Experimental Section

N-Substituted 2,2′-Diphenamic Acids.—A $CHCl_3$ solution of the amine was added to an equivalent amount of diphenic anhydride[8] dissolved in $CHCl_3$ and the mixture was stirred and refluxed gently for 2 hr. The solvent was evaporated on a steam bath and the residue recrystallized. When necessary the crude residue was purified by dissolving in dil NaOH, filtering, and precipitating with dil HCl. For **6**, **9**, **10**, **11**, and **14**, PhMe was used as 50–90% of the reaction solvent to increase amine solubility and to raise the temperature at reflux.

N-Substituted 2,2′-Diphenimides.—A mixture of 0.01 mol of the N-substituted diphenamic acid, 10 ml of Ac_2O, and 1 g of fused NaOAc was heated with constant mixing on a steam bath for 15–20 min. The mixture was then triturated with hot H_2O to remove excess Ac_2O. The product was filtered, washed with H_2O, dried, and recrystd.

For **25**, the reaction was carried out on a low temperature hot plate at 120–130° for 35–45 min.

Acknowledgment.—We thank Alice C. Lee for determining the ir spectra.

(8) Diphenic anhydride was prepared by refluxing diphenic acid with 8 equiv of Ac_2O for 0.5 hr and recrystallizing from Me_2CO to give 95%, mp 225–226° (lit. mp 217°, E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley & Sons, New York, N. Y., 1941, p. 170).

Diphenimides. 2.[1a,b] Some Ring Substituted *N*-2-Fluorenyl-2′,2″-diphenamic Acids and Diphenimides. Derivatives of Fluorene. XXXII.[1c]

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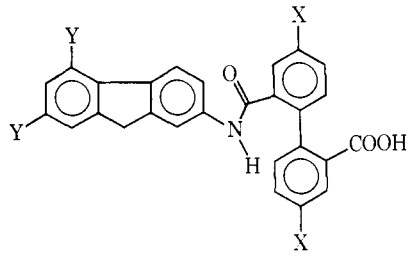
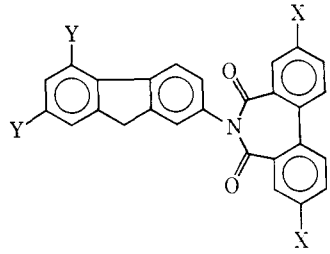
In view of the preliminary report of antimalarial activity in rodents exhibited by *N*-2-fluorenyl-2′,2″-diphenimide (II, X = Y = H),[1a] attempts were made to obtain increased activity by substitution of Cl on the rings.[2]

Preparation of the diphenamic acids (I) was carried out by condensation of the aminofluorenes with the corresponding diphenic anhydrides in CH_2Cl_2. Ring closure of I in Ac_2O (with fused NaOAc) gave II in excellent yields. The diphenic anhydrides were synthesized from the appropriately substituted 2-bromobenzoic acid methyl esters through Ullmann coupling, followed by hydrolysis of the acid ester and dehydration of the diphenic acids in Ac_2O. The ir absorptions are essentially as discussed in paper 1 of this series.[1a]

The antimalarial screening of these compounds was carried out by subcutaneous administration in young ICR/Ha Swiss mice infected with *Plasmodium berghei*. All of these compounds were inactive. The Cancer Chemotherapy National Service Center is also screening these compounds for antitumor effects in BDF_1 mice



I



II

a, X = Cl; Y = H
b, X = Cl; Y = Cl
c, X = NO_2; Y = H

with L1210 leukemia, with negative results from the testing thus far.[3]

Experimental Section[4]

Methyl 2-Bromo-5-chlorobenzoate.—Methyl 2-bromo-5-nitrobenzoate[5] (150 g) was reduced with Zn dust (300 g) in 80% EtOH (1.5 l.) containing NH_4Cl (45 g) giving **methyl 5-amino-2-bromobenzoate** (123 g) which was used directly in the next step.[6]

The amine (97 g) was diazotized at −10° in 8 *N* HCl (0.6 l) with $NaNO_2$ (35 g) and the diazonium salt was reacted with freshly prepared Cu_2Cl_2 (160 g) at 60°. The reaction mixture was then cooled in ice with rapid stirring until crystallization of the chloro compound took place. The product was collected on a prerefrigerated filter and taken up in ether which was washed with dil HCl, dil $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated. The residue was recrystallized from MeOH–H_2O giving 87 g (83%), mp 37–38° (MeOH). *Anal.* ($C_8H_6BrClO_2$) C, H, Br, Cl.

