Substitution in the Hydantoin Ring. II.[1,2] Aryl Derivatives

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Preparation of *N*-arylhydantoins by the reaction of *N*-halohydantoins with anthracene, benzene, phenanthrene, and naphthalene was tried; only the latter two gave the expected substances, in low yields.

The formation of an alkali-soluble substance assumed to be a 5,5-dimethyl-*N*-naphthylhydantoin, has been observed during attempts to halogenate naphthalene[4] with 1,3-dibromo-5,5-dimethylhydantoin (DBH). This led us to study the amidation of aromatic hydrocarbons by *N*-halohydantoins.[5]

Some analogous reactions using *N*-halosuccinimides are described in the literature. The bromosuccinimide converted acridine[6,7] to 9-succinimidoacridine (1%) and unidentified bromo derivatives. Benzene[8,9] when used as a solvent in several brominations of olefins in the presence of peroxide, gave *N*-phenylsuccinimide (1–15%). Similarly *N*-chlorosuccinimide converted benzene and nitrobenzene to their corresponding succinimide derivatives.[10]

The reaction conditions used here involved heating the reactants in carbon tetrachloride at 76° with illumination. By this procedure naphthalene and phenanthrene, but not benzene and anthracene, gave arylhydantoins. Attempts to react naphthalene with 5,5-dimethylhydantoin and bromine (under illumination), or with 1,3-dichloro-5,5-dimethylhydantoin, were unsuccessful. The amidation reaction probably occurs through a homolytic cleavage of the N—Br bond since the yield is increased by use of direct illumination.

From the reaction of naphthalene with DBH, 5,5-dimethyl-1-(α-naphthyl)hydantoin (I), 5,5-dimethyl-1-(4-bromo-α-naphthyl)hydantoin (II), and 5,5-dimethyl-1,3-bis(α-naphthyl)hydantoin (III) were obtained in 8, 0.6, and 0.1% yields, respectively. Another possible product of this reaction, the 5,5-dimethyl-3-(α-naphthyl)hydantoin, could not be found.

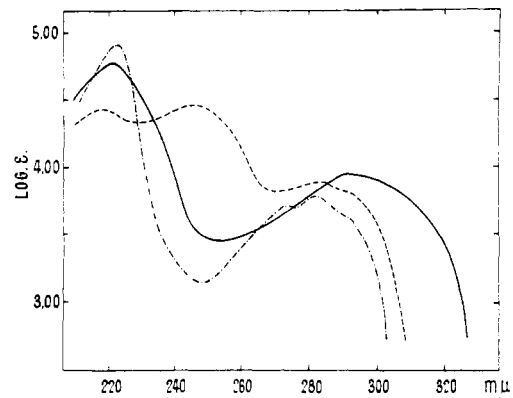

Fig. 1.—Ultraviolet spectra of (I) (- · · · -); 1-acetyl-3-(α-naphthyl)urea (———); 1-acetyl-3-(β-naphthyl)urea (– – – –).

The structure of I was proved as follows: besides analytical data, the infrared spectra (Nujol) supported the presence of an aromatic ring (6.27, 6.36, 6.67 μ), N—H (3.22 μ) and the two carbonyls groups (5.65, 5.91 μ) of hydantoin[11,12]; certainly this N—H bond corresponds to position 3 since I is alkali soluble,[13] readily forms a silver derivative,[14] and is monomethylated[15] on reaction with methyl iodide and an equivalent of alkali. It was established as the α-naphthyl isomer by the close resemblance of its ultraviolet spectrum to those of α-naphthylamine[16] and 1-acetyl-3-(α-naphthyl) urea and the remarkable differences from those of the corresponding β-isomers (Fig. 1). In addition, the above-mentioned methyl derivative of I, 3,5,5-trimethyl-1-(α-naphthyl)hydantoin, is identical with the product obtained from naphthalene and 1-bromo-3,5,5-trimethylhydantoin.

Compound II was generally similar to I in its alkali solubility and infrared and ultraviolet absorption maxima. Comparison of its spectrum to those of 1-acetylamino-4-bromonaphthalene [λ_{max} 223 mμ(log ε 4.70), 298(3.96); λ_{min} 258(3.23)]

(1) Part I, O. O. Orazi and R. A. Corral, *Tetrahedron*, **15**, 93 (1961).

