ethanol) gave a peak of 280 mμ typical for indoles and it did not change after acidification. The nmr spectrum contained five peaks and was interpreted after integration as representative of eight aromatic hydrogens (τ 1.0–3.0), two pyrrole N–*H*, two N–N*H*$_2$, four C*H*$_2$, and two indole-2 hydrogens.

2-Hydrazino-8-quinolinol and Derivatives[1]

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Hydrazones of carbonyl compounds and 2-hydrazino- and 2-(1-methylhydrazino)-8-quinolinols were prepared for antitumor tests. Those hydrazones from formyl-8-quinolinols might be of further interest as bifunctional chelating agents.[2,3]

2-(1-Methylhydrazino)-8-quinolinol.—2-Chloro-8-quinolinol (1 g) and 0.39 g of methylhydrazine in 1-propanol as solvent were refluxed 24 hr. Evaporation of solvent, addition of 50 ml of water, and neutralization with K_2CO_3 precipitated the product, mp 106° after recrystallization from ligroin (80% yield). The ultraviolet spectra showed λ_{max} [mμ (log ε)]: EtOH, 250 s (4.27), 269 (4.52), 351 (3.56); 0.1 *N* HCl, 244 (4.23), 269 (4.48), 312 (3.48), 351 (3.71); 0.1 *N* NaOH, 279 (4.56), 318 s (3.18), 360 s (3.69).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.80; N, 22.19. Found: C, 63.49; H, 5.70; N, 22.12.

Preparation of Hydrazones.—Equimolar amounts of the hydrazine and aldehyde or ketone were refluxed in ethanol for 0.5–5 hr to precipitate the hydrazones, generally yellow solids. Aldehydes reacted more quickly than ketones. Filtration of the products and recrystallization, generally from benzene, gave 80–95% yields of the compounds listed in Table I. Absorption spectra of some of these hydrazones were determined as follows for the carbonyl compound: λ_{max}^{EtOH} [mμ (log ε)]: 7-formyl-8-quinolinol, 249 (4.33), 290 s (4.27), 306 (4.40), 381 (4.37), 436 (3.69); 5-acetyl-8-quinolinol, 243 (4.51), 289 (4.46), 359 (4.12); 2-formylpyridine, 238 (4.19), 264 (4.17), 274 s (4.12), 318 s (4.34), 352 (4.45), 439 s (3.30).

TABLE I

HYDRAZONES FROM 2-HYDRAZINO-8-QUINOLINOL AND CARBONYL COMPOUNDS

Carbonyl compd	Mp, °C[a]	Formula	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found	% nitrogen Calcd	% nitrogen Found
5-Acetyl-8-quinolinol	218	$C_{22}H_{16}N_4O_2$	69.75	69.60	4.68	4.75	16.26	16.10
5-Acetyl-2-methyl-8-quinolinol	207	$C_{21}H_{18}N_4O_2$	70.38	70.45	5.06	5.20	15.63	15.83
4-Formyl-8-quinolinol	292	$C_{19}H_{14}N_4O_2$	69.93	69.24	4.32	4.40	15.94	16.15
5-Formyl-2-methyl-8-quinolinol	233	$C_{20}H_{16}N_4O_2$	69.75	69.57	4.68	4.84	16.26	16.11
7-Formyl-8-quinolinol	289	$C_{19}H_{14}N_4O_2$	69.93	70.08	4.32	4.52	15.94	16.08
7-Formyl-2-methyl-8-quinolinol	277	$C_{20}H_{16}N_4O_2$	69.75	69.53	4.68	4.83	16.26	16.14
7-Formyl-5-methyl-8-quinolinol	268	$C_{20}H_{16}N_4O_2$	69.75	69.92	4.68	4.91	16.26	16.09
Salicylaldehyde	239	$C_{16}H_{13}N_3O_2$	68.81	68.43	4.69	4.75	15.04	14.77
p-Dimethylaminobenzaldehyde	239	$C_{18}H_{18}N_4O$	70.58	70.30	5.92	6.14	18.28	17.98
Pentafluorobenzaldehyde	254	$C_{16}H_{18}F_5N_3O$	54.40	54.23	2.28	2.17	11.89	11.76
Phthalaldehydic acid	225	$C_{17}H_{13}N_3O_3$	66.45	66.64	4.26	4.46	13.67	13.47
2-Formylpyridine	214	$C_{15}H_{12}N_4O$	68.17	68.19	4.57	4.66	21.19	21.32
3-Formylpyridinium methiodide	231	$C_{16}H_{15}IN_4O$					13.79	14.60
4-Antipyrinecarboxaldehyde	248	$C_{21}H_{19}N_5O$	67.55	67.33	5.13	5.17	18.74	18.53
Salicylaldehyde[b]	206	$C_{17}H_{15}N_3O_2$	69.62	69.90	5.15	5.30	14.32	13.96

