TABLE I
ESTROGENIC AND HYPOCHOLESTEROLEMIC ACTIVITY OF 5

Daily dose		Body wt (g)			Uterine		Plasma cholesterol (mg/dl) mean ±
mg/kg	No. of rats	Onset	Final	Δ	wt (mg)	Vaginal smears	standard error
0	6	210	248	38	74.7	6 of 6 diestrus	71.2 ± 5.4
1	6	211	246	35	82.7	6 of 6 diestrus	73.5 ± 4.9
10	6	215	229	14	164.6	6 of 6 proestrous	51.2 ± 3.8 ($p < 0.05$)

Experimental Section[9]

16-Methylene-17α,19-dihydroxy-4-pregnene-3,20-dione Diacetate (2).—A solution of 16-methylene-17α,19-dihydroxy-4-pregnene-3,20-dione 17-acetate (**1**)[10] (1.628 g) in C_5H_5N (8 ml) was allowed to stand with Ac_2O (1.2 ml) for 18 hr. The reaction mixture was added to H_2O, the precipitate collected, dried, and used without any further purification for the preparation of **3**. A 100-mg sample was crystallized from Et_2O–C_6H_{14} affording 56 mg of **2**: mp 216–218°; $[\alpha]D$ −18°; λ_{max} 239 mμ (ε 16,800). *Anal.* ($C_{26}H_{34}O_6$) C, H.

16-Methylene-17α,19-dihydroxy-1,4-pregnadiene-3,20-dione Diacetate (3).—A solution of **2** (2.11 g) in dioxane (70 ml) was heated at reflux with DDQ (2.45 g) for 17 hr. The solids were removed by filtration and the filtrate passed through a neutral alumina column (Woelm, act. I, 37 × 2.5 cm). Elution with $CHCl_3$ gave 1.488 g (70.7%) of **3**, crystallized from CH_2Cl_2–C_6H_{14}: mp 183–185°; $[\alpha]D$ −110°; λ_{max} 241.5 mμ (ε 15,200); nmr, δ 4.47, 4.62 (C_{19}-CH_2O, d, J = 10.5 Hz), 5.49 and 5.62 (C_{16}-=CH_2) ppm. *Anal.* ($C_{26}H_{32}O_6$) C, H.

3,17α-Dihydroxy-16-methylene-19-nor-1,3,5(10)-pregnatrien-20-one 17-Acetate (4). (A) By SeO_2 Dehydrogenation of 1.—A solution of **1** (900 mg) and SeO_2 (414 mg) in t-$C_5H_{11}OH$ (45 ml) was heated at reflux for 4 hr. The solids were removed by filtration. The filtrate was diluted with EtOAc, washed (H_2O), dried, and evaporated to a residue which was chromatographed over silica gel (Baker, 35 × 2.5 cm). Elution with C_6H_{14}–Et_2O (9:1) gave 100 mg of **4**, crystallized from Et_2O–C_6H_{14}: mp 219–223° dec; $[\alpha]D$ −64°; λ_{max} 281 mμ (ε 2120), 287 (1900, inflexion); nmr, δ 5.09 (C_3-O**H**), 6.59 (C_4-H), 6.63 (C_2-H), and 7.17 (C_1-H) ppm. *Anal.* ($C_{23}H_{28}O_4$) C, H.

(B) By Base Treatment of 3.—A solution of **3** (1.32 g) in EtOH (24 ml), CH_2Cl_2 (24 ml), and H_2O (2.4 ml) was stirred with 1 N ethanolic KOH (12 ml) for 20 min. After neutralization with AcOH and dilution with H_2O, the steroid was extracted with CH_2Cl_2. Evaporation of the solvent gave 1.05 g (95%) of crystalline **4**, which after recrystallization from Et_2O–C_6H_{14} was identical with the product obtained by the SeO_2 dehydrogenation of **1**, as determined by tlc, ir, and nmr.

