TABLE I

3-AMINOSPIROHYDANTOINS

Compd[a,b]	Yield,[c] %	Mp, °C[d]	Nmr,[e] N_1–H[f]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, %[g] C	Found, %[g] H	Found, %[g] N
I	67[h]	141.5–144.5	8.30	$C_7H_{11}N_3O_2$	49.70	6.55	24.84	49.68	6.75	25.13
II[i]	65	165.5–166	8.53	$C_8H_{13}N_3O_2$	52.45	7.15	22.94	52.38	7.28	23.31
III	65	162–163.5	8.40 (7.10[j])	$C_9H_{15}N_3O_2$	54.81	7.67	21.30	54.88	7.81	21.41
IV	70	174.5–176.5	8.33 (7.50[k])	$C_{10}H_{17}N_3O_2$	56.85	8.11	19.89	57.04	8.04	19.97
V[l]	55	161.5–162.5	8.55	$C_9H_{15}N_3O_2$	54.81	7.67	21.30	55.00	7.80	21.32
VI[m]	43	222.5–224	8.60	$C_9H_{15}N_3O_2$	54.81	7.67	21.30	54.88	7.82	21.18

[a] None of the 3-aminospirohydantoins reported exhibited a uv maximum in CH_3OH (Cary Model 15). [b] Infrared spectrograms were obtained in this laboratory (Perkin-Elmer Model 137B; Nujol mulls) and by Sadtler Research Laboratories, Inc., Philadelphia, Pa. (Beckman Model IR-4 and Perkin-Elmer Model 521; KBr wafer) and appear in "Sadtler Standard Spectra Catalog," Philadelphia, Pa., 1966. Compounds I–VI exhibited N–H stretching frequencies at 3320 ± 25, 3250 ± 5, and 3200 ± 5 cm^{-1}, C=O stretch at 1775 ± 10 and 1720 ± 10 cm^{-1}, NH_2 in-plane deformation at 1612 ± 13 cm^{-1}. [c] Compounds I–III were readily soluble in 3 N HCl and 5% NaOH; I was very soluble, and II and III were slightly soluble in H_2O. Compounds IV–VI were slowly soluble in these reagents. [d] Melting points were determined in a Mel-Temp apparatus and are corrected. [e] A 60-Mcps Varian Model A-60A instrument was used to record the nmr spectrograms in $(CD_3)_2SO$; values are reported as δ in parts per million downfield from $(CH_3)_4Si$ internal reference. Methyl and methylene signals were as expected; NH_2 signal occurred at 4.65 ± 0.03 ppm. [f] If, instead of the product reported, the N-1-aminospirohydantoin had been formed, a N_3–H signal would have been expected to occur at *ca.* δ 10.6–11.1 [in $(CD_3)_2SO$] or *ca.* 9.3 (in $CDCl_3$). An offset of 300 cps (on a 500-cps sweep width scale) gave no indication of the presence of this imide proton. The N_1–H proton signal is reported to occur at *ca.* δ 8–9 in $(CD_3)_2SO$ and *ca.* 6.6 (in $CDCl_3$) [R. A. Corral and O. O. Orazi, *Spectrochim. Acta*, **21,** 2119 (1965)]. [g] Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Inc., Knoxville, Tenn. [h] Recrystallized from benzene-ethanol. [i] The optimum reflux time for the preparation of II was found to range between 4–5 hr. This was based on varying the reaction time of 5,5-pentamethylenehydantoin (5 g) and 64% hydrazine hydrate (10 g) from 4–30 hr. The following per cent yield of II was obtained: 4 hr, 55; 4.5 hr, 65; 5 hr, 69; 6 hr, 51; 15 hr, 35; 24 hr, 13; 30 hr, 8. It has been reported that prolonged refluxing of a 5,5-disubstituted hydantoin with 64% hydrazine hydrate results in a decreased yield of the 3-aminohydantoin and the formation of carbohydrazide.[6] [j] δ value in $CDCl_3$. [k] δ value in CF_3COOH. [l] In one preparation of V the starting hydantoin was refluxed for 8 hr in triple its weight of 95% hydrazine; yield 66%, mp[d] 163–164.5° (recrystallized from ethanol), mixture melting point with V prepared in the usual manner gave no depression, and infrared spectrograms of the two products were identical. [m] Due to its decreased solubility, the starting hydantoin was refluxed in triple its weight of 64% hydrazine hydrate.

from the reaction of hydantoins with hydrazine hydrate.[6] We have adopted this latter and more direct method for preparing the following 3-aminospirohydantoins.

