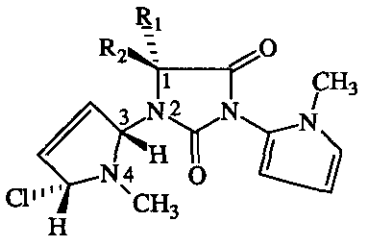
Scheme 2

AM1 STUDY OF INTERMEDIATES

The reaction of 1-methylpyrrole (**1**) with 1,3-dichloro-5-methyl-5-phenylhydantoin (**3**) and 1,3-dichloro-5,5-diphenylhydantoin (**4**) did not lead to products analogous to the dipyrroylhydantoin (**8**) obtained when 1,3-dichloro-5,5-dimethylhydantoin (**2**) was used. In Scheme 3 can be seen the addition intermediates which would have to form in order to get products such as **8**. Absence of such products when **3** and **4** were used would seem to indicate that their formation is prohibited by the activation barrier under the reaction conditions used. The mostly likely reason for this is the interaction between the substituents on C-5 and N_1 in the transition state leading to the addition products (**10**) and (**11**).

Nmr[13] and MMX molecular mechanics[11] studies of conformational isomerism in 1-aryl-5,5-disubstituted hydantoins have previously appeared. The rotational barrier for 1-phenyl-5,5-dimethylhydantoin was calculated to be 2.8 kcal/mol.[11] In contrast this value increased to 15.5 kcal/mol when a 2-methylphenyl group was introduced in place of a C-5 methyl group. It was concluded that a strong steric interaction existed between the substituents on C-5 and N_1. An analogous steric interaction would be expected to be present in intermediates (**10**) and (**11**) (see Scheme 3 below) and in the transition states leading to their formation.

Another way to gauge the steric effect is to examine how the interaction of the groups on C-5 and $\underline{N}_1$ distort the ideal geometry of the intermediate. An AM1[14] study was carried out to look at the effect on the geometry of the interaction between the substituents on C-5 and $\underline{N}_1$. The semiempirical calculations were performed using the AM1 method as implemented in the AMPAC 2.1 series of programs[15] with previously published parameter sets.[16] Geometries were fully optimized with no symmetry constraints and the force constants were computed to characterize all points on the potential surface.[17] The AM1 optimization predicted that rotation about the N-C bonds between the central and outlying rings produced a more stable (though not necessarily the *most* stable) conformation as illustrated below. In this conformation, the effect of altering the identity of R_1 and R_2 had some effect on the geometric angles and bond orders (see Table 1). In the cases of **9** and **10**, the exterior ring is twisted almost perpendicular (94°, 87° respectively) to the internal ring to alleviate strain due to geometric interactions.



9, $R_1 = R_2 = CH_3$; **10**, $R_1 = CH_3$, $R_2 = C_6H_5$; **11**, $R_1 = R_2 = C_6H_5$

Scheme 3

This is directly evidenced by the opening of the interring bond angle to 128° and 129° respectively. The predicted geometry of **11** shows a much more significant rotation about the bond, relieving more steric strain. In this case the interring bond angle has relaxed to near it's ideal value of 120°. Given this method of calculation, it is not possible to evaluate the possible energetic contribution of this added strain or to assess its effect on reactivity, but is does appear to be present.

Table 1

Bond and Dihedral Angles and Bond Orders in **9-11**

	9	**10**	**11**
Bond Angle[a]	127.6	128.9	118.6
Bond Angle[b]	119.5	118.7	119.6
Dihedral[c]	-94.5	-86.8	146.6
Bond order[d]	0.9	0.9	0.9

[a]Bond angle $C_1N_2C_3$. [b]Bond angle $N_2C_3N_4$. [c]Dihedral angle $C_1N_2C_3N_4$. [d]N_2C_3

The results of the AM1 calculations in this study and previous work by Colebrook and coworkers strongly suggest that a steric interaction is responsible for the absence of dipyrroylhydantoins when dichlorohydantoin (**4**) was used but were not as clear with respect to **3**.

