Amidoalkylation of a Phenol by a Hydantoin. Construction of a New Hetero-tricyclic System.

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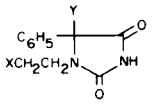
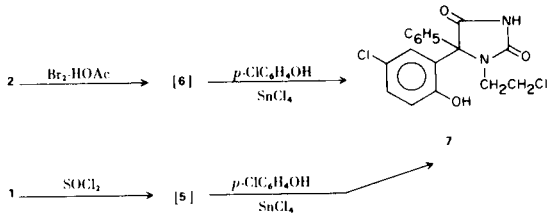
In continuation of a study (1) of the electrophilic reactivity of 5-halohydantoins, condensations of 1-(2-chloroethyl)-5-chloro- or bromo-5-phenylhydantoin (**5** or **6**) with several aromatic systems were examined. The necessary bromide **6** was prepared from the known (2) 1-(2-hydroxyethyl)-5-phenylhydantoin (**1**) by treatment with thionyl chloride (3 hours) to give **2**, followed by bromination. Reaction of the crude bromide **6** directly with *p*-chlorophenol in the presence of anhydrous stannic chloride led to a 74% yield (from **2**) of pure diarylhydantoin **7**.



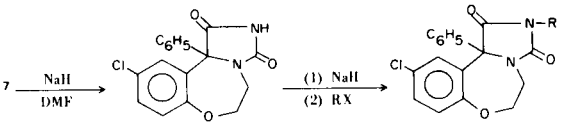
1, X = OH, Y = H
2, X = Cl, Y = H
3, X = Cl, Y = OH
4, X = Cl, Y = OC_2H_5
5, X = Y = Cl
6, X = Cl, Y = Br



Prolonged treatment (28 hours) of **1** with boiling thionyl chloride produced the dichloride **5** which, with *p*-chlorophenol, gave only a 37% yield (from **1**) of **7**. Dichloride **5** was further characterized by ethanolysis to **4**.

Extension of this condensation to several other aromatic systems was not successful. From the reaction of **6** with *p*-chlorothioanisole, only the hydrolysis product **3** could be identified. Although not fully characterized, the product from *p*-chlorothiophenol appeared to be the corresponding 5-arylthiohydantoin (*i.e.*, X = Cl, Y = *p*-ClC_6H_4S-). Likewise, *p*-chloroacetanilide, indole, and 3-methylindole all failed to react with **6**.

Conversion of the phenol **7** to its sodium salt resulted in cyclization to **8**, which could be substituted further at the nitrogen atom to give **9 a-c**. These tricyclic compounds



9a, R = CH_3
9b, R = $CH_2CH_2N(C_2H_5)_2$
9c, R = $SO_2C_6H_5$

(**8**, **9**) appear to be the first reported examples of the imidazo[5,1-*d*][1,4]benzoxazepine ring system.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 521 spectrophotometer. Pmr spectra were recorded on a Varian T-60 (60 MHz) spectrometer. Chemical shifts are reported as δ relative to TMS (δ = 0.00 ppm), using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. The mass spectrum was obtained in an AEI Model MS902 spectrometer.

1-(2-Chloroethyl)-5-phenylhydantoin (**2**).

A solution of 45 g. (0.204 mole) of 1-(2-hydroxyethyl)-5-phenylhydantoin (**1**) (2) in 73 g. (0.612 mole) of thionyl chloride was heated under reflux for 3 hours. The excess thionyl chloride was removed by distillation under vacuum (water pump) in a rotary evaporator, and the residue was taken up in a minimum amount of hot ethanol. Product crystallized from the cooled solution. Filtration and drying gave 40.4 g. (83%) of **2**, m.p. 135-137°. Another recrystallization of a sample gave pure **2**, m.p. 137-139°; ir (chloroform): 3430 (ν NH), 1790 and 1740 (ν C=O); pmr (deuteriochloroform): δ 3.0-4.4 (m, 4H, $ClCH_2CH_2N$), δ 5.33 (s, 1H, ArCHCO), δ 7.3-7.9 (m, 5H, C_6H_5), δ 9.3-9.7 (m, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; Cl, 14.85; N, 11.74. Found: C, 55.65; H, 4.80; Cl, 15.02; N, 11.61.