3-Hydroxy-1,3,5(10)-estratrieno[17,16-*c*]-2′-methylfuran (5) and 16-Acetoxymethyl-19-nor-1,3,5(10),16-pregnatetraen-3-ol-20-one (7).—A fine suspension of **4** (2.42 g) in mineral oil (50 ml) was passed through a heated column of glass beads[5] at 280°. The resulting pyrolysate was extracted with MeOH. After evaporation of the solvent, the residue was chromatographed over Florisil (33 × 3 cm). Elution with C_6H_{14}–Et_2O (19:1) yielded a small amount (less than 20 mg) of crystalline **6**: mp 152–153°; $[\alpha]D$ +54°; λ_{max} 267 mμ (ε 1350), 274 (1010, inflexion); ν_{max} 1765, 1213 cm^{-1}. *Anal.* ($C_{23}H_{26}O_3$) C, H.

Further elution with the same solvent mixture gave 441.5 mg (22%) of **5**, crystallized from Et_2O–C_6H_{14}: mp 212–214°; $[\alpha]D$ +59°; λ_{max} 281 mμ (ε 2070), 286 (1840, inflexion); ν_{max} 3545, 1621, 1587, 1087 cm^{-1}; nmr, δ 2.20 (C_{20}-CH_3), 6.59 (C_4-H), 6.62 (C_2-H), 6.93 (furanyl-H), 7.18 (C_1-H) ppm. *Anal.* ($C_{21}H_{24}O_2$) C, H.

Elution with CH_2Cl_2–MeOH (9:1) gave an oil which was rechromatographed over deactivated silica gel (Baker, 15% H_2O, 30 × 2.7 cm). Elution with C_6H_6 gave 481 mg (20%) of **7** as a homogeneous oil: λ_{max} 249 mμ (ε 6300), 287 (1750, inflexion); nmr, δ 2.09 (C_{16}-CH_2OCOCH_3), 2.30 (C_{20}-CH_3), 4.93 (s, C_{16}-CH_2O) ppm.

3-Hydroxy-16-hydroxymethyl-19-nor-1,3,5(10),16-pregnatetraen-3-one (8).—A solution of **7** (450 mg) in MeOH (10 ml) and 2 N NaOH–H_2O (1.5 ml) was stirred under N_2 for 45 min. After neutralization with AcOH, the reaction mixture was added to H_2O. The precipitate was collected, dried, and crystallized several times from Me_2CO–C_6H_{14} affording 56 mg of **8** as a Me_2CO solvate: mp 128° (transition), 203–206° dec; $[\alpha]D$ +29°; λ_{max} 252 mμ (ε 7300), 287 (2120, inflexion); nmr (DMSO-d_6), δ 2.29 (C_{20}-CH_3), 2.17 (acetone), 4.27 (C_{16}-CH_2OH) ppm. *Anal.* ($C_{21}H_{26}O_3 \cdot 0.5C_3H_6O$) C, H. The combined mother liquor contained large amounts of **5** as indicated by tlc.

Acknowledgments.—We are indebted to Dr. H. L. Herzog and Mr. E. L. Shapiro for helpful discussions, and to Mrs. H. M. Marigliano and Mr. M. D. Yudis for interpretation of the nmr spectra.

(9) Melting points were determined on a Kofler hot stage microscope and are uncorrected. Rotations are in dioxane at 25° at about 1% concentration, uv spectra are of MeOH solutions and ir spectra were measured in Nujol. The nmr spectra were measured on a Varian A60-A spectrometer in $CDCl_3$ (Me_4Si) unless otherwise stated. Solutions were dried over anhyd Na_2SO_4. Analyses were determined by the Physical Organic Chemistry Department of Schering Corporation. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(10) We are indebted to Mr. L. Finckenor, Process Research Laboratories, Schering Corp., for supplying us with this compound.

N-Substituted 2,2′-Diphenamic Acids and Diphenimides. I[1]

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Received January 5, 1970

Some time ago we submitted a large number of compounds to the Walter Reed Army Medical Center for antimalarial screening, compounds which had been screened earlier for antitumor activity by the Cancer Chemotherapy National Service Center. We were recently notified that one of these substances (**19**) showed significant antimalarial activity in preliminary testing in mice (T-C, 6.9 days, or more than doubled survival time at a dose of 640 mg/kg; 4.9 days at 160 mg/kg; 3.7 days at 40 mg/kg).[2]

There appeared to be few, if any, N-substituted diphenimides of this type in the literature, and certainly none screened for biological activity; therefore, we synthesized the 32 new compounds shown in Table I. Unfortunately, none of these have shown significant activity against malaria in mice, chickens, or mosquitoes and **19** did not give evidence of activity in further testing in Rhesus monkeys against two *Plasmodium* species. All of the compounds were screened by the CCNSC in BDF_1 mice with L1210 lymphoid leukemia and were inactive.[3] *N*-2-(7-Flurofluorenyl)-2′,2″-diphenamic acid was toxic at a dosage of 150 mg/kg.