4,4′-Dichloro-2,2′-diphenic Acid.—The above ester (77 g) and Cu powder (450 A; Metal Distintegrating Co.) (30 g) were rapidly stirred at 200° while a second portion of Cu (30 g) was added in small amounts over a period of 20 min. The temperature was then kept at 205° for 0.5 hr and the cooled mixture was extracted with Me_2CO. The crystalline solid from the Me_2CO extract was recrystallized from MeOH giving 31.1 g (61%) of the dimethyl ester, mp 103–106°, which was hydrolyzed in a refluxing mixture of AcOH (420 ml), H_2SO_4 (240 ml), and H_2O (120 ml) (30 hr) to the diacid, 22.5 g (80%), mp 255–261° (H_2O) (lit.[7] mp 264–265°). *Anal.* ($C_{14}H_8Cl_2O_4$) Cl.

4,4′-Dichloro-2,2′diphenic Anhydride.—The diphenic acid (3.1 g) in Ac_2O (20 ml) was boiled with stirring for 45 min, cooled, and the product filtered off giving 2.6 g (89%), mp 325–326° (C_6H_6) (lit.[7] mp 308–310°). *Anal.* ($C_{14}H_6Cl_2O_3$) C, H, Cl.

(1) (a) Part 1: C. Cole, H.-L. Pan, M. J. Namkung, and T. L. Fletcher, *J. Med. Chem.*, **13**, (565) (1970); (b) this work was supported in part by Grant CA-01744, and by Career Development Award 5KO-3-CA-14991, from the National Cancer Institute; (c) Part XXXI: M. J. Namkung and T. L. Fletcher, *Chem. Commun.*, 1052 (1969).

(2) This type of modification was suggested by Dr. T. R. Sweeney, Walter Reed Army Institute of Research, to whom we are grateful for a supply of diphenic acid and the antimalarial screening data.

(3) The data were kindly supplied by Dr. Harry B. Wood, Jr.

(4) Melting points below 250° were taken on a Fisher–Johns block and are corrected to standards. The melting points above 250° were determined with a Thomas–Hoover apparatus in open capillaries and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results, obtained for those elements were within ±0.4% of the theoretical values. The ir spectra (KBr) were made on a Beckman IR-5. The elemental analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West Germany.

(5) A. E. Holleman and B. R. deBruyn, *Rec. Trav. Chim. Pays-Bas*, **20**, 206 (1901).

(6) The amine is *not distilled* because of the possibility of violent decomposition; for example, see (a) H.-L. Pan and T. L. Fletcher, *J. Med. Chem.*, **8**, 491 (1965), footnote 15, and (b) M. J. Namkung, T. L. Fletcher, and W. H. Wetzel, *ibid.*, 551, footnote 15.

(7) E. H. Huntress, I. S. Cliff, and E. R. Atkinson, *J. Amer. Chem. Soc.*, **55**, 4262 (1933).

4,4'-Dinitro-2,2'-diphenic Anhydride.—As described previously, methyl 2-bromo-5-nitrobenzoate (130 g) and Cu powder (40 g) were allowed to react at 200–205° for 40 min giving 46 g (51.2%) of 4,4'-dinitro-2,2'-diphenic acid dimethyl ester which was refluxed for 26 hr in a mixture of AcOH (670 ml), H_2SO_4 (400 ml), and H_2O (200 ml) giving 35.8 g (85%) of the dinitrodiphenic acid, mp 255–257° dec (lit.[8] mp 257–258°). The diphenic acid (18.4 g) was then heated in an open flask with Ac_2O (100 ml) until the temperature of the mixture reached 160°. It was cooled and the product was separated by filtration, giving 14.5 g (83.5%), mp 231–233° (C_6H_6). *Anal.* ($C_{14}H_8N_2O_7$) C, H, N.

