et al.[2] For the preparation of 1-alkyl- and 1-aryl-5-(5-nitro-2-furyl)tetrazoles (compounds **2a–m**) the method of Harvill, *et al.*,[3] was utilized.

The synthesis of the tetrazoles proceeded smoothly in all cases except when **3n** was used as the starting amide. In that instance, the product isolated from the reaction mixture (**4**) was not the expected tetrazole, but a compound having an imino chloride structure. This compound was unusually stable and resisted reaction with solutions of sodium azide and hydrazoic acid.

Screening Results.—The *in vitro* antibacterial testing data, given in Table I, were determined using methods described previously.[4] Data for nitrofurazone[5] are included for comparison. None of the compounds prepared possessed activity that was significantly better than that of nitrofurazone.

Experimental Section

All melting points were determined on a hot stage (Mel-Temp) melting point apparatus and are uncorrected. The infrared spectrum was obtained on a Perkin-Elmer infrared spectrophotometer Model 21.

5-(5-Nitro-2-furyl)tetrazole (1).—A mixture of 5-nitro-2-furonitrile[6] (138 g, 1.0 mole), sodium azide (72 g, 1.1 moles), and NH_4Cl (58 g, 1.1 moles) in DMF (500 ml) was stirred and heated cautiously. At first a very exothermic reaction occurred which quickly subsided. Stirring was continued for 3 hr at 100°. The solvent was removed under reduced pressure. After the residue was dissolved in water, the solution was acidified to pH 2 with concentrated HCl. A black, tarry mass formed which slowly crystallized upon cooling. The crude material was collected and recrystallized from glacial acetic acid.

N-Cyclohexyl-5-nitro-2-furamide (**3f**).—A solution of cyclohexylamine (182 g, 1.84 moles) in dioxane (800 ml) was placed in the flask and stirred while 5-nitro-2-furoyl chloride[7] (161 g, 0.92 mole) dissolved in dioxane (800 ml) was added. The reaction mixture was refluxed for 1 hr and poured into a large volume of water. After collecting, the product was recrystallized from 2-propanol (charcoal). Other derivatives of **3** listed in Table I except **3e** were prepared in a similar manner from the appropriate amine and were recrystallized from methanol or 2-propanol.

Ethyl N-(5-Nitro-2-furoyl)glycinate (**3e**).—Ethyl glycinate hydrochloride (560 g, 4 moles) was placed in the flask together with water (1000 ml) and ethylene chloride (1000 ml). Calcium carbonate (340 g) was added and the mixture was stirred vigorously for 15 min. The stirring was continued while 5-nitro-2-furoyl chloride (350 g, 2 moles) in ethylene chloride (1000 ml) was added. Stirring was continued for 3 hr, and the mixture was allowed to stand overnight at room temperature. The mixture was filtered and the two layers were separated. After the solvent was removed from the organic layer under reduced pressure, the crystallized residue was recrystallized from 2-propanol (charcoal).

1-Methyl-5-(5-nitro-2-furyl)tetrazole (**2a**).—Benzene (500 ml) was placed in a flask together with **3a** (44 g, 0.26 mole). The mixture was stirred while PCl_5 (54 g, 0.26 mole) was added in small portions which was accompanied by a slight endothermic reaction and the evolution of HCl. The reaction mixture was stirred at room temperature while a solution of HN_3[8] (13 g, 0.3 mole) in benzene (220 ml) was added. After stirring the mixture at room temperature for 1 hr, it was stirred at reflux for about 18 hr. After the benzene was removed under reduced pressure, the residue was poured into water and the crude product was collected and recrystallized from 2-propanol (charcoal). Other alkyl derivatives (**2b–f**) listed in Table I were prepared in a similar manner and recrystallized from methanol or 2-propanol.

The aryl derivatives (**2g-m**) were prepared in a similar manner. However, after the addition of PCl_5, it was necessary to heat the mixture to affect the formation of the imino chloride intermediate. Once a clear solution was obtained, the reaction mixture was cooled to room temperature and the procedure was continued as above.

Methyl *p*-[(α-Chloro-5-nitrofurfurylidene)amino]benzoate (**4**).—Compound **3n** (126 g, 0.435 mole) was placed in a flask together with PCl_5 (91 g, 0.435 mole) and toluene (1000 ml). The mixture was refluxed for 15 hr. The reaction mixture was cooled in an ice bath and filtered. The crude product was washed with water and recrystallized from 2-propanol (charcoal).

