Design of Antineoplastic Agents on the Basis of the "2-Phenylnaphthalene-Type" Structural Pattern. 3. Synthesis and Biological Activity Evaluation of 5*H*-Benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione Derivatives

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A number of 5*H*-Benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione derivatives were synthesized. Their biological activity was compared with that of the corresponding benzoxazolo- and benzthiazolo-analogues.

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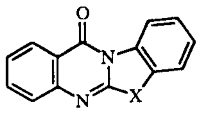
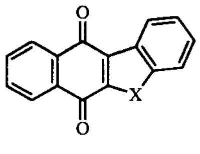
On the basis of a common 2-phenylnaphthalene-type tricyclic chemical structural pattern observed among a large number of biologically active and medically useful compounds [1,2], some 3-phenylquinazolones, benzoxazolo[2,3-*b*]quinazolones (**1a**) and benzothiazolo[2,3-*b*]quinazolones (**1b**) [3] as well as many benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione derivatives (**2a**) [4] were synthesized in our laboratory. These compounds were evaluated for their inhibitory action against the growth of human promyelocytic leukemia cells (HL-60), small-cell lung cancers sensitive (SCLC) or resistant to cisplatin (SCLC/CDDP), National Cancer Institute's disease-oriented primary antitumor 60 cell-line panels, and drug-stimulated topoisomerase II-mediated DNA cleavages. Several compounds in the condensed quinazolone series showed strong cytotoxicity against the HL-60 cells [3] and, in the benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione series, potent inhibitory activity was found in one or more of these biological test systems. *In vivo* studies of several compounds in the **2a** series are currently being conducted.

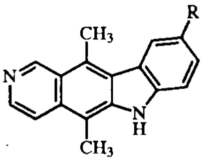


1a, X = O
b, X = S

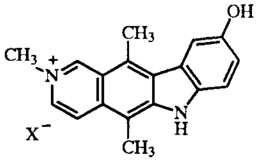


2a, X = O
b, X = NH

The encouraging test results generated by the benzonaphthofurandiones led us to investigate compounds in the corresponding aza series **2b**. The reason for choosing this group for the present study is because of the fact that a number of antitumor agents, including ellipticine (**3a**) [5], 9-hydroxyellipticine (**3b**) [5], elliptinium salts **4** [6], pazelliptine (BD-40, PZE, **5**) [7] and BD-84 (**6**) [8] possess similar structural pattern with an azo linkage connecting the "phenyl" and the "naphthalene" units of the 2-phenylnaphthalene-type arrangement.



3a, R = H
b, R = OH



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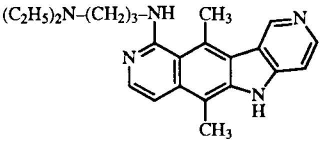

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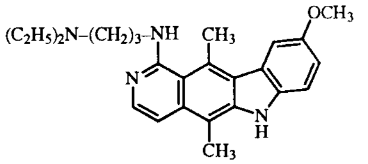