5,7-Dichlorofluoren-2-amine.—A mixture of 2,4-dichloro-7-nitro-9-oxofluorene[6a] (7.3 g), 85% $N_2H_4 \cdot H_2O$ (40 ml), and 2,2'-oxydiethanol (400 ml) was refluxed gently for 24 hr. The solution was evaporated until its temperature reached 210°. Upon H_2O dilution there was obtained 5.7 g (91%), mp 124–125° (EtOH). *Anal.* ($C_{13}H_9Cl_2N$) C, H, N.

N-2-Fluorenyl-4',4''-dichloro-2',2''-diphenamic Acid (Ia).—Fluoren-2-amine (1.1 g), 4,4'-dichloro-2,2'-diphenic anhydride (1.8 g), and CH_2Cl_2 (175 ml) were refluxed for 24 hr and the mixture was stripped of solvent giving 2.9 g (100%), mp 132–135° (glassy melt). *Anal.* ($C_{27}H_{17}Cl_2NO_3$) C, H, Cl, N.

N-2-(5,7-Dichlorofluorenyl)-4',4''-dichloro-2',2''-diphenamic Acid (Ib).—Similarly, 5,7-dichlorofluoren-2-amine (2.5 g) and 4,4'-dichloro-2,2'-diphenic anhydride (2.9 g) gave 5.3 g (98%), mp 256–261° dec (C_6H_6–CH_2Cl_2–Me_2CO). *Anal.* ($C_{27}H_{15}Cl_4NO_3$) C, H, Cl, N.

N-2-Fluorenyl-4',4''-dinitro-2',2''-diphenamic Acid (Ic).—Fluoren-2-amine (1.8 g) and 4,4'-dinitro-2,2'-diphenic anhydride (3.1 g) were treated in like manner to give 4.8 g (98%), mp 259–260° (Me_2CO). *Anal.* ($C_{27}H_{17}N_3O_7$) C, H, N.

N-2-Fluorenyl-4',4''-dichloro-2',2''-diphenimide (IIa).—Ia (1 g), freshly fused NaOAc (0.5 g), and Ac_2O (10 ml) were mixed and heated with vigorous shaking on a steam bath for 15 min, cooled, and the Ac_2O was destroyed with H_2O giving 0.9 g (94%), mp 311–312° (Me_2CO). *Anal.* ($C_{27}H_{15}Cl_2NO_2$) C, H, Cl, N.

N-2-(5,7-Dichlorofluorenyl)-4',4''-dichloro-2',2''-diphenimide (IIb).—Likewise, Ib (1.5 g) and fused NaOAc (0.5 g) in Ac_2O (15 ml) gave 1.4 g (100%), mp 298–299° (AcOH). *Anal.* ($C_{27}H_{13}Cl_4NO_2$) C, H, Cl, N.

N-2-Fluorenyl-4',4''-dinitro-2',2''-diphenimide (IIc).—Heating Ic (2.5 g) with NaOAc (0.5 g) in Ac_2O (15 ml) gave 2.4 g (100%), mp 302–303° (PhMe). *Anal.* ($C_{27}H_{15}N_3O_6$) C, H, N.

Acknowledgment.—We thank Miss Alice C. Lee for determining the ir spectra.

(8) R. Kolen and O. Albrecht, *Justus Liebigs Ann. Chem.*, **455**, 272 (1927).