1-(2-Chloroethyl)-5-(5-chloro-2-hydroxyphenyl)-5-phenylhydantoin (**7**).

(a) From **2**.

A stirred solution of 9.52 g. (0.04 mole) of **2** in 65 ml. of glacial acetic acid (containing 0.1 ml. of acetic anhydride) was heated on the steam-bath, treated with three drops of glacial acetic acid previously saturated with anhydrous hydrogen bromide, and then dropwise (45 minutes) with a solution of 6.72 g. (0.042 mole) of bromine in 10 ml. of glacial acetic acid. After another 3 hours of heating, the solvent was removed by vacuum distillation in a rotary evaporator, 100 ml. of heptane was added and immediately removed by distillation in the same way. This process was repeated

with another 100-ml. portion of heptane and two successive 100-ml. portions of dry chloroform. The crude bromo compound **6** was then taken up in 60 ml. of dry 1,2-dichloroethane, cooled in an ice bath, and 5.66 g. (0.044 mole) of *p*-chlorophenol was added, As soon as it was dissolved, 20.8 g. (0.08 mole) of anhydrous stannic chloride was added dropwise (30 minutes) to the stirred mixture which was then kept in the ice bath for another hour followed by heating under reflux for 3 hours. To the hot reaction mixture was added 100 ml. of 10% hydrochloric acid and heating under reflux was continued for another hour. Cooling to room temperature gave precipitated product which was collected at the filter. The organic phase of the filtrate was separated from the aqueous phase and concentrated to dryness in the rotary evaporator. The residue crystallized on trituration with a benzene-ethanol mixture. This product was collected, added to the main portion, and the total product (11.32 g.) was slurried in dry ether, collected at the filter and dried. There was obtained 10.8 g. (74%) of pure **7**, m.p. 250-251° (recrystallizable from benzene-ethanol with no change in m.p.); ir (Nujol): 3230 (broad, ν bonded NH), 1775, 1715 (ν C=O); pmr (DMSO-d_6): δ 2.7-4.4 (m, 4H, $ClCH_2CH_2N$), δ 6.7-7.7 (m, 8H, ArH), δ 10.5-11.3 (m, 2H, NH and OH); high resolution mass spectrum (70 eV) m/e 364.0377. Calcd. for $C_{17}H_{14}Cl_2N_2O_3$: 364.0380.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_3$: C, 55.91; H, 3.86; Cl, 19.44; N, 7.67. Found: C, 56.05; H, 3.95; Cl, 19.99; N, 7.47.

In the absence of stannic chloride in the foregoing procedure, no product **7** was obtainable. Likewise, only low yields (<40%) of **7** were produced when anhydrous aluminum chloride was used instead of stannic chloride.

(b) From **1**.

A solution of 10 g. (0.045 mole) of **1** in 30 ml. of thionyl chloride was heated under reflux. After 28 hours, a sample of the product (submitted for pmr analysis) no longer contained any detectable methine proton. The excess thionyl chloride was removed by distillation and the residue of crude **5** treated exactly as described in the foregoing procedure for the corresponding bromo analog **6**. In this way was obtained 6.2 g. (37% yield from **1**) of less pure **7**, m.p. 244-248°.

1-(2-Chloroethyl)-5-ethoxy-5-phenylhydantoin (**4**).

Crude dichloride **5** prepared from 36 g. (0.163 mole) of **1** and 58 g. (0.49 mole) of thionyl chloride according to the foregoing procedure was taken up in a minimum quanity of warm absolute ethanol. After addition of hexane the solution was cooled and crude **4** (22.3 g., 48%) crystallized, m.p. 127-129°. Recrystallization from ethanol-hexane gave pure **4**, m.p. 128-130°; ir (deuteriochloroform): 3400 (ν NH), 1795, 1740 (ν C=O); pmr (deuteriochloroform): δ 1.37 (t, 3H, C-CH_3), δ 3.0-4.0 (m, 6H, OCH_2C, and $ClCH_2CH_2N$), δ 7.48 (s, 5H, C_6H_5), δ 9.0-9.5 (m, 1H, NH).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_3$: C, 55.23; H, 5.35; Cl, 12.54; N, 9.91. Found: C, 54.95; H, 5.42; Cl, 12.82; N, 9.88.