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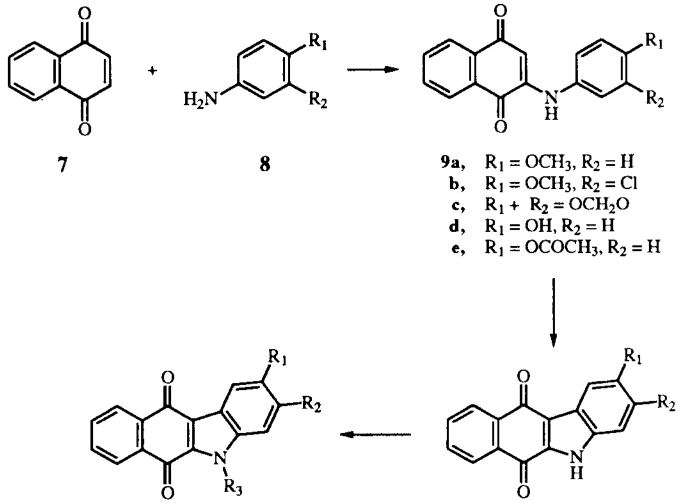
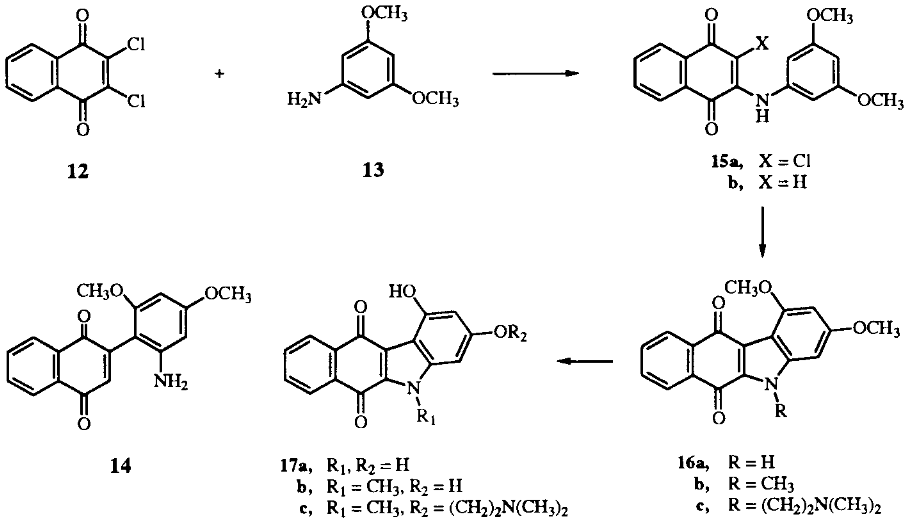
A general preparative route for some benzonaphthopyrrolediones described here involves condensation of two equivalents of 1,4-naphthalenedione (**7**) with one equiva-



9a, $R_1 = OCH_3$, $R_2 = H$
b, $R_1 = OCH_3$, $R_2 = Cl$
c, $R_1 + R_2 = OCH_2O$
d, $R_1 = OH$, $R_2 = H$
e, $R_1 = OCOCH_3$, $R_2 = H$

11a, $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$
b, $R_1 = OCOCH_3$, $R_2 = H$, $R_3 = CH_3$
c, $R_1 = OCOCH_3$, $R_2 = H$, $R_3 = (CH_2)_2N(CH_3)_2$
d, $R_1 = OH$, $R_2 = H$, $R_3 = CH_3$
e, $R_1 = O(CH_2)_2N(CH_3)_2$, $R_2 = H$, $R_3 = CH_3$
f, $R_1 = O(CH_2)_2N[CH(CH_3)_2]_2{\bullet}HCl$, $R_2 = H$, $R_3 = CH_3$

10a, $R_1 = OCH_3$, $R_2 = H$
b, $R_1 = OCH_3$, $R_2 = Cl$
c, $R_1 + R_2 = OCH_2O$
d, $R_1 = OCOCH_3$, $R_2 = H$



lent of substituted aniline **8** to give **9**, followed by a ring closure with palladium acetate [9], then derivation of the resulting cyclized product **10** with functional groups to yield **11**. The reason of using two equivalents of **7** is due to the fact that the initial condensation reaction between **7** and **8** involves a nucleophilic addition of the amine **8** to the quinone **7**, and the intermediate hydroquinone needs to be oxidized to the desired product **9** during the course of the reaction by the second equivalent of the unreacted quinone **7**.