Experimental Section

The spirohydantoin (5 or 10 g) was refluxed in double its weight of 64% hydrazine hydrate for 4-5 hr; the reaction mixture was cooled, then poured over a small amount of crushed ice. Upon standing, the product crystallized slowly and was filtered, washed with a minimum of cold water, dried, and recrystallized from water or aqueous ethanol. Results are recorded in Table I.

The preparation of 3-amino-1,3-diazo-6-methylspiro[4.5]decane-2,4-dione was attempted four times: twice refluxing with 64% hydrazine hydrate, and twice refluxing with 95% hydrazine, 4 and 8 hr, respectively. In each case the reaction failed to yield any of the 3-aminospirohydantoin. The starting spirohydantoin was recovered, as shown by mixture melting point and ir spectra. Similarly, no reaction occurred with menthonespirohydantoin in a 4-, 8-, and 30-hr reaction time.

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(5) K. Schlögl, F. Wessely, and E. Wawersich, *Monatsh.*, **85**, 957 (1954).

(6) J. S. Davidson, *J. Chem. Soc.*, 4646 (1964).

Syntheses of Unsymmetric *o*-Phthalic Acid Diamides

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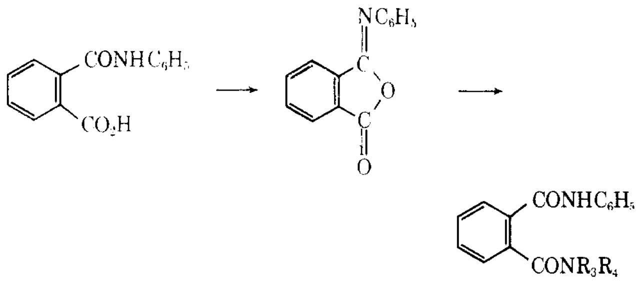
Although many symmetric *o*-phthalic acid diamides, *o*-$R_1R_2NCOC_6H_4CONR_1R_2$ (**1**) are recorded in the literature, very few unsymmetric diamides, *o*-$R_1R_2NCOC_6H_4CONR_3R_4$ (**2**) have been reported, and all of them have been prepared by specific rather than general syntheses. In view of the antileukemic action of several phthalanilides,[2] we now wish to report a general preparative method for compounds of type **2** with R_1 = H and R_2 = C_6H_5 based on the reaction of an amine with N-phenylphthalisoimide.



Experimental Section[3]

General Procedure.—A mixture of 31.5 g (0.15 mole) of freshly distilled trifluoroacetic anhydride and 30.4 g (0.3 mole) of triethylamine was added to a dry dioxane solution of 24.1 g (0.1 mole) of N-phenylphthalamic acid and after 5 min the mixture was poured into ice; N-phenylphthalisoimide precipitated at once. After washing (H_2O, 10% $NaHCO_3$ solution, H_2O), the product (20.5 g, 92% yield) was dried (vacuum, KOH). This is essentially the Roderick and Bhatia[4] procedure except for adding triethylamine as an acid acceptor. The dry product was dissolved in ether and a solution of the desired amine in ether was added in equimolecular quantities. The diamide was isolated and when dry crystallized once from a convenient solvent. Compounds prepared in this way are listed in Table I.

The unsymmetric *o*-phthalic acid diamides give phthalimides easily, under suitable conditions (*i.e.*, in solution in some solvents used for crystallization or on heating above their melting point). Infrared spectra are useful to distinguish both types of structures since the appearance of two bands at 1790–1720 and 1710–1670

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(1) (a) Taken in part from the thesis submitted by E. G. D. de T. in partial fulfillment of the requirements for the Doctor's degree, Buenos Aires University, 1966. (b) To whom correspondence should be addressed c/o Ducilo, S.A.I.C., Casilla Correo 1888, Correo Central, Buenos Aires, Argentina.