An infrared spectrum in $CHCl_3$ displayed absorption peaks at 1720 (C=O) and 1620 cm^{-1} (C=N).

Acknowledgments.—The author is indebted to F. Abbott, C. Benson, and S. Binder for assistance in the preparation of these compounds, to G. Gustin and M. Tefft for elemental analyses, and to H. E. Russell, R. A. Dobson, and R. Freedman for the microbiological testing data.

(2) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(3) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(4) F. F. Ebetino, W. F. Carey, and B. F. Stevenson, *J. Med. Chem.*, **6**, 663 (1963).

(5) Furacin®, 5-nitro-2-furaldehyde semicarbazone.

(6) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).

(7) H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **56**, 464 (1934).

(8) H. Wolff, *Org. Reactions*, **3**, 327 (1946).

N^3-(2-Aminoethyl)-5,5-diphenylhydantoin and Derivatives[1]

JOHN W. SHAFFER, RICHARD SHEASLEY,[2] AND MELDRUM B. WINSTEAD

Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania 17837

Received February 21, 1967

The imide hydrogen of the hydantoin ring has been found sufficiently acidic to undergo aminoethylation in an alcoholic solution. Thus, the reaction of 5,5-diphenylhydantoin with ethylenimine produced N^3-(2-aminoethyl)-5,5-diphenylhydantoin (I) in good yield. That the 2-aminoethyl group is located at N-3 and not at N-1 is suggested by the insolubility of I in aqueous alkali and from the observation that basic hydrolysis of I produced the amino acid, diphenylglycine. Infrared and nmr data also support structure I. Corral and Orazi have shown that the chemical shift of a hydantoin proton located at the N-1 position occurs at a higher field than that of a corresponding N-3 proton.[3] The N_1-H signal of I was coincident with that of the aromatic ring proton signal and was observable in the integration.

A number of examples of ethylenimine reacting with compounds containing an active hydrogen are described to form the corresponding 2-aminoethyl derivative, but apparently the only reported example with a hydantoin describes the preparation of the benzoate salt of N^3-(2-aminoethyl)-5,5-diphenylhydantoin. The free amine (I) was not isolated and characterized.[4]

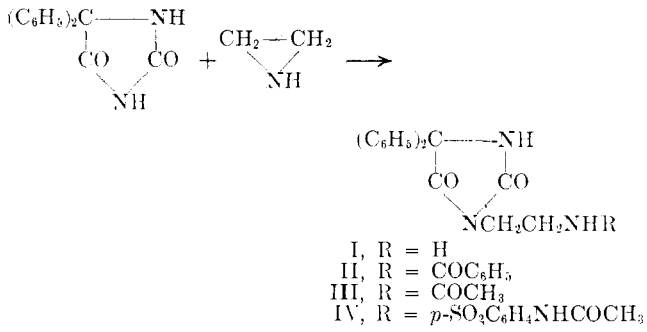
We have prepared the benzoate salt of I and obtained a melting point considerably different from that reported.[4] N^3-(2-Benzamidoethyl)-5,5-diphenylhydan-

(1) Taken in part from the M.S. Thesis of J. W. S., Bucknell University, 1966.

(2) Undergraduate research participant, Bucknell University, 1965–1966.

(3) R. A. Corral and O. O. Orazi, *Spectrochim. Acta*, **21**, 2119 (1965).

(4) H. Stamm and E. Stieglitz, German Patent 1,173,101 (1964); *Chem. Abstr.*, **61**, 12012 (1964).



I, R = H
II, R = COC_6H_5
III, R = $COCH_3$
IV, R = p-$SO_2C_6H_4NHCOCH_3$

toin (II) and N^3-(2-acetamidoethyl)-5,5-diphenylhydantoin (III) were prepared by the reaction of I with benzoyl chloride and acetic anhydride, respectively. The reaction of *p*-acetamidobenzenesulfonyl chloride with I produced N^1-[2-(2,5-dioxo-4,4-diphenyl-1-imidazolidinyl)ethyl]-*p*-acetamidobenzenesulfonamide (IV).

Pharmacology.—Chemotherapeutic and pharmacologic evaluations of compounds I and IV were conducted by Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc. The behavior of these compounds was studied in the following programs as previously described:[5] screening against *Escherichia coli in vitro*, testing in animals for antiinflammatory activity, and testing in mice for effects on the nervous system. In the *E. coli in vitro* assay both compounds were inactive at a level of 1 mg/ml. No significant effects on the nervous system were observed for I, but it did show a low order of antiinflammatory activity.