Synthesis of Potential Anticancer Agents. 5,12-Naphthacenequinones

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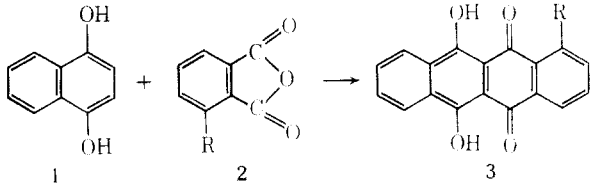
This report describes the syntheses and biological activities of several naphthacenequinones, an area of increasing interest.[1]

In a Friedel-Crafts type of reaction, 1,4-dihydroxynaphthalene (**1**) was allowed to react with several 3-substituted phthalic anhydrides (**2**) according to the B_2O_3 method of Weizmann and coworkers,[2] or in the presence of anhydrous $AlCl_3$, to give the compounds **3** listed in Table I.



a, R = NO_2
b, R = OCOCH$_3$
c, R = OH
d, R = $NHCOCH_3$
e, R = $(CH_3)_2N$
f, R = NH_2

TABLE I
INFRARED AND ULTRAVIOLET SPECTRAL DATA

No.	Derivative of 5,12-naphthacenequinone	$\nu_{C=O}$, cm^{-1}	λ_{max}, mμ (ε)
	5,12-Naphthacenequinone[a]	1680	265, 275, 293, 373, 395, 415, 440, 468 (7,400; 2,400; 1,200; 2,400; 4,500; 7,600; 9,900)
3	6,11-(OH)$_2$	1629, 1585	263, 452, 483, 515 (24,800; 5,200; 7,200; 6,800)
3c	1,6,11-(OH)$_3$	1600	265, 460, 490, 525 (54,000; 14,4000; 26,000; 26,800)
3a	1-NO_2-6,11-(OH)$_2$	1631, 1580	264, 487, 517 (47,900; 12,000; 8,700)
3f	1-NH_2-6,11-(OH)$_2$	1595	254, 374, 393, 507, 539 (50,800; 1,800; 1,900; 20,350; 21,600)
3d	1-AcNH-6,11-(OH)$_2$	1580 broad	248, 271, 468, 497, 534 (39,800; 54,200; 15,050; 26,300; 28,200)
3e	1-Me_2N-6,11-(OH)$_2$	1582, 1567	266, 520–530 sh, 550 (59,200; 16,000; 18,400)

[a] The authors are grateful to Dr. H. Vollmann, Bayer, A. G., Leverkusen, West Germany for an authentic sample of 5,12-naphthacenequinone, *Justus Liebigs Ann. Chem.*, **669**, 43 (1963).

For preparation of the larger amounts of **1** required, we found that the Fieser[3] method of reductive acetylation of naphthoquinone followed by hydrolysis was rather tedious. We discovered that 1,4-dihydroxynaphthalene (**1**) could be prepared easily and in good yield by hydrogenation of naphthoquinone at low pressure.

When **2** (**a**,**c**,**d**) was fused with **1** at 190° in the presence of B_2O_3, the corresponding **3** was obtained. However, when **2b** was used under similar conditions, *in situ* deacetylation took place, and the resulting 1,6,11-trihydroxynaphthacenequinone (**3c**) was obtained, identical with the product obtained from **1** and **2c**. Upon hydrolyzing 1-acetamido-6,11-dihydroxynaphthacenequinone (**3d**) in HCl, 1-amino-6,11-dihydroxynaphthacenequinone (**3f**) was obtained. Compound **3e** was prepared by the $AlCl_3$ fusion procedure of **1** with 3-dimethylaminophthalic anhydride (**2e**), which was

(1) (a) F. Arcamone, C. Franceschi, P. Orezzi, and S. Penco, *Tetrahedron Lett.*, 3349 (1968); (b) J. R. D. McCormick, J. Reichenthal, S. Johnson, and N. O. Sjolander, *J. Amer. Chem. Soc.*, **85**, 1694 (1963); (c) H. Brockmann and J. Niemeyer, *Chem. Ber.*, **101**, 2409 (1968); (d) H. Brockmann, R. Kunker, and H. Brockmann, Jr., *Justus Liebigs Ann. Chem.*, **696**, 145 (1966), and other references cited therein.

(2) C. Weizmann, L. Haskelberg, and T. Bertin, *J. Chem. Soc.*, 398 (1939).

(3) L. Fieser, *J. Amer. Chem. Soc.*, **70**, 3165 (1948).