(2) This paper includes part of the doctoral thesis of one of us (R. J.).

(3) Fellow of the Consejo Nacional de Investigaciones Científicas y Técnicas (1958).

(4) O. O. Orazi and J. F. Salellas, *Anales asoc. quim. Argentina*, **38**, 188 (1950).

(5) For the use of halohydantoins as halogenating agents of aromatic hydrocarbons, see O. O. Orazi, J. F. Salellas, M. E. Fondovila, R. A. Corral, N. M. Mercère, and E. R. de Alvarez, *ibid.*, **40**, 61 (1952); R. A. Corral, O. O. Orazi, and J. D. Bonafede, *ibid.*, **45**, 151 (1957) and references therein cited.

(6) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(7) H. Schmid and W. Leutenegger, *ibid.*, **30**, 1965 (1947).

(8) D. R. Howton, *J. Am. Chem. Soc.*, **69**, 2060 (1947).

(9) E. R. Buchman and D. R. Howton, *ibid.*, **70**, 2517, 3510 (1948).

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(12) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures," Van Nostrand Co., New York, 1949.

(13) See for example, G. P. Lampson and H. O. Singher, *J. Org. Chem.*, **21**, 684 (1956).

(14) R. A. Corral and O. O. Orazi, *Anales asoc. quim. Argentina*, **44**, 11 (1956).

(15) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

(16) R. Friedel and N. Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley & Sons, New York, 1951.

and 2-acetylamino-1-bromonaphthalene [λ_{max} 238 mμ(log ε 4.63), 278 infl.(3.86), 285(3.93), 296 infl. (3.80); λ_{min} 262(3.67)] and more importantly its preparation from I, by bromination under conditions in which the hydantoin moiety[17] is unattacked, established the assigned structure.

The structure of III was established by comparison of its analytical data and absorption spectra to those of I and 5,5-dimethyl-3-(α-naphthyl)-hydantoin.

Amidation of phenanthrene afforded a 2.8% yield of an alkali-soluble substance that by analytical data and degradative oxidation to 9,10-phenanthrenequinone was proved to be 5,5-dimethyl-1-(9-phenanthryl)hydantoin (IV).

It is worth noting that Stuckey's spectroscopic method[18] was not suitable for distinguishing between N_1- and N_3-substitution in compounds II and IV. Only a slight change in ultraviolet spectra occurred in shifting from a neutral solution to an alkaline one; this was probably because the expected absorption increases in the latter are hidden by the strong general absorptions of those compounds.

Experimental[19]

Reaction of Naphthalene with 1,3-Dibromo-5,5-dimethylhydantoin (DBH).—Initial experiments showed that the yields of the alkali-soluble products when using diffuse daylight with or without dibenzoyl peroxide (freshly recrystallized) were similar and poorer than under irradiation.

A solution of 12.82 g. (0.1 mole) of naphthalene in 150 ml. of anhydrous carbon tetrachloride with 14.30 g. (0.05 mole) of recrystallized DBH was heated at 76° while stirred and irradiated by a 200-w. tungsten lamp. In the course of the reaction presence of free bromine was observed.

After disappearance of the bromohydantoin from the bottom (about 20 hr.), filtration gave a solid, 5 g., containing nearly 3% positive bromine, that after being treated with 20 ml. of hot water containing 0.5 g. of sodium sulfite, left 0.5 g. of a dark brown powder. This material was dissolved in chloroform and added to the first carbon tetrachloride filtrate.

The aqueous solution upon concentration and cooling afforded 2.8 g. (44%) of 5,5-dimethylhydantoin identified by melting point and mixture melting point.

The organic solution, after being washed with aqueous 10% sodium sulfite and water, was exhaustively extracted with a 0.2% aqueous sodium hydroxide solution. Acidification of the extract[20] with carbon dioxide or acetic acid provided 1.6 to 2.0 g. of a light colored product (alkali-soluble fraction) melting at 220–225°.