(2) L. Lee Bennett, *Progr. Exptl. Tumor Res.*, **7**, 259 (1965).

(3) All melting points are uncorrected and were determined on a Kofler melting point apparatus with a heating rate of 0.75°/sec.

(4) W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, **28**, 2018 (1963).

TABLE I
o-PHTHALIC ACID DIAMIDES

R_3	R_4	Over-all yield, %	Re-crystn solvent[a]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	H	85	M	257	$C_{14}H_{12}N_2O_2$	70.06	69.88	5.04	4.94	11.67	11.78
H	CH_3	54	E_{abs}	228 dec	$C_{15}H_{14}N_2O_2$	70.87	70.50	5.52	5.92	11.02	11.02
H	C_2H_5	85	E	208	$C_{16}H_{16}N_2O_2$	71.70	71.78	6.02	6.19	10.45	10.10
H	*n*-C_3H_7	77	E	212	$C_{17}H_{18}N_2O_2$	72.40	72.11	6.43	6.35	9.95	9.95
H	*n*-C_4H_9	81	E	208	$C_{18}H_{20}N_2O_2$	73.03	73.28	6.81	6.98	9.46	9.44
H	i-C_3H_7	67	E	233	$C_{17}H_{18}N_2O_2$	72.40	72.28	6.43	6.50	9.93	9.68
H	*t*-C_4H_9	74	E	245	$C_{18}H_{20}N_2O_2$	73.03	73.08	6.81	7.03	9.46	9.20
H	C_6H_{11}	68	E	225	$C_{20}H_{22}N_2O_2$	74.60	74.44	6.89	6.87	8.70	8.87
H	$CH_2C_6H_5$	82	E	203	$C_{21}H_{18}N_2O_2$	76.43	76.56	5.50	5.78	8.49	8.33
H	C_6H_5	67	N	259[b]	$C_{20}H_{16}N_2O_2$	76.01	76.21	5.10	5.11	8.87	9.00
H	*o*-$CH_3C_6H_4$	78	B	217	$C_{21}H_{18}N_2O_2$	76.43	76.03	5.50	5.32	8.49	8.61
H	*m*-$CH_3C_6H_4$	81	B	203	$C_{21}H_{18}N_2O_2$	76.43	76.69	5.50	5.70	8.49	8.57
H	*p*-$CH_3C_6H_4$	73	B	228[c]	$C_{21}H_{18}N_2O_2$	76.43	76.39	5.50	5.38	8.49	8.56
H	*o*-OHC_6H_4	60	E_{abs}	263	$C_{26}H_{16}N_2O_3$	72.35	72.33	4.86	4.89	8.44	8.67
H	*m*-OHC_6H_4	74	A_{60}	211	$C_{20}H_{16}N_2O_2$	72.35	72.59	4.86	4.74	8.44	8.53
H	*p*-OHC_6H_4	75	A_{50}	190	$C_{20}H_{16}N_2O_2$	72.35	72.44	4.86	5.13	8.44	8.53
CH_3	CH_3	39	A_{50}	182	$C_{16}H_{16}N_2O_2$	71.64	72.02	5.97	6.15	10.44	10.05
C_2H_5	C_2H_5	76	A_{50}	124	$C_{20}H_{18}N_2O_2$	73.03	72.95	6.81	6.82	9.46	9.20
$CH_2C_6H_5$	$CH_2C_6H_5$	39	E_{75}	161	$C_{28}H_{24}N_2O_2$	80.07	79.90	5.76	6.03	6.67	6.59
C_5H_{10}		64	A	168.5	$C_{19}H_{20}N_2O_2$	74.90	73.95	6.55	6.59	9.10	9.34

