Intramolecular Cyclizations Leading to Bridgehead Bicyclics 2. 5,5-Dialkylhydantoin Derivatives

Katsuhide Okada (1), James A. Kelley and John S. Driscoll (2)

Drug Design and Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

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The effect of substituents in the 5-position on the course of hydantoin intramolecular alkylation reactions was studied. Dialkyl and diaryl substituted intermediates resulted in the same type product, 2,3-dihydro-6,6-disubstituted imidazo[2,1-*b*]oxazole-5(6*H*)ones, indicating alkylation on oxygen rather than nitrogen. The mass spectral and nmr characteristics of these bicyclic compounds are discussed.

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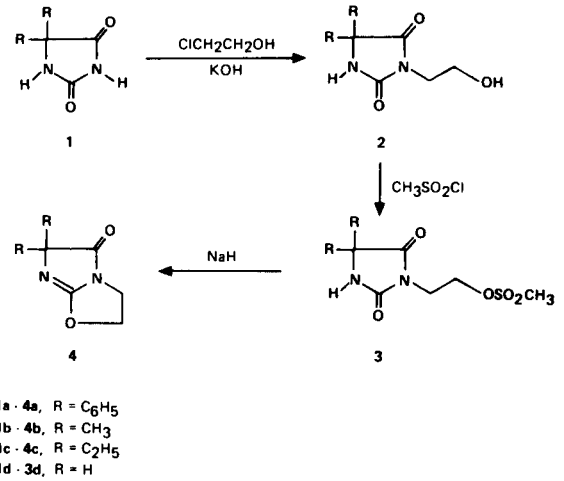
During a study of hydantoin alkylating agents for possible use against tumors of the central nervous system, it was found that bicyclic derivatives such as **4a** were obtained through an intramolecular alkylation reaction (3). These compounds were good electrophiles and acted as strong alkylating agents.

While **3a** had the possibility of also undergoing intramolecular *N*-alkylation to produce the bridged bicyclic **5**, only one compound was isolated from the reaction and this was assigned structure **4a** based on nmr evidence (3). It became of interest to determine whether the nature of the substituents in the 5-position could influence the course of the intramolecular alkylation reaction. A *N*-alkylation pathway would provide an entry into the relatively unknown 1,4-diazabicyclo[2.2.1]heptane system (4). Conversely, intramolecular alkylation on oxygen would provide oxygen analogues of levamisole **6**, a compound reported to have immunopotentiating properties (5).

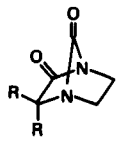
SCHEME I



Treatment of the 5,5-dialkyl mesylates **3b** and **3c** with sodium hydride in monoglyme resulted in intramolecular *O*-alkylation to produce two new 2,3-dihydro-6,6-dialkylimidazo[2,1-*b*]oxazole-5(6*H*)one derivatives (Scheme 1). While it was possible to synthesize the bicyclic 6,6-dimethyl (**4b**) and diethyl (**4c**) compounds, it was not possible to isolate the 6,6-unsubstituted bicyclic analogue. This may be due to the instability of this compound since **4b** and **4c** were found to be much more unstable than **4a**. The dialkyl derivatives appeared to polymerize over a period of several months at 4° while the diphenyl analogue was stable for several years at that temperature.

The nmr spectra of **4b** and **4c** were characteristic of intramolecular *O*-alkylation rather than alkylation of *N*-1 of the hydantoin to give the bridged bicyclic **5**. The two methylene groups of the bridge absorbed as triplets and possessed significantly different chemical shifts [δ 3.7 (CH_2N); δ 4.8 (CH_2O)]. These methylene groups would be expected to be nearly equivalent (6) if *N*-alkylation had occurred to produce **5**. The nmr spectra of **4b** and **4c** are also consistent with that reported (3) for **4a**. The structure of **4a** had additional support from hydrolysis studies.