CONCLUSION

The reaction of 1-methylpyrrole with 1,3-dichloro-5,5-dimethylhydantoin gave a mixture of monopyrroyl- and dipyrroylhydantoin and it was estimated that the $\underline{N}_3$-Cl group was three orders of magnitude more reactive than the $\underline{N}_1$-Cl group. A steric interaction prevented formation of the dipyrroylhydantoin products when other hydantoins bearing sterically bulky substituents at C-5 were used.

EXPERIMENTAL

A Varian EM-360 and a Bruker AM 300 were used to record ^{1}H nmr spectra. Mass spectra were taken with a Hitachi-Perkin Elmer RMU-6H spectrophotometer. AM1 computations were carried out on the UMKC VAX 6540V from Digital Equipment Corporation. Melting points were taken on a Meltemp and are uncorrected. 1,3-Dichloro-5,5-dimethyl-, 5-methyl-5-phenyl- and 5,5-diphenylhydantoin were commercially available and used without further purification. 1-Methylpyrrole was distilled from zinc dust prior to use.

PREPARATION OF 1,3-DICHLOROHYDANTOINS: 1,3-Dichloro-5,5-diphenylhydantoin was obtained in 25 % yield (85% chlorine) mp 158-165 °C (lit.,[8c] mp 158-165 °C) by a literature[8c] procedure. Using the same procedure 4.75 g (25 mmol) of 5-methyl-5-phenylhydantoin was combined with 90 ml (50 mmol) of sodium hypochlorite (Clorox^R) and stirred mechanically for 3 h. The solid was filtered and washed with petroleum ether (35-60 °C). A 41 % yield (91 % chlorine), mp 134-135 °C, of 1,3-dichloro-5-methyl-5-phenylhydantoin was obtained.

GENERAL REACTION PROCEDURE: To a mixture containing 10 mmol of 1,3-dichlorohydantoin and 3.5 g of sodium bicarbonate in 100 ml of chloroform there was added 2.028 g (25 mmol) of 1-methylpyrrole. The mixture was stirred in the dark until it tested negatively with KI/2-propanol/acetic acid solution (57 h). In those systems where only the monopyrroylhydantoin was formed the reaction mixture was filtered to remove the sodium bicarbonate, the chloroform was removed under reduced pressure and addition of petroleum ether (35-60 °C) to the residue precipitated the product. In the case of 1,3-dichlorohydantoin (**2**) the two products were separated by flash chromatography on silica gel using methylene chloride/ethyl acetate 65:35 v/v as the eluent. To reactions run for 5 min there was added a KI/2-propanol/acetic acid solution to destroy the unreacted $\underline{N}$-Cl groups. A solution of sodium thiosulfate was added to reduce the iodine generated and the organic layer was separated, washed 3 times with water and dried over calcium chloride. The chloroform was removed under reduced pressure and the product was precipitated by treatment with petroleum ether (35-60 °C).

3-(1-Methyl-1H-pyrrol-2-yl)-5,5-dimethylhydantoin (**5**): recrystallized from methanol/ water, mp 180 °C; 300 Mz ^{1}H nmr ($CDCl_3$) d 6.78 (br s, 1H, NH), 6.68 (m, 1 H, C5H), 6.18 (m, 2 H, C4H and C3H), 3.48 (s, 3 H, NCH_3), 1.54 (s, 6 H) ppm. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.08; H, 6.27; N, 20.08.

1,3-Di-(1-methyl-1H-pyrrol-2-yl)-5,5-dimethylhydantoin (**8**): recrystallized from methanol, mp 143-145 °C; 300 Mz ^{1}H nmr ($CDCl_3$) d 6.66 (m, 2 H, C5H and C5'H), 6.15 (m, 4 H, C4H, C3H, C4'H and C3'H), 3.54 (s, 3 H, NCH_3), 3.50 (s, 3 H, NCH_3),1.55 (s, 6 H) ppm. Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.71; H, 6.27; N, 19.51. Found: C, 62.52; H, 6.27; N, 19.38.