[a] M = MeOH dried following the method of R. Lund and J. Bjerrum [*Ber.*, **64,** 210 (1931)], E_{abs} = EtOH dried by the same method, E = EtOH, N = $C_6H_5NO_2$, B = C_6H_6 dried and distilled over Na, A_{60} = 60% aqueous Me_2CO, A_{50} = 50% aqueous Me_2CO, E_{75} = 75% aqueous EtOH, A = dry Me_2CO. [b] R. D. Reynolds and G. L. Anderson [*J. Org. Chem.*, **28,** 3223 (1963)] report mp 230–231°. [c] J. B. Tingle and H. F. Rolker [*Am. Chem. J.*, **30,** 1889 (1908)] report mp 168°. Some of our samples melted sharply at 219° but in most cases the recorded melting point was registered. Nevertheless all samples gave good analytical data.

cm⁻¹, instead of bands at 3300, 1680–1630, and 1570–1515 cm⁻¹, is a clear indication that the diamide compound has been transformed into one of the two possible imides, usually N-phenylphthalimide. Ultraviolet spectroscopy is less useful since no correlation between absorption bands at 224–230 and 250–260 mμ and structure is apparent.

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Possible Antifertility Compounds. IV.[1] Diphenylnaphtho[1,2-*b*]- and Diphenylnaphtho[2,1-*b*]furans

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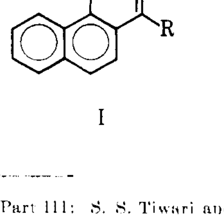
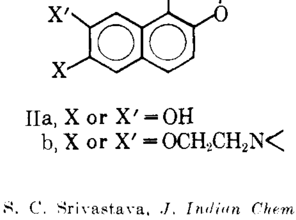
In view of the potent estrogenic activity shown by a large series of phenanthrene compounds, the presence of this nucleus in the steroidal sex hormones and the close resemblance of naphthofuran to phenanthrene, the naphthofurans of type I and II were synthesized (see Tables I and II on the following page).



I



IIa, X or X' = OH
b, X or X' = $OCH_2CH_2N<$

Experimental Section[2]

2,3-Bis(*p*-methoxyphenyl)naphthol[1,2-*b*]furan (1).—α-Naphthol (0.01 mole), *p,p'*-dimethoxybenzoin (0.01 mole), freshly distilled peroxide-free dioxane (30 ml), and concentrated HCl (10 ml) were refluxed for 24 hr. The solution was poured into water, the oily layer was taken up in ether, and the ethereal layer which exhibited a blue-violet fluorescence was washed with 1% NaOH until the alkaline layer was colorless and finally with water. Sufficient petroleum ether (bp 60–80°) was added to the dried clear ethereal solution, and the yellowish solid which separated out was filtered. Two recrystallizations from hot petroleum ether yielded the pure compound, mp 120–121°, yield 29.6%.

Anal. Calcd for $C_{26}H_{20}O_3$: C, 82.12; H, 5.26. Found: C, 81.02; H, 5.18.

7-Hydroxy-1,2-bis(*p*-methoxyphenyl)naphtho[2,1-*b*]furan (5) was prepared from 2,6-dihydroxynaphthalene and *p,p'*-dimethoxybenzoin as described above. In this case the ethereal extract was treated with 8% NaOH, and the alkaline extract was acidified. The separated product on isolation with ether and subsequent treatment with petroleum ether gave a dark oily material. The granular crystals which separated out from the oil after 2–3 days, on recrystallization from benzene–petroleum ether, gave pure **5**, mp 167°, yield 67%.

Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.80; H, 5.04. Found: C, 78.70; H, 5.57.

Dialkylaminoethyl Ethers (IIb) of Substituted Diphenylnaphtho[2,1-*b*]furans (IIa).—A mixture of the appropriate dialkylaminoethyl chloride hydrochloride (0.001 mole), hydroxynaphthofuran (0.001 mole), freshly dried K_2CO_3 (1 g), and acetone (25 ml) was refluxed for 24 hr. After removal of acetone, the mixture was treated with warm water and cooled, and the solid which separated out was filtered and recrystallized from aqueous acetone.

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(1) Part III: S. S. Tiwari and S. C. Srivastava, *J. Indian Chem. Soc.*, **44,** 121 (1967).

(2) Melting points were taken in capillary tubes and are uncorrected.