Mass spectral data were also consistent with the structures proposed for the bicyclic products. The mass



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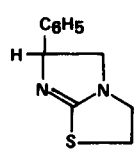

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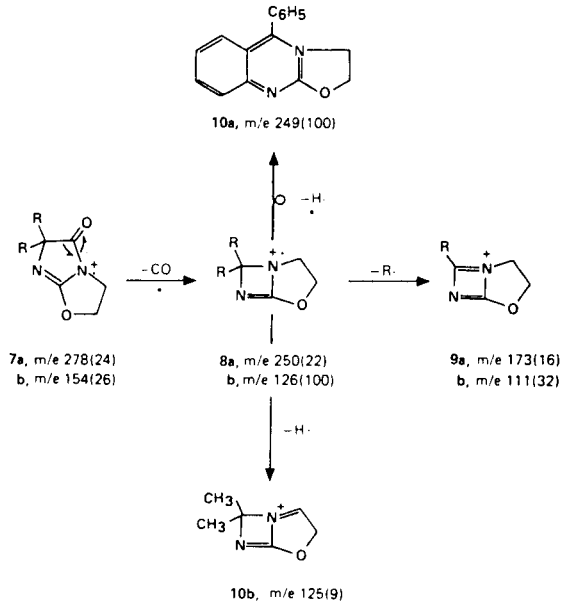
Figure 1. PROBABLE FRAGMENTATION PATHWAYS FOR BICYCLOHYDANTOINS



7a - 9a, R = C_6H_5
7b - 9b, R = CH_3

* Metastable peak observed.

spectra of the two aliphatic analogues **4b** and **4c** indicate similar fragmentation pathways: however, the participation of the 6-substituted phenyl groups allows additional rearrangements to occur with **4a**. Figure 1 shows the postulated structure of some of the major ions produced by **4a** and **4b** and their relative abundances. Both analogues extrude carbon monoxide from moderately abundant molecular ions to give **8a** and **8b**, respectively: this transition is confirmed by the appropriate metastable ions in both instances. In the case of the aliphatic dimethyl analogue **4b**, ion **8b** results in the base peak, while the corresponding ion for the phenyl-substituted analogue, **8a**, may rearrange *via* loss of a hydrogen radical to form the more stable tricyclic ion **10a** (3,7). This latter decomposition is marked by a very intense metastable peak (Calcd: m/e 248.1, Found: m/e 248.2) and results in the base peak in the mass spectrum of **4a**. Ions **8a** and **8b** may also fragment by simple cleavage alpha to the unsaturated nitrogen to give ions **9a**, **9b** or **10b**. Accurate masses were also determined for the major ions of interest in **4a** and were found to be consistent with the structures postulated in Figure 1.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 621 and 137 spectrometers as Nujol mulls unless otherwise specified. Nmr spectra were determined in deuterochloroform unless otherwise indicated on a Varian T-60 instrument. Chemical shifts are given as delta values with reference to tetramethylsilane. Electron impact mass spectra were obtained on a DuPont 21-492B gas chromatograph-mass spectrometer system consisting of a Varian 2740 gas chromatograph interfaced to the mass spectrometer *via* a single stage glass jet separator. Mass spectra were normally acquired from samples of the pure compound by direct probe insertion into the ion source. When mixtures were analyzed, *e.g.*, decomposed samples of **4b** and **4c**, the components were separated on a 1.83 m x 2 mm i.d. glass column packed with 3% SE-30 on 100/120 mesh Gas Chrom Q. Mass spectra were recorded for all peaks of interest. Standard mass spectrometer operating conditions were: transfer line and jet separator, 240°; ion source, 240°; electron energy, 75eV; ionizing current 250 μamp.; and scan speed, 4 or 10 seconds per decade.

Compounds were tested for alkylating ability with *p*-nitrobenzylpyridine (NBP) as previously described (3). Hydantoin and its 5,5-dimethyl and 5,5-diphenyl derivatives were obtained commercially. Elemental analyses were carried out by the NIAMDD, NIH.

5,5-Diethylhydantoin (**1c**).

This compound was prepared on a 100 g. scale in 50% yield, by the method of Upham and Dermer (8) m.p. 165-165.5° (lit. (8) m.p. 163°).