Experimental Section[6]

N^3-(2-Aminoethyl)-5,5-diphenylhydantoin (I).—A mixture of 530 ml of absolute ethanol and 100 g (0.4 mole) of 5,5-diphenylhydantoin was heated and held at reflux temperature while a solution of 25.7 g (0.6 mole) of ethylenimine in 90 ml of absolute ethanol was added dropwise over a period of 4 hr. Reflux was then continued for an additional 6 hr. Approximately 500 ml of ethanol was distilled. The concentrated reaction mixture was cooled to room temperature and drowned in 1500 ml of iced water maintained at pH 11 by the addition of 10% NaOH. The white precipitate of product was filtered, washed alkaline free, and dried; yield 88.5 g (75.7%). Repeated recrystallizations from ethanol or benzene gave purified product, mp 154.5–155.5°.

Acidification of the alkaline filtrate from the drowned reaction mixture allowed recovery of 17% of unreacted 5,5-diphenylhydantoin, mp 290–292°. Mixture melting point with pure 5,5-diphenylhydantoin (mp 294–294.5°) showed no depression. Potentiometric titration of I (0.5699 g suspended in 100 ml of water and titrated with 0.1003 *N* HCl) gave a pK_b of 6.53; $\lambda_{max}^{CH_3OH}$ 264, 257.7 mμ (ε 449, 717); no change in CH_3OH–KOH or CH_3OH–HCl; nmr,[7] 100 mg of I/0.5 ml of $CDCl_3$, pair of CH_2 triplets δ 2.78 and 3.49, ten aromatic protons and N_1-H *ca.* δ 7.25, NH_2 observable only on integration.

Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23; mol wt, 295.3. Found: C, 68.95; H, 5.88; N, 14.26; mol wt, 296.1.

The benzoate salt of I was prepared by adding a hot solution of 0.3 g (1 mmole) of I in 5 ml of C_6H_6 to a stirred solution of 0.122 g (1 mmole) of benzoic acid in 2 ml of hot C_6H_6. Upon cooling, a quantitative yield of the benzoate salt was obtained which, after recrystallization from C_6H_6, melted at 141–142°, lit.[9] mp 118–121°; infrared, 1550 and 1385 cm^{-1} (COO^-).

Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.84; H, 5.53; N, 9.68.

Diphenylglycine.—To a 1-l. stainless steel autoclave were added 8.9 g (0.03 mole) of I, 40 g (0.127 mole) of $Ba(OH)_2 \cdot 8H_2O$, and 300 ml of water. The mixture was heated at 110° for 24 hr, then steam distilled. The residue was diluted with water and acidified with H_2SO_4 to pH 1, and the precipitate of $BaSO_4$ was filtered. The pH of the filtrate was adjusted to 9 with NH_4OH. Upon concentrating the solution *in vacuo* to 75 ml, 2.4 g of diphenylglycine was obtained, mp 238° dec. Upon standing several days an additional 3.8 g of diphenylglycine was obtained, mp 233–235° dec, total yield 91%, mp 238° dec after recrystallization, lit. mp 238° dec,[8] 245–246° dec.[9] On several occasions repetition of this procedure produced diphenylglycine melting at 247–249° dec. Mixture melting point with diphenylglycine produced by a similar basic hydrolysis of 5,5-diphenylhydantoin showed no depression, and infrared spectra of the two products were identical. A sample of diphenylglycine produced from I was converted into benzilic acid upon treatment with $NaNO_2$ and HCl.[8]

N^3-(2-Benzamidoethyl)-5,5-diphenylhydantoin (II) was prepared by the benzoylation of I with benzoyl chloride in 10% NaOH.[10] After recrystallization from ethanol it showed mp 201–201.5°; *sec*-amide I, II, and III infrared bands were observed at 1675, 1550, and 1300 cm^{-1}, respectively; nmr,[7] 50 mg of II/0.5 ml of $(CD_3)_2SO$, $(CH_2)_2$ *ca.* δ 3.65, ten aromatic protons δ 7.38, C_6H_5CO protons δ 7.35–7.67 (3) and 7.77 (2-*ortho*), acyclic CO–NH *ca.* δ 8.51, N_1-H δ 9.53.

Anal. Calcd for $C_{24}H_{21}N_3O_3$: N, 10.52. Found: N, 10.48.