This material was fractionated in a 100-tube Craig countercurrent distribution machine using *n*-butyl alcohol–acetone–2*N* ammonia (5:1:5) solvent system (10 ml. of each phase; 23°). After 100 transfers compound I (K: 0.84; 0.68 g.) was obtained from tubes 35–47; fractions 48–70 subjected to 200 transfers in "closed circuit" furnished 0.28 g. more of I (tubes 129–145) along with 0.37 g. of II (K: 1.40) from tubes 165–183. Crystallization from alcohol gave a total of 0.76 g. (8%) of I, m.p. 244–245°, and 0.10 g. (0.6%) of II, m.p. 261–263°, raised to 265–267° by further purification.

In attempts to separate I and II by repeated crystallizations from alcohol, instead of countercurrent distribution, a much lower yield of I (m.p. 244–244.5°) and a small quantity of impure II (m.p. *ca.* 250°) were obtained.

The alkali-extracted organic solution after being washed with water, was evaporated to dryness and the residue was steam distilled. Upon vacuum distillation the steam-volatile material furnished first naphthalene, then 2.85 g. (14%) of α-bromonaphthalene (b.p. 135–138° at 12 mm.) identified by conversion to its picrate, m.p. 131–132°. The steam-involatile fraction (1.6 g.) was chromatographed on 20 g. of alumina (Woelm, neutral, activity II) and eluted successively with benzene, benzene–chloroform, chloroform, chloroform–alcohol, alcohol, and alcohol–water.

The eluates of 70 tubes (10 ml. each) were combined according to the weight distribution into eight fractions whose infrared spectra showed the typical bands of both hydantoin carbonyl groups (at 5.6–5.9 μ) and aromatic structures (at 6.2–6.7 μ). Each fraction was sublimed at 30 μ and bath temperatures up to 225°. The benzene-eluted fractions 1 and 2 (*ca.* 55% of the total eluate) furnished, after rechromatographing, only a few milligrams of a crystalline material containing bromine but no hydantoin ring (Beilstein test; infrared spectra). The sublimate from fraction 3 (elution with benzene plus 5–20% chloroform), on recrystallization from benzene–hexane gave 23 mg. (0.13%) of alkali-insoluble III, m.p. 223–224°. Fraction 6 (from chloroform–alcohol 1:1), after recrystallization, afforded 4 mg. of a mixture of I and II; the remaining fractions yielded, on sublimation, a small quantities (4–45 mg.) of deeply colored solids that failed to crystallize.

5,5-Dimethyl-1-(α-naphthyl)hydantoin (I).—Scarcely soluble in carbon tetrachloride and practically insoluble in water; λ_{max} 222 mμ (log ε 4.93), 273 (3.75), 282 (3.81), 290 infl. (3.67); λ_{min} 246 (3.26), 275 (3.72).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02; O, 12.58. Found: C, 70.66; H, 5.44; N, 10.87; O, 12.50.

The silver salt of I was obtained in 88% yield, by following the published procedure.[14]

Anal. Calcd. for $C_{15}H_{13}N_2O_2Ag$: Ag, 29.88. Found: Ag, 29.4 (Volhard).

A solution of 0.254 g. (0.001 mole) of I in 2 ml. of alcohol containing 0.001 mole of potassium hydroxide was mixed with 0.5 ml. of methyl iodide and left 4 hr. at room temperature; on evaporation, extraction with ethyl ether, and concentration, 60 mg. of crystalline 3,5,5-trimethyl-1-(α-naphthyl)hydantoin, m.p. 116–117°, separated; λ_{max} 222 mμ (log ε 4.96), 273 infl. (3.81), 281 (3.88), 291 infl. (3.71); λ_{min} 245 (3.23).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.61; H, 6.02; N, 10.44; O, 11.92. Found: C, 71.64; H, 6.06; N, 10.49; O, 11.98; OCH_3, 0.00.

Attempts to hydrolyze I with concentrated hydrochloric acid in a sealed tube at 160–170° for 24 hr., or by refluxing with 5% aqueous potassium hydroxide for 6 hr., gave 90–100% recovery of starting material.