3-Hydroxyethyl-5,5-diethylhydantoin (**2c**). General Method for **2b**.

A mixture of **1c** (10.0 g., 0.032 mole), ethylene chlorohydrin (5.2 g., 0.064 mole) and potassium hydroxide (2.8 g., 0.05 mole) in absolute ethanol (60 ml.) was refluxed overnight. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate which was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 4.15 g. (64%) of crude **2c**, m.p. 72-78°. This material was satisfactory for the next reaction step without further purification: ir: ν 3400, 3250, 1700, 1250, 1125, 1080, 1075, 1050, 990, 940, 875, 855, 810, 792, 762 cm^{-1}; nmr: δ 0.9 (t, 6, CH_3), 1.7 (q, 4, CH_2), 3.75 (broad, 4, CH_2CH_2), 6.6 (broad, 2, OH, NH, deuterium oxide exchangeable).

Compound **2b** was produced as an oil which solidified on standing. Recrystallization from benzene gave 4.5 g. (67%) m.p. 63.5-64.5°; ir: ν 3250, 1760, 1720, 1700, 1025, 1003, 850, 770, 710 cm^{-1}; nmr: δ 1.45 (s, 6, CH_3), 3.70 (m, 4, CH_2CH_2), 6.80, 6.85 (broad, 2, OH, NH, deuterium oxide exchangeable).

3-Hydroxyethylhydantoin (**2d**).

Hydantoin (10.0 g., 0.1 mole) was added to a stirred solution of sodium metal (2.3 g., 0.1 mole) in absolute ethanol (400 ml.). After refluxing overnight, ethylene bromohydrin (25.0 g., 0.2 mole) was added to the suspension and reflux was continued for an additional 48 hours. The resulting transparent solution was evaporated and the residue was extracted with three 150 ml. portions of hot ethyl acetate. Removal of the solvent and recrystallization from ethanol-ethyl acetate gave 2.81 g. (19%) of **2d**, m.p. 102-102.5° (lit. (9) m.p. 102-104°); ir: ν 3400-3100, 1750, 1700, 1200, 1150, 1080, 1060, 990, 955, 930, 760, 750 cm^{-1}; nmr: (DMSO-d_6) δ 3.4 (broad, 4, CH_2CH_2) 3.82 (s, 2, CH_2-ring), 4.7 (broad, 1, OH), 7.8 (broad, 1, NH), 4.7 and 7.8 are deuterium oxide exchangeable.

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.44. Found: C, 41.68; H, 5.68; N, 19.19.

3-(2-Hydroxyethyl)-5,5-diethylhydantoin Methanesulfonate Ester (**3c**). General Procedure for **3b**.

Methanesulfonyl chloride (1.9 g., 0.017 mole) was added in one portion to a solution of **2c** (3.0 g., 0.015 mole) in dry

pyridine (60 ml.). The reaction mixture was stirred overnight with the exclusion of moisture and poured into 40 ml. of chilled, concentrated hydrochloric acid solution. After extraction of the aqueous solution with ethyl acetate, the organic extract was washed first with 2.5% aqueous sodium carbonate solution and then with water to neutrality. Evaporation of the solvent produced a solid which gave 3.15 g. (75%) of product m.p. 98.5-99.5° after recrystallization from chloroform-ether (3:1); positive NBP test; ir: ν 3280, 1775, 1750, 1700, 1170, 1080, 1055, 1020, 950, 905, 870, 805, 760 cm^{-1}; nmr: δ 0.85 (t, 6, CH_3), 1.8 (m, 4, CH_2), 3.00 (s, 3, CH_3SO_2), 3.82 (t, 2, CH_2N), 4.40 (t, 2, CH_2O), 5.8 (broad, 1, NH).

Anal. Calcd. for $C_{10}H_{18}N_2O_5S$: C, 43.15; H, 6.52; N, 10.07; S, 11.52. Found: C, 43.08; H, 6.59; N, 9.91; S, 11.48.