For the synthesis of 1,3-dihydroxy-5*H*-benzo[*b*]carbazole-6,11-dione (**16a**), the aza analog of the biologically active 1,3-dihydroxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione [4], the starting 1,4-naphthalenedione (**7**) was replaced by 2,3-dichloro-1,4-naphthalenedione (**12**) for the initial condensation with 3,5-dimethoxyaniline (**13**). The reason is that the carbon atom of the aromatic ring on compound **13** is activated in the presence of two methoxyl substituents which preferentially undergo a nucleophilic addition to the quinone **7** to give the 2-aryl-1,4-naphthoquinone (**14**) as the main product together with the formation of a small amount of the amino-substituted compound **15a**. This situation has also been observed earlier by Blackburn and Griffiths [10]. Dechlorination of the condensed product **15a** obtained from **12** and **13** followed by cyclization and derivatization yielded compounds **16** and **17**, respectively.

In contrast to the relative amount of reactants used in the condensation reaction between compounds **7** and **8**, reaction between the dichloronaphthoquinone **12** and the aromatic amine **13** required the use of excess amount (two equivalents) of **13** to one equivalent of **12**. The excess **13** was used as an acid scavenger and also used to react with any unused dichloronaphthaquinone **12**. The latter was difficult to be removed from the crude product by conventional purification means.

Biological Testing Results.

Compounds synthesized in the present study were evaluated for their inhibitory action against the growth of human promyelocytic leukemia cells (HL-60). The test procedure and criteria of activity were reported previously [4].

Compound	**10a**	**10b**	**10c**	**10d**	**11a**	**11b**	**11c**	**11d**	**11e**
IC_{50} (μ*M*)	45.4	53.1	>100	1.31	not tested	1.01	0.17	1.10	0.28

Compound	**11f**	**16a**	**16b**	**16c**	**17a**	**17b**	**17c**
IC_{50} (μ*M*)	0.80	>100	100	0.42	5.31	5.49	0.32

In general, a compound is considered active when the IC_{50} (μM) value is less than 1. From the test results it can be readily seen that compounds possessing a dimethylaminoethyl chain, whether it is substituted to the hydroxyl oxygen or the ring nitrogen atom, are more active than the unsubstituted compounds. This structure-activity relationship is similar to that of the corresponding benzoxazolo- and benzthiazolo-analogues reported earlier [3,4]. This test assay also indicated that the oxygen analogues are more active than the corresponding aza compounds.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were determined on a Perkin-Elmer 337 grating infrared spectrometer. The mass spectra were conducted at the Mass Spectra Laboratory of the University of Kansas, Lawrence, Kansas and the elemental analyses were performed by the M-H-W Laboratories at Phoenix, Arizona.

2-[*N*-(4-Methoxyphenyl)]amino-1,4-naphthalenedione (**9a**).

To a solution of 9.5 g (0.06 mole) of 1,4-naphthalenedione (**7**) in 700 ml of absolute ethanol was added dropwise a solution of 3.7 g (0.03 mole) of *p*-anisidine in 50 ml of ethanol at 10°. The mixture was stirred at room temperature overnight. The resulting solid was collected by filtration, washed with ethanol and dried to give 6.4 g (76% yield) of **9a**, mp 155-157°. The product was recrystallized from ethanol, mp 155-157° (lit [11], mp 155-157°).

Other intermediates were prepared in a similar manner from two equivalents of **7** and one equivalent of the appropriate aniline: **9b** (refluxed for 12 hours in ethanol, mp 231-233° from 2-ethoxyethanol, 54% yield); **9c** (room temperature overnight in ethanol, mp 202-205° from ethanol-pyridine, 39% yield); **9d** (room temperature overnight, mp 250-252° from ethanol-pyridine, 59% yield).

2-[*N*-(4-acetoxyphenyl)]amino-1,4-naphthalenedione (**9e**).

A mixture of 2.3 g (0.087 mole) of **9d** in 40 ml of acetic anhydride and 1 ml of concentrated sulfuric acid was stirred at room temperature overnight. The reaction mixture was added slowly, with stirring, to 400 ml of water at 0°. After 30 minutes the resulting product was collected by filtration, washed with water and recrystallized from ethanol to give 1.7 g (64% yield) of **9e**, mp 170-171°; ir (nujol): ν max 3270, 1740, 1675, 1625 and 1575 cm^{-1}.