5,5-Dimethyl-1-(4-bromo-α-naphthyl)hydantoin (II).—Its solubility is similar to that of I; λ_{max} 225 mμ (log ε 5.04), 283 infl. (4.09), 290 (4.20), 299 infl. (4.06); λ_{min} 250 (3.39).

Anal. Calcd. for $C_{15}H_{13}N_2O_2Br$: C, 54.07; H, 3.93; N, 8.41; O, 9.65. Found: C, 54.57; H, 3.93; N, 8.96; O, 10.09.

It was also obtained by halogenation of I: 0.254 g. (0.001 mole) of I and 0.208 g. (0.0013 mole) bromine in 5 ml. of acetic acid were kept 24 hr. at 95°. The mixture was evaporated to dryness under reduced pressure and the resi-

(17) E. J. McMullen, H. R. Henze, and B. W. Wyatt, *J. Am. Chem. Soc.*, **76**, 5636 (1954).

(18) R. E. Stuckey, *J. Chem. Soc.*, 331 (1947).

(19) Melting points are not corrected. Ultraviolet (in alcohol 96%) and infrared spectra were taken with Cary-14 and Perkin Elmer-21 recording spectrophotometers. Microanalyses were performed by Dr. A. Bernhardt (Mülheim, Germany).

(20) Using in the extraction smaller volumes of 5% sodium hydroxide solution led to 2.5 g. of deeply colored product without definite melting point. Prior to its fractionation it was sublimed (200–220°/5 μ) affording 1.5 g., melting *ca.* 210°.

due, after being washed with a dilute solution of sodium sulfite, then water, was recrystallized twice from alcohol, yielding 0.170 g. (51%) of II, m.p. 263–264°, identified by mixture melting point and coincidence of the infrared spectra (KBr).

Anal. Calcd. for $C_{15}H_{13}N_2O_2Br$: C, 54.07; H, 3.93; N, 8.41; O, 9.65. Found: C, 54.16; H, 3.93; N, 8.08; O, 10.10.

An attempt to convert I to II using DBH as brominating agent (72 hr., boiling carbon tetrachloride) failed, recovering 70% of I.

5,5-Dimethyl-1,3-bis(α-naphthyl)hydantoin (III).—λ_{max} 219 mμ (log ε 5.02), 272 infl. (3.98), 281 (4.07), 289 infl. (3.97); λ_{min} 244 (3.45).

Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.92; H, 5.30. Found: C, 78.51; H, 5.46.

Reaction of Naphthalene with 1-Bromo-3,5,5-trimethylhydantoin.[21]—The reaction was run as with DBH; a homogeneous medium was obtained and the consumption of the bromohydantoin was almost complete after 15 hr. as indicated by iodometric titration. On being cooled, the solution precipitated 1.9 g. of 3,5,5-trimethylhydantoin; an additional 1.2 g. (total yield 44%) was obtained from the alkaline extract of the filtrate after acidification, evaporation, and extraction with chloroform.

The alkali-extracted and washed organic phase was evaporated to dryness and the residue, after being extracted with hot hexane, was steam distilled. The undistilled material (0.57 g.) was chromatographed through 60 g. of alumina (Woelm, neutral, activity II), collecting 10-ml. fractions by elution with benzene and benzene–ethyl ether mixtures. The combined fractions 14–20, eluted with benzene–ethyl ether 19:1 (0.170 g.; negative Beilstein test), crystallized from ethyl ether, gave 0.115 g. (0.86%) of 3,5,5-trimethyl-1-(α-naphthyl)hydantoin, m.p. 115–116°, undepressed on admixture with the sample prepared above by methylation of I.

Reaction of Phenanthrene with DBH.—The reaction was run as described for naphthalene; the disappearance of DBH was complete after 20 hr. The carbon tetrachloride-insoluble fraction (6 g. containing about 3% positive bromine) furnished 2.9 g. (45%) of pure 5,5-dimethylhydantoin. Acidification of the alkaline extract yielded 1.24 g. of light yellow solid that, by several recrystallizations from 70% alcohol gave 0.43 g. (2.8%) of colorless crystals of 5,5-dimethyl-1-(9-phenanthryl)hydantoin (IV), m.p. 289–291°, raised by additional recrystallization to 291–293°; λ_{max} 220 mμ (log ε 4.46), 246 (4.73), 253 (4.84), 260 infl. (4.45), 275 (4.10), 286 (4.07), 297 (4.13); λ_{min} 218 (4.43), 227 (4.13), 271 (4.07), 281 (3.94), 291 (3.89).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21; O, 10.51. Found: C, 74.75; H, 5.52; N, 9.35; O, 10.39.