Compound **3b** was prepared on a 20 g. scale in 53% yield by a similar procedure. Recrystallization of the product from ethyl acetate-benzene (1:3) gave **3b**, m.p. 93-94.5°; NBP positive; ir: ν 3280, 1790, 1750, 1705, 1180, 1080, 1030, 995, 980, 950, 900, 880, 808, 770 cm^{-1}; nmr: δ 1.40 (s, 6, CH_3), 3.00 (s, 3, CH_3SO_2) 3.80 (t, 2, CH_2N), 4.40 (t, 2, CH_2O), 6.2 (broad, 1, NH).

Anal. Calcd. for $C_8H_{14}N_2O_5S$: C, 38.39; H, 5.64; N, 11.19; S, 12.81. Found: C, 38.50; H, 5.93; N, 11.40; S, 12.64.

Compound **3d** was prepared on a 5 g. scale in 65% yield by the above procedure with the following exceptions. The solution of **2d** in pyridine was cooled to 4° prior to methanesulfonyl chloride addition and ethyl acetate extraction was carried out overnight in a liquid-liquid extractor; ir: ν 3350, 1760, 1700, 1350, 1180, 1118, 1070, 1020, 975, 955, 915, 810, 768, 755, 735, 720 cm^{-1}; nmr: δ 3.08 (s, 3, CH_3SO_2), 3.80 (t, 2, CH_2N), 3.90 (d, 2, CH_2-ring), 4.40 (t, 2, CH_2O), 7.6 (broad, 1, NH).

Anal. Calcd. for $C_6H_{10}N_2O_5S$: C, 32.42; H, 4.54; N, 12.61; S, 14.43. Found: C, 32.51; H, 4.63; N, 12.41; S, 14.42.

2,3-Dihydro-6,6-diethylimidazo[2,1-*b*]oxazole-5(6*H*)one (**4c**). General Method for **4b**.

A 50% mineral oil suspension of sodium hydride (2.0 g., 1.0 g. sodium hydride, 0.04 mole) was washed with monoglyme (which had been dried over lithium aluminum hydride) and was added to a stirred cold (0°) solution of **3c** (10.0 g., 0.036 mole) in dry monoglyme (100 ml.). The mixture was stirred for 3 hours at 0° and overnight at room temperature. Insoluble material was filtered and the solvent removed *in vacuo* to give a high viscosity oil. High vacuum distillation of a small portion of the oil gave a solid. Use of this material as a seed crystal caused the original oil to solidify. Recrystallization from ether gave 3.1 g. (49%) of white crystals, m.p. 77-79°. This compound also could be purified by column chromatography on silica gel (ethyl acetate-benzene 3:1). Compound **4c** decomposes on the column, however, if it is not eluted immediately; NBP positive; ir: ν 1720, 1680, 1250, 1190, 1110, 1062, 1010, 940, 860, 790, 750 cm^{-1}; nmr: δ 0.80 (t, 6, CH_3), 1.70 (q, 4, CH_2), 3.70 (t, 2, CH_2N), 4.82 (t, 2, CH_2O); mass spectrum: m/e (relative intensity) 182 (M^+, 18), 154 (31), 153 (16), 139 (23), 125 (56), 99 (100), 84 (21), 70 (30), 57 (57), 42 (44).

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.33; H, 7.74; N, 15.37. Found: C, 59.50; H, 7.90; N, 15.20.

Compound **4b** was prepared on a 2 g. scale in 76% yield by the above method. Recrystallization from ethyl acetate gave white crystals, m.p. 116.5-118°; NBP positive; ir: ν 1730, 1680, 1325, 1260, 1022, 1008, 990, 945, 915, 842, 750 cm^{-1}; nmr: δ 1.40 (s, 6, CH_3), 3.79 (t, 2, CH_2N), 4.90 (t, 2, CH_2O); mass spectrum: m/e (relative intensity) 154 (M^+, 26), 126 (100), 125 (9), 111 (32), 96 (23), 85 (58), 84 (17), 70 (22), 42 (42), 41 (25).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.23; H, 6.69; N, 18.17.

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