N^3-(2-Acetamidoethyl)-5,5-diphenylhydantoin (III) was prepared by the acetylation of I with Ac_2O and AcOH[11] and recrystallized from ethanol; yield 82%, mp 215–216°; $\lambda_{max}^{CH_3OH}$ 264 mμ (ε 206), 258 mμ (ε 322), no change in CH_3OH–KOH or CH_3OH–HCl; ir, N–H stretch 3280, 3200 cm^{-1}; C=O stretch 1760, 1700 cm^{-1}; *sec*-amide I, II, and III bands 1650, 1530, and 1290 cm^{-1}; CO–CH_3 bend 1360 cm^{-1}; nmr,[7] 50 mg of III/0.5 ml of CF_3COOH, CH_3 δ 2.15, $(CH_2)_2$ *ca.* δ 3.98, ten aromatic protons δ 7.41, N_1-H δ 7.92, acyclic CO–NH *ca.* δ 8.0–8.5.

Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.59; H, 5.81; N, 12.30.

N^1-[2-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)ethyl]-*p*-acetamidobenzenesulfonamide (IV).—A mixture of 150 ml of dioxane and 37.0 g (0.125 mole) of I was stirred at room temperature until solution was completed after which 20.7 g (0.30 equiv) of anhydrous K_2CO_3 was added. A solution of 29.2 g (0.125 mole) of *p*-acetamidobenzenesulfonyl chloride[12] in 150 ml of dioxane was added with agitation. This mixture was stirred at room temperature for 12 hr and then refluxed 3 hr. Dark brown discoloration appeared during reflux. Approximately 225 ml of dioxane was distilled. The concentrated reaction mixture was cooled to room temperature and drowned in 2 l. of iced water to yield 40.5 g (66%) of product, mp 217–224°. Several recrystallizations from either ethanol or aqueous 2-methoxyethanol resulted in a 50% yield of pure product: mp 232–233°; $\lambda_{max}^{CH_3OH}$ 259 mμ (ε 22,751), no change in CH_3OH–KOH or CH_3OH–HCl; ir, N–H stretch 3330, 3200 cm^{-1}; C=O stretch 1775, 1710 cm^{-1}; *sec*-amide bands at 1530, 1310 cm^{-1}; $-SO_2-$ stretch 1335, 1150 cm^{-1}; CO–CH_3 bend 1370 cm^{-1}; nmr,[7] 80 mg of IV/0.5 ml of $(CD_3)_2SO$, CH_3 δ 2.12, pair of CH_2 signals (broad) δ 3.06 and 3.58, ten aromatic protons δ 7.40, SO_2N–H *ca.* δ 7.72, four aromatic protons of benzenesulfonamide ring δ 7.79, N_1-H δ 9.67, acyclic CO–NH δ 10.37.

Anal. Calcd for $C_{25}H_{24}N_4O_5S$: C, 60.96; H, 4.91; N, 11.38; S, 6.51. Found: C, 61.57; H, 4.81; N, 11.59; S, 6.44.

(5) M. B. Winstead and C. R. Hamel, *J. Med. Chem.*, **8**, 120 (1965).

(6) Melting points were determined with a Mel-Temp apparatus and are corrected. Analyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. A Beckman Model G pH meter with a glass electrode and a saturated calomel electrode was used in the potentiometric titration. Standardization was against Beckman standard buffer solutions of pH 4.00, 7.00, and 10.00. Ultraviolet (Beckman Model DK-2) and infrared (Perkin-Elmer Model 137) spectrograms were conducted both in this laboratory and by the Sadtler Research Laboratory, Philadelphia, Pa. (Cary Model 15 and Beckman Model IR-4, respectively), and appear in the "Sadtler Standard Spectra Catalog," 1966. The nmr spectra were recorded on a Varian A-60A instrument.

(7) As δ, downfield from internal TMS.

(8) A. Dornow and S. Lupfert, *Chem. Ber.*, **89**, 2718 (1956).

(9) H. Biltz and K. Seydel, *Ann.*, **391**, 226 (1911).

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 114.

(11) A. I. Vogel, "Elementary Practical Organic Chemistry. Part 2," John Wiley and Sons, Inc., New York, N. Y., 1957, p 452.

(12) R. Adams, J. R. Johnson, and C. F. Wilcox, "Laboratory Experiments in Organic Chemistry," 5th ed, The Macmillan Co., New York, N. Y., 1963, p 326.