2-Chloro-3-[*N*-(3,5-dimethoxyphenyl)]amino-1,4-naphthalenedione (**15a**).

To a stirred solution of 100 ml of absolute ethanol was added 15.7 g (0.1 mole) of 98% 3,5-dimethoxyaniline (**13**). All solids dissolved quickly. To the solution was added 11.5 g (0.05 mole) of 2,3-dichloro-1,4-naphthanenedione (**12**). The color of the yellow suspension soon turned to brown. The mixture was refluxed with stirring and, within 30 minutes, a dark brown solution was formed. The mixture was refluxed for a total of 6 hours, then allowed to stir overnight at room temperature. The solid product was collected by filtration, washed with ethanol and dried to give 16.2 g (94% yield) of **15a**, mp 169-171°. Recrystallized from 1-butanol yielded shinny rusty red crystals with gold luster, mp 185-185.5°; ir (nujol): ν max 3310, 1660, 1630, 1580, 1550, 1290 and 1150 cm^{-1}; ms: m/z 343 (M$^+$).

Anal. Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.11; N, 4.08. Found: C, 62.93, H, 4.23; N, 3.96.

2-[*N*-(3,5-Dimethoxyphenyl)]amino-1,4-naphthalenedione (**15b**).

A solution of 1 g (0.029 mole) of **15a** in 35 ml of dry 3-picoline was refluxed for 60 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was triturated with warm benzene several times. The combined organic extract was chromatographed on a silica gel column using benzene as the eluent yielding 460 mg (51% yield) of **15b**, mp 176-178°; ir (nujol): ν max 3320, 1670, 1625, 1600 and 1570 cm^{-1}; ms: m/z 309 (M$^+$).

1,3-Dimethoxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**16a**).

A mixture of 6 g (0.019 mole) of **15b**, 2.1 g (0.019 mole) of benzoquinone and 4.35 g (0.019 mole) of palladium(II) acetate in 400 ml of glacial acetic acid was refluxed under nitrogen for 2 hours, and filtered while hot. After standing overnight at room temperature, the resulting solid was collected by filtration to give 3.1 g (52% yield) of **16a**, mp 280-281°. Recrystallized from nitrobenzene gave an analytically pure compound, mp 280.5-282°; ir (nujol): ν max 3250, 1640, 1610, 1570, 1520 and 1500 cm^{-1}; ms: m/z 307 (M$^+$).

Anal. Calcd. for $C_{18}H_{13}NO_4$(307.3): C, 70.34; H, 4.27; N, 4.56. Found: C, 70.27; H, 4.45; N, 4.61.

The Following compounds were prepared in a similar manner:

2-Methoxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrolo-6,11-dione (**10a**).

This compound had mp 310-311° from nitrobenzene (lit [9c] mp 299-300°); ir (nujol): ν max 3200 (br), 1650, 1630, 1580, 1520 and 1260 cm^{-1}; ms: m/z 277 (M$^+$).

3-Chloro-2-methoxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**10b**).

This compound had mp >330° from dimethylformamide; ir (nujol): ν max 3250 (br), 1660, 1640, 1590, 1510 and 1260 cm^{-1}; ms: m/z 311 (M$^+$).

Anal. Calcd. for $C_{17}H_{10}ClNO_3$ (311.7): C, 65.50; H, 3.24; N, 4.49; Cl, 11.37. Found: C, 65.45; H, 3.20; N, 4.53; Cl, 11.49.

2,3-Methylenedioxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**10c**).

This compound was obtained in 59% yield, mp >330° from nitrobenzene; ir (nujol): ν max 3250 (br), 1630, 1580, 1500 and 1250 cm^{-1}; ms: m/z 291 (M$^+$).

Anal. Calcd. for $C_{17}H_9NO_4$ (291.3): C, 70.10; H, 3.12; N, 4.81. Found: C, 70.16; H, 3.20; N, 4.81.

2-Acetoxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**10d**).

This compound was obtained in 66% yield, mp >310° from dimethylformamide; ir (nujol): ν max 3230 (br), 1750, 1650, 1590 and 1220 cm^{-1}; ms: m/z 305 (M$^+$).