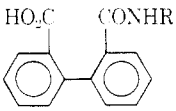
(1) Supported in part by Grant CA-01744 and by Research Career Award No. 5K03-CA14991 from the National Cancer Institute.

(2) We are grateful to Dr. T. R. Sweeney, Walter Reed Army Medical Center, for this data, and also for a gift of diphenic acid (Aldrich Chemical Co.) used in this study.

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

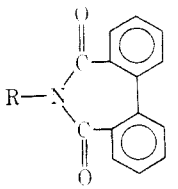
TABLE I

N-SUBSTITUTED 2,2′-DIPHENAMIC ACIDS



Compd No.	R	Mp,[a,g] °C	Yield,[b] %	Formula[c]
1	1-Fluorenyl[e]	217.5–218.5 (A)	83	$C_{27}H_{17}NO_3$
2	2-Fluorenyl[d]	216.5–217.5 (A)	83	$C_{27}H_{19}NO_3$
3	3-Fluorenyl[d]	212–213 (A)	71	$C_{27}H_{19}NO_3$
4	4-Fluorenyl[d]	241.5–242.5 (A)	56	$C_{27}H_{19}NO_3$
5	Fluorenylene-2,7-bis[d]	177–180 (G)	65	$C_{41}H_{28}N_2O_6$
6	2-(7-F-fluorenyl)[d]	177–181 (I)	90	$C_{27}H_{18}FNO_3$
7	2-(7-MeO-fluorenyl)[d]	229.5–231 (A)	82	$C_{28}H_{21}NO_4$
8	3-(2-MeO-fluorenyl)[d]	250–251.5 (A)	90	$C_{28}H_{21}NO_4$
9	7-(3,4-Benzocoumarinyl)[d,e]	260–261 (A)	75	$C_{27}H_{17}NO_5$
10	6-(3,4-Benzocoumarinyl)[d,e]	257–258 (A)	79	$C_{27}H_{17}NO_5$
11	6-Chrysenyl[d,f]	264–266 (A)	75	$C_{32}H_{21}NO_3$
12	3-(9-Et-carbazolyl)[d]	166.5–168.5 (C)	80	$C_{28}H_{22}N_2O_3$
13	Phenyl[g]	182.5–184 (B)	81	$C_{20}H_{15}NO_3$
14	Thioureido[h]	189.5–192 dec (A)	65	$C_{15}H_{12}N_2O_3S$
15	Anilino[i]	177.5–178.5 (D)	85	$C_{20}H_{16}N_2O_3$
16	1-Adamantyl[h]	220–221 (E)	50	$C_{24}H_{25}NO_3$
17	2-(4-Me-pyridinyl)[d]	87–92 (F)	33	$C_{20}H_{16}N_2O_3$

N-SUBSTITUTED 2,2′-DIPHENIMIDES



18	1-Fluorenyl	146.5–150 (C)	80	$C_{27}H_{17}NO_2$
19	2-Fluorenyl	239–240 (B)	97	$C_{27}H_{17}NO_2$
20	3-Fluorenyl	253.5–254.5 (B)	87	$C_{27}H_{17}NO_2$
21	4-Fluorenyl	236–237 (B)	96	$C_{27}H_{17}NO_2$
22	Fluorenylene-2,7-bis	357–358.5 dec (H)	82	$C_{41}H_{24}N_2O_4$
23	2-(7-F-fluorenyl)	276.5–277.5 (B)	60	$C_{27}H_{16}FNO_2$
24	2-(7-MeO-fluorenyl)	212.5–213.5 (B)	88	$C_{28}H_{19}NO_3$
25	3-(2-MeO-fluorenyl)	249–250 (B)	87	$C_{28}H_{19}NO_3$
26	7-(3,4-Benzocoumarinyl)	315–316 (D)	91	$C_{27}H_{15}NO_4$
27	6-(3,4-Benzocoumarinyl)	353–354 (D)	82	$C_{27}H_{15}NO_4$
28	6-Chrysenyl	247–248 (B)	97	$C_{32}H_{19}NO_2$
29	3-(9-Et-carbazolyl)	188.5–190.5 (C)	80	$C_{28}H_{20}N_2O_2$
30	Phenyl	198–199 (B)	90	$C_{20}H_{13}NO_2$
31	Anilino	194–195 (B)	93	$C_{20}H_{14}N_2O_2$
32	Piperonyl[h]	146–147 (B)	100	$C_{22}H_{15}NO_4$