3-(1-Methyl-1H-pyrrol-2-yl)-5-methyl-5-phenylhydantoin (6): recrystallized from methanol/water, mp 182-185 °C; 300 Mz ^{1}H nmr ($CDCl_3$) d 7.59-7.38 (m, 5 H, arom H), 6.76 (bs, 1H, NH), 6.64 (m, 1 H, C5H), 6.17 (m, 2 H, C4H and C3H), 3.38 (s, 3 H, NCH_3),1.94 (s, 3 H) ppm. HRms Calcd for $C_{15}H_{15}N_3O_2$: 269.3030. Found 269.1165.

3-(1-Methyl-1H-pyrrol-2-yl)-5,5-diphenylhydantoin (7): recrystallized from toluene, mp 186-195 °C; 300 Mz ^{1}H nmr ($CDCl_3$) d 7.45-7.35 (m, 10 H, arom H), 6.65 (m, 1 H, C5H), 6.18 (m, 2 H, C4H and C3H), 3.37 (s, 3 H, NCH_3) ppm. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.25; H, 5.33; N, 12.34.

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REFERENCES

1. The Pennsylvania State University Delaware County Campus
2. University of Missouri Kansas City
3. A. H. Jackson, 'Pyrroles', chapt. 3.1, ed. by R. A. Jones, Wiley, New York, 1990.
4. M. De Rosa and I. Brillembourg, J. Chem. Soc., Chem. Commun., 1986, 1585.
5. M. De Rosa and G. Cabrera Nieto, Tetrahedron Lett., 1988, 29, 2405.
6. M. De Rosa, G. Cabrera Nieto, and F. Ferrer Gago, J. Org. Chem., 1989, 54, 5347.
7. M. De Rosa and G. Cabrera Nieto, Gazz. Chim. Ital., 1991, 121, 73.
8. (a) L. W. Pickett and M. McLean, J. Am. Chem. Soc., 1939, 61, 423. (b) R. A. Corral and O. O. Orazi, J. Org. Chem., 1963, 28, 1100. (c) C. A. Lipinski, J. Bordner, G. C. Butterfield, and L. C. Marinovic, J. Heterocycl. Chem., 1990, 27, 1793.
9. D. Neuhaus and M. Williamson, 'The Nuclear Overhauser Effect in Structural and Conformational Analysis', VCH Publishers, Inc., New York 1989.
10. H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima, and T. Haneishi, J. Chem. Soc., Perkin Trans. 1, 1991, 1637.
11. L. D. Colebrook, Can. J. Chem., 1991, 69, 1957.
12. W. Sankhavasi, S. Kohmoto, M. Yamamoto, T. Nishio, I. Iida, and K. Yamada, Bull. Chem. Soc. Jpn., 1992, 65, 935.
13. L. D. Colebrook, H. G. Giles, A. Granata, S. Icli, and J. R. Fehlner, Can. J. Chem.,1973, 51, 3635. L. D. Colebrook, S. Icli, and F. H. Hund, Can. J. Chem., 1975, 53, 1556.
14. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, J. Am. Chem. Soc.,1985, 107, 3902.
15. M. J. S. Dewar, 'AMPAC', Quantum Chemistry Program Exchange, Bloomington, IN, QCPE # 506.
16. C, H, O, N: reference 14. Cl: M. J. S. Dewar, and E. G. Zoebisch, J. Mol. Struct. (THEOCHEM), 1988, 180,1.
17. J. W. McIver and A. Komornicki, Chem. Phys. Lett. , 1971, 10, 303. J. W. McIver and A. Komornicki, J. Am. Chem. Soc., 1972, 94, 2625.

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