[a] Upper end of a 1–2° range. [b] Hydrazone of 2-(1-methylhydrazino)-8-quinolinol.

Experimental Section[4]

2,8-Quinolinediol[5] was tosylated and chlorinated with PCl_5–$POCl_3$ in agreement with the literature,[6] although final hydrolysis with alkali to 2-chloro-8-quinolinol gave a product of substantially higher melting point (83–84°) than reported.

2-Hydrazino-8-quinolinol.—2-Chloro-8-quinolinol (5 g) was refluxed in 20 ml of 40% hydrazine for 4 hr. Solvent was removed under vacuum and 15 ml of water was added to precipitate the product. Recrystallization from 95% ethanol yielded a tan solid, mp 177–178° (81% yield).

Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.17; N, 23.97. Found: C, 61.87; H, 5.09; N, 23.84.

Although reasonably stable as the solid, the hydrazine in solution decomposed in a few hours. The ultraviolet spectra in various solvents showed λ_{max} [mμ (log ε)]: EtOH, 245 (4.27), 263 (4.46), 280 s (4.04); 0.1 *N* HCl, 240 (4.12), 264 (4.40), 304 (3.87), 340 s (3.52); 0.1 *N* NaOH, 252 (4.36), 274 s (4.02), 330 (3.46), 356 s (3.41). The infrared spectra (KBr) showed bands at 3345, 3330, 1520, 1240, 820, and 738 cm^{-1} (strongest bands).

(1) This work was supported by a grant from the U. S. Public Health Service (CA 07403).

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3-Aminospirohydantoins

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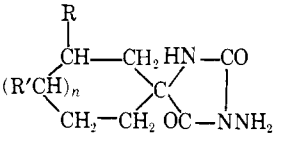
Some 3-amino-5,5-disubstituted hydantoins have a pronounced diuretic effect.[2] Such hydantoins have been prepared from the dihydrazide of α-substituted glycine-N-carboxylic acids,[2–5] and



I, $n = 0$; R = H
II, $n = 1$; R, R′ = H
III, $n = 2$; R, R′ = H
IV, $n = 3$; R, R′ = H
V, $n = 1$; R = CH_3; R′ = H
VI, $n = 1$; R = H; R′ = CH_3

(1) National Science Foundation Undergraduate Research Participant, summer 1965.

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TABLE I
3-AMINOSPIROHYDANTOINS

Compd[a,b]	Yield,[c] %	Mp, °C[d]	Nmr,[e] N_3-H[f]	Formula	Calcd, %[g] C	H	N	Found, %[g] C	H	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[n]	222.5–224	8.60	$C_{11}H_{19}N_3O_2$	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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Syntheses of Unsymmetric *o*-Phthalic Acid Diamides

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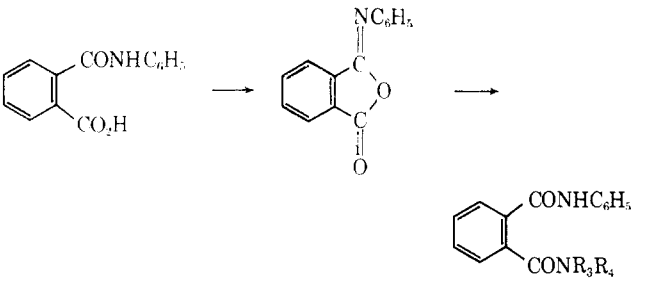
Although many symmetric *o*-phthalic acid diamides, *o*-$R_1R_2NCOC_6H_4CONR_1R_2$ (**1**) are recorded in the literature, very few unsymmetric diamides, *o*-$R_1R_2NCOC_6H_4CONR_3R_4$ (**2**) have been reported, and all of them have been prepared by specific rather than general syntheses. In view of 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

(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.

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