By evaporation of the organic solution to dryness and repeated extractions with hot alcohol (100 ml. total) was obtained, on cooling the extract a partly waxy precipitate (4.3 g.). Its benzene solution, filtered through neutral alumina, evaporated, and crystallized from alcohol, yielded 2.2 g. (8.6%) of 9-bromophenanthrene, identified by m.p. and mixed m.p.

Oxidation of 50 mg. of IV with 60 mg. of chromium trioxide in 0.6 ml. of acetic acid (4 hr. at 95°) yielded 2 mg. of 9,10-phenanthrenequinone, m.p. 205–207° (from alcohol) identified by admixture m.p. and infrared spectra.

Other Attempted Amidations.—Reaction of naphthalene with 1,3-dichloro-5,5-dimethylhydantoin (homogeneous medium), and benzene and anthracene with DBH, under conditions described above, yielded no alkali-soluble fractions.

1-Acetyl-3-(α-naphthyl)urea.—This substance and its β isomer were obtained by following essentially the directions of the literature[22]: Refluxing 2 hr. a solution of 0.186 g. (0.001 mole) of 1-(α-naphthyl)urea in 4 ml. of acetyl chloride, followed by evaporation to dryness and recrystallization of the residue from alcohol, afforded the desired compound, yield 94%, m.p. 219–220° (literature 214–215°); λ_{max} 221 mμ (log ε 4.78), 291 (3.96), 313 infl. (3.73); λ_{min} 252 (3.47).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27; O, 14.02. Found: C, 68.01; H, 5.38; N, 12.50; O, 14.46.

1-Acetyl-3-(β-naphthyl)urea.—Yield 73%, m.p. 204.5–205° (literature[22] 202–202.5°); λ_{max} 219 mμ (log ε 4.42), 243 infl. (4.45), 246 (4.47), 284 (3.89), 294 infl. (3.78); λ_{min} 229 (4.34), 270 (3.82).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27; O, 14.02. Found: C, 68.04; H, 5.48; N, 12.58; O, 14.36.

5,5-Dimethyl-3-(α-naphthyl)hydantoin.—α-Aminoisobutyronitrile was prepared by a slightly modified known method[23]: acetone cyanohydrin (5 ml.) was mixed at 0° with 10 ml. of concd. ammonia and, after some hours at room temperature, it was extracted with ethyl ether. To the chilled and stirred dry extract, an ethereal solution of 4.23 g. (0.025 mole) of α-naphthyl isocyanate was added dropwise; filtration and recrystallization of the crude product gave 3.4 g. (54%) of 1-(α-cyano-α-methylethyl)-3-(α-naphthyl) urea m.p. 205–208°.

Anal. Calcd. for $C_{15}H_{15}N_3O$: N, 16.59. Found: N, 16.16.

Cyclization of this urea derivative was accomplished by heating 2.53 g. (0.01 mole) in a mixture of 15 ml. of dioxane, 5 ml. of water and 10 ml. of conc. hydrochloric acid at 95° for 6 hr. On concentration and dilution with water, there was obtained 2.46 g. (97%) of 5,5-dimethyl-3-(α-naphthyl)-hydantoin, m.p. 208–209°, raised by recrystallization from ethyl acetate or alcohol to 209–210°. It sublimes easily under the conditions used during the fractionation of the amidation products of naphthalene; λ_{max} 221 mμ (log ε 5.04), 272 infl. (3.89), 279 (3.97), 289 infl. (3.83); λ_{min} 244 (3.30).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02; O, 12.58. Found: C, 71.03; H, 5.49; N, 11.00; O, 12.77.

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(23) J. V. Dubsky and N. D. Wensink, *Ber.*, **49**, 1134 (1916).