Anal. Calcd. for $C_{18}H_{11}NO_4$ (305.3): C, 70.81; H, 3.64; N, 4.57. Found: C, 70.65; H, 3.88; N, 4.38.

1,3-Dimethoxy-5-methyl-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**16b**).

To 1.53 g (0.05 mole) of **16a** in 100 ml of chloroform was added 1.27 ml (0.15 mole) of dimethyl sulfate, 2.65 g (0.25 mole) of sodium carbonate in 10 ml of water and 60 mg of tetrabutylammonium hydrogen sulfate successively. The mixture was refluxed for 2 hours under vigorous stirring. The reaction mixture was allowed to stand and the aqueous phase was extracted with 100 ml of chloroform. The combined organic solution was washed with water, brine and dried over anhydrous sodium sulfate, then concentrated *in vacuo*. The resulting solid was recrystallized from 1-butanol to give 1.37 g (86% yield) of **16b**, mp 252-254°; ir (nujol): ν max 1640, 1610, 1580, 1260, 1240 and 1210 cm^{-1}; ms: m/z 321 (M$^+$).

Anal. Calcd. for $C_{19}H_{15}NO_4$ (321.3): C, 71.01; H, 4.71; N, 4.36. Found: C, 70.81; H, 4.85; N, 4.35.

Other *N*-alkyl derivatives were prepared by analogous procedures:

2-Methoxy-5-methyl-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**11a**).

This compound was obtained in 86% yield, mp 253.5-254.5° from 1-butanol and pyridine; ir (nujol): ν max 1640, 1610, 1590, 1270 and 1230 cm^{-1}; ms: m/z 291 (M$^+$).

Anal. Calcd. for $C_{18}H_{13}NO_3$ (291.3): C, 74.20; H, 4.51; N, 4.81. Found: C, 74 21; H, 4.50; N, 4.80.

2-Acetoxy-5-methyl-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**11b**).

This compound was obtained in 94% yield, mp 254-256° from 1-butanol; ir (nujol): ν max 1740, 1640, 1580, 1500 and 1240 cm^{-1}; ms: m/z 319 (M$^+$).

Anal. Calcd. for $C_{19}H_{13}NO_4$ (319.3): C, 71.46; H, 4.11; N, 4.39. Found: C, 71.55; H, 4.03; N, 4.35.

2-Acetoxy-5-(dimethylaminoethyl)-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**11c**).

This compound was prepared from **10d** and dimethylaminoethyl chloride hydrochloride in 76% yield, mp 179-181° from 1-butanol; ir (nujol): ν max 1750, 1660, 1590, 1500, 1250 and 1205 cm^{-1}; ms: m/z 376 (M$^+$).

Anal. Calcd. for $C_{22}H_{20}N_2O_4$ (376.4): C, 70.19; H, 5.37; N, 7.44. Found: C, 70.15; H, 5.45; N, 7.21.

1,3-Dimethoxy-5-(2-dimethylaminoethyl)-5*H*-benzo[*b*]naphtho-[2,3-*d*]pyrrole-6,11-dione (**16c**).

This compound was obtained in 95% yield, mp 162-164°; ir (nujol): ν max 1630, 1600, 1580 and 1270 cm^{-1}; ms: m/z 378 (M$^+$).

Anal. Calcd. for $C_{22}H_{22}N_2O_4$ (378.5): C, 69.81; H, 5.87; N, 7.40. Found C, 69.65; H, 5.86; N, 7.04.

2-Hydroxy-5-methyl-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**11d**).

A mixture of 5.45 g (0.17 mole) of **11b** in 350 ml of 2% ethanolic sodium hydroxide was stirred at 60° for 4 hours then evaporated to dryness under reduced pressure. To the residue was added 300 ml of water and the resulting solution was acidified to *p*H 2 with hydrochloric acid. The precipitate which formed was collected by filtration. Recrystallization of the solid from a mixture of 1-butanol and pyridine gave 3.4 g (72% yield) of **11d**, mp 313-315°; ir (nujol): ν max 3250 (br), 1650, 1620, 1580 and 1240 cm^{-1}; ms: m/z 277 (M$^+$).