[a] Melting points (determined on a Fisher–Johns block and corrected to standards) are reported for the compound after crystallization from (A) Me_2CO, (B) C_6H_6, (**32**, C_6H_6–EtOH), (C) MeOH, (D) $C_6H_5CH_3$, (E) EtOH–H_2O, (F) C_6H_{12}; extraction with hot (G) $C_6H_5CH_3$, (H) HOAc; or purification by (I) treatment with aq base. The melting points above 300° were taken on a Hoover capillary melting point apparatus and are uncorrected. [b] Yield after crystallization from respective solvent or other purification method as indicated for melting point. [c] All of the compounds had either neutralization equivalents within 5% or analyses for C, H, and N within ±0.4% of the theoretical values except **11** (*Anal.* Calcd: C, 82.21; H, 4.53; N, 3.00. Found: C, 81.31; H, 4.41; N, 3.06), and **27** (*Anal.* Calcd: C, 77.69; H, 3.62; N, 3.35. Found: C, 77.04; H, 3.95; N, 3.33). All analyses were done by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany. [d] These amines were synthesized in this laboratory. [e] See H.-L. Pan and T. L. Fletcher, *J. Org. Chem.*, **25**, 1106 (1960). [f] The aminochrysene was prepared by reduction of the nitro compound using $N_2H_4 \cdot H_2O$ (85%) and 5% Pd–C. [g] Obtained from Allied Chemical and Dye Corp. [h] Aldrich Chemical Co. [i] Eastman Kodak Co. [j] Reilly Tar and Chemical Corp.

The ir spectra (Beckman IR5, KBr disks) of the diphenamic acids show weak bands around 2597 cm^{-1} characteristic of bonded OH stretching of the COOH group[4] and a strong band at ~1527 cm^{-1} (amide II band for secondary amide).[5] Neither band is present in the diphenimide spectra which show CO bands[6] at 1709–1689 cm^{-1} and 1667–1642 cm^{-1}. The CO bands for these 7-membered, cyclic, aryl imides are at somewhat lower frequencies than those cited for α,β-unsaturated, 5-membered, cyclic imides (1790 and 1710 cm^{-1}) and α,β-unsaturated, 6-membered, cyclic imides (1730 and 1670 cm^{-1}),[7] undoubtedly reflecting the lowered strain in the larger ring.

(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley & Sons, New York, N. Y., 1958, pp 163–164.

(5) Reference 4, p 216.

(6) Reference 4, p 221.

(7) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 36.

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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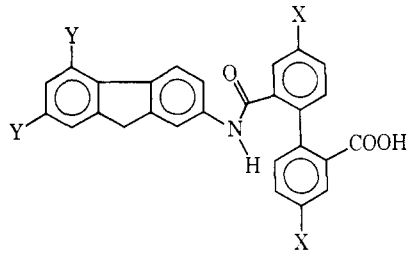
Received January 5, 1970

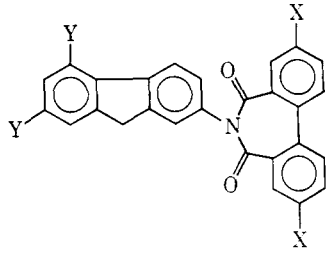
In view of the preliminary report of antimalarial activity in rodents exhibited by *N*-2-fluorenyl-2′,2″-diphenimide (II, X = Y = H),[1a] attempts were made to obtain increased activity by substitution of Cl on the rings.[2]

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).