1-(2-Chloroethyl)-5-hydroxy-5-phenylhydantoin (**3**).

In an attempt to condense the bromo compound **6** with 4-chlorothioanisole according to the procedure described above for the preparation of **7**, the only product isolated was a poor yield (~30%) of **3**, m.p. 136-137° (from chloroform); ir (Nujol): 3450 (ν NH and OH), 1780, 1720 (ν C=O); pmr (DMSO-d_6): δ 3.3-3.7 (m, 4H, $ClCH_2CH_2N$), δ 7.45 (s, ~5H, C_6H_5), δ 7.5-7.8 (m, ~2H, OH and NH).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; Cl, 13.92; N, 11.00. Found: C, 51.80; H, 4.33; Cl, 13.82; N, 11.10.

10-Chloro-11b-phenyl-2,5,6,11b-tetrahydroimidazo[5,1-*d*][1,4]-benzoxazepine-1,3-dione (**8**).

To an ice-cold, stirred suspension of 2.76 g. (0.115 mole) of sodium hydride in 100 ml. of dry dimethylformamide was added dropwise (1 hour) a solution of 28.0 g. (0.0766 mole) of **7** in 250 ml. of dry dimethylformamide. After sitrring overnight at room temperature the mixture was heated on the steam bath for 1 hour, cooled and taken up in a mixture of ether and water. The ether layer was washed well with water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a colorless solid residue that was recrystallized once from ethanol to give 9.8 g. (39%) of **8**, m.p. 257-259° (a less pure second crop was obtainable from the filtrate). Another recrystallization of a sample gave pure **8**, m.p. 259-260°; ir (Nujol): 3150 (ν bonded NH), 1785 and 1715 (ν C=O); pmr (DMSO-d_6): δ 2.7-4.7 (m, 4H, OCH_2CH_2N), δ 6.7-8.0 (m, 9H, ArH and NH).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_3$: C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 62.39; H, 4.11; Cl, 11.12; N 8.70.

10-Chloro-2-methyl-11b-phenyl-2,5,6,11b-tetrahydroimidazo[5,1-*d*][1,4]benzoxazepine-1,3-dione (**9a**).

The sodium salt of **8**, prepared using sodium hydride in dimethylformamide, was methylated with dimethyl sulfate according to the usual procedure (1). There was obtained a 78% yield of **9a**, m.p. 204-205° (from 2-butanone); pmr (deuteriochloroform): δ 3.18 (s, 3H, NCH_3).

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.57; H, 4.47; N, 8.26.

10-Chloro-2-(2-diethylaminoethyl)-11b-phenyl-2,5,6,11b-tetrahydroimidazo[5,1-*d*][1,4]benzoxazepine-1,3-dione (**9b**).

From the sodium salt of **8** with 2-diethylaminoethyl chloride in the usual manner (1) was obtained a 65% yield of **9b**, m.p. 108-109° (from methanol).

Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: C, 64.56; H, 6.12; N, 9.82. Found: C, 64.65; H, 6.24; N, 9.86.

10-Chloro-11b-phenyl-2-phenylsulfonyl-2,5,6,11b-tetrahydroimidazo[5,1-*d*][1,4]benzoxazepine-1,3-dione (**9c**).

The sodium salt of **8**, prepared from sodium hydride, in 1,2-dimethoxyethane as solvent instead of dimethylformamide, was heated under reflux for 30 minutes with a 10% excess quantity of benzenesulfonyl chloride. There was obtained an 80% yield of **9c**, m.p. 199-201° (from benzene).

Anal. Calcd. for $C_{23}H_{17}ClN_2O_5S$: C, 58.91; H, 3.65; Cl, 7.56; N, 5.97; O. 17.06. Found: C, 59.03; H, 3.70; Cl, 7.61; N, 5.99; O, 17.03.

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