Anal. Calcd. for $C_{17}H_{11}NO_3$ (277.3): C, 73.63; H, 4.01; N, 5.05. Found: C, 73.82; H, 4.02; N, 4.87.

1,3-Dihydroxy-5-methyl-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**17b**).

To a solution of 3.0 g (0.093 mole) of **16b** in 500 ml of dry benzene was added portionwise 7.4 g (0.56 mole) of aluminum chloride, with stirring. The mixture was refluxed with continuous stirring for 4 hours under nitrogen, then evaporated to dryness under reduced pressure. The residue was carefully decomposed with ice and 2*N* hydrochloric acid. The precipitated solid was collected by filtration, washed with water and dried. Recrystallization from a mixture of 1-butanol and dimethylformamide gave 2.05 g (75% yield) of **17b**, mp 279-281° dec; ir (nujol): ν max 3450, 1640, 1620, 1575, 1500 and 1240 cm^{-1}; ms: m/z 293 (M$^+$).

Anal. Calcd. for $C_{17}H_{11}NO_4$ (293.3): C, 69.61; H, 3.79; N, 4.78. Found: C, 69.52; H, 4.00; N, 4.83.

1,3-Dihydroxy-5*H*-benzo[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione (**17a**).

This compound was prepared from **16a** by a method similar to that for the preparation of **17b** in 57% yield, mp >340°; ir (nujol): ν max (nujol): 3250 (br), 1650, 1620, 1570 and 1510 cm^{-1}; ms: m/z 279 (M$^+$).

Anal. Calcd. for $C_{16}H_{19}NO_4$ (279.3): C, 68.82; H, 3.26; N, 5.02. Found: C, 68.84; H, 3.13; N, 5.00.

3-(2-Dimethylamino)ethoxy-1-hydroxy-5-methyl-5*H*-benzo-[*b*]naphtho[2,3-*d*]pyrrolo-6,11-dione Hydrochloride (**17c**).

To a solution of 586 mg (0.002 mole) of **17b** in 100 ml of chloroform was added 860 mg (0.008 mole) of sodium carbonate in 10 ml of water followed by the addition of 580 mg (0.004 mole) of 2-dimethylaminoethyl chloride hydrochloride. The mixture was refluxed for 6.5 hours with vigorous stirring, cooled, and placed in a separatory funnel. The aqueous layer was separated and extracted with 2 x 100 ml of chloroform. The combined organic solution was washed with water and brine. It was dried over anhydrous sodium sulfate and concentrated *in vacuo*. To the residue was added 30 ml of ethanol and 1 ml of concentrated hydrochloric acid. The mixture was stirred for 30 minutes and the resulting solid was collected by filtration. Recrystallization of the solid from dimethylformamide and water afforded 460 mg (58% yield) of **17c**, mp 276° dec; ir (nujol): ν max 2600-2350 (br), 1650, 1620, 1580 and 1250 cm^{-1}; ms: m/z 364 (M$^+$).

Anal. Calcd. for $C_{21}H_{20}N_2O_4$•HCl (364.3 + 36.5): C, 62.91; H, 5.29; N, 6.99. Found: C, 63.04; H, 5.06; N, 7.12.

Compounds **11e** and **11f** were prepared by an analogous procedure:

2-(2-Dimethylamino)ethoxy-5-methyl-5*H*-benzo[*b*]naphtho-[2,3-*d*]pyrrole-6,11-dione (**11e**).

This compound was prepared from **11d** and 2-dimethylaminoethyl chloride hydrochloride in 58% yield, mp 134-137° from 1-butanol; ir (nujol): ν max 1650, 1590 and 1240 cm^{-1}; ms: m/z 348 (M$^+$).

Anal. Calcd. from $C_{21}H_{20}N_2O_3$ (348.4): C, 72.38; H, 5.80; N, 8.04. Found: C, 72.43; H, 5.61; N, 7.89.

2-[2-Bis(1-methylethyl)amino]ethoxy-5-methyl-5*H*-benzo-[*b*]naphtho[2,3-*d*]pyrrole-6,11-dione Hydrochloride (**11f**).

This compound was prepared from **11d** and 2-isopropylaminoethyl chloride hydrochloride in 57% yield, mp 243-244.5° dec from 1-butanol; ir (nujol): ν max 2700-2300 (br), 1640, 1580, 1270 and 1240 cm^{-1}; ms: m/z 404 (M$^+$).

Anal. Calcd. for $C_{25}H_{28}N_2O_3$•HCl (404.5 + 36.5): C, 68.08; H, 6.64; N, 6.35. Found: C, 68.09; H, 6.56; N, 6.33.

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REFERENCES AND NOTES

[1] C. C. Cheng, Med. Hypotheses, **20**, 157 (1986).

[2] C. C. Cheng, in Progress in Medicinal Chemistry, Vol **25**, G. P. Ellis and G. B. West, eds, Elsevier, Amsterdam, 1988, pp 35-83.

[3] C. C. Cheng, D. F. Liu and T. C. Chou, *Heterocycles*, **35**, 775 (1993).

[4] C. C. Cheng, Q. Dong, D. F. Liu, Y. L. Luo, L. F. Liu, A. Y. Chen, C. Yu, N. Savaraj and T. C. Chou, *J. Med. Chem.*, **36**, 4108 (1993).

[5a] R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *J. Am. Chem. Soc.*, **81**, 4434 (1959); [b] K. W. Kohn, W. E. Ross and D. Glaubiger, in Antibiotics, Vol **5**, Part **2**, F. E. Hahn, ed, Springer-

Verlag, Berlin, 1979, pp 195-213.

[6a] P. Juret, J. F. Heron, J. F. Couette, T. Delozier and J. Y. LeTalaer, *Cancer Treat. Rep.*, **66**, 1909 (1982); [b] E. M. Acton, V. L. Narayanan, P. A. Risbood, R. H. Shoemaker, D. T. Vistica and M. R. Boyd, *J. Med. Chem.*, **37**, 2185 (1994); [c] J. Jurayj, R. D. Haugwitz, R. K. Varma, K. D. Paull, J. F. Barrett and M. Cushman, *J. Med. Chem.*, **37**, 2190 (1994).

[7a] J. C. Chermann, J. Greust, L. Mantagnier, F. Wendling, P. Tambourn, M. Perrin, F. Pochon, C. Duerocq, C. Rivalle and E. Bisagni, *Compt. Rend. Acad. Sci. Paris (D)*, **285**, 945 (1977); [b] C. Ducrocq, E. Bisagni, C. Rivalle and J. M. Lhosta, *J. Chem. Soc., Perkin Trans. I*, 142 (1979), [c] C. Ducrocq, F. Wendling, M. Tourbez-Perrin, C. Rivalle, P. Tambourin, F. Pochon and E. Bisagni, *J. Med. Chem.*, **23**, 1212 (1980).

[8] L. Larue, C. Rivalle, G. Muzard, C. Paoletti, E. Bisagni and J. Paoletti, *J. Med. Chem.*, **31**, 1951 (1988).

[9a] L. S. Hegedus, *Angew. Chem.*, **100**, 1147 (1988); [b] R. B. Miller and T. Hoock, *Tetrahedron Letters*, **21**, 3319 (1980); [c] S. Bittner, P. Krief and T. Massil, *Synthesis*, 215 (1991).

[10] L. Blackburn and J. Griffiths, *J. Chem. Res. (S)*, 320 (1982).

[11] N. G. Clark, *Pestic. Sci.*, **16**, 23 (1985).

[12] H. J. Kallmayer, *Arch. Pharm.*, **306**, 713 (1973).