Synthesis and Cytotoxic Activity of 2-Dialkylaminoalkyl-1,3-dihydropyrrolo[3,4-*c*]quinoline-1,3-diones and 6-(2-Dimethylaminoethyl)-1*H*-dibenz[*c,e*]azepine-5,7-dione

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The title compounds were synthesized. Cyclodehydration of aromatic 1,2-dicarboxylic acids, in the presence of dicyclohexylcarbodiimide, to the corresponding *N*-substituted imides is discussed. Compounds **8** and **10** were tested *in vitro* against K562 and HL-60 cell lines. Compound **10** exhibited moderate cytotoxic activity.

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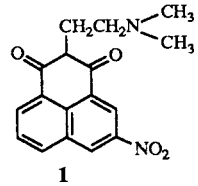
A large number of fused *N*-dialkylaminoalkylsuccinimides and glutarimides were reported to have significant antitumor activities [1]. *N*-Substituted imides of 3-nitro-1,8-naphthalic acid (Mitonafide **1**) and derivatives were reported to exhibit antineoplastic activity against mouse Ehrlich ascites and rat Yoshida carcinoma and *in vitro* cyctotoxicity against the HeLa cells [2].

Quinolinic acid imides of type **2** and arylnaphthalene-2,3-dicarboxylic acid imides of type **3** are other examples of this class of antitumor agents [3,4].

More recently, Zee Cheng and Cheng [1] synthesized several series of *N*-aminoalkylimides. These are *N*-dialkylaminoalkyl-1,8-naphthylimides **4** and *N,N*-bis[2-[(2-hydroxyethyl)amino]ethyl]-1,4,5,8-naphthalenetetracarboximide (**5**).

In continuation of our interest in the synthesis of potential antitumor agents [5,6], we decided to synthesize quinoline analogues of compounds **2** and **3** hoping that the nitrogen of the quinoline ring would increase the solubility of the active naphthalenic compounds **3**. A series of twelve compounds were synthesized. These are 2-dialkylaminoalkyl-1,3-dihydropyrrolo[3,4-*c*]quinoline-1,3-diones **8a-l**.



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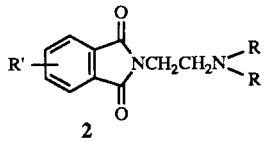

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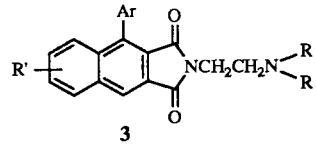

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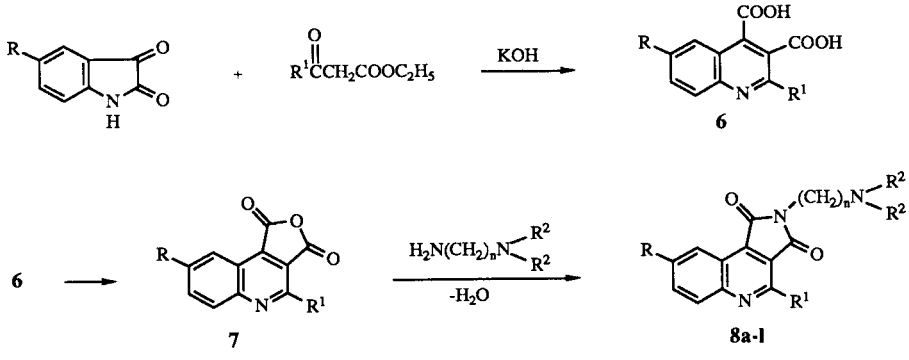
Isatin or 5-bromoisatin served as the starting material for the synthesis of compounds **8**. Substituted quinoline-3,4-dicarboxylic acids **6** were prepared according to the Pfitzinger reaction [7a] by treatment of isatin or 5-bromoisatin with ethyl acetoacetate or ethyl benzoylacetate in strong aqueous potassium hydroxide at room temperature. Acids **6** were converted to the corresponding anhydrides **7** by refluxing in acetic anhydride. The anhydrides obtained were used in the next step without further purification. Reaction of the anhydrides **7** with various *N,N*-disubsti-

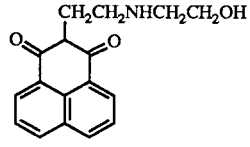
Scheme 1



R = H or Br; R^1 = CH_3 or C_6H_5; R^2 = CH_3 or C_2H_5; n = 2 or 3

tuted dialkylaminoalkylamines in refluxing toluene afforded the desired compounds **8** (see Scheme 1).

During a series of related experiments, we found that the reaction of phthalic acids with 2-phenethylamine or dialkylaminoalkylamines in the presence of dicyclohexylcarbodiimide in tetrahydrofuran produced high yields of the corresponding *N*-substituted phthalimides **9a,b**. Although this method was not satisfactory in the synthesis of compounds **8**, it gave excellent results in the systhesis of 6-[2-dimethylaminoethyl]-1*H*-dibenz[*c,e*]azepine-5,7-dione (**10**) from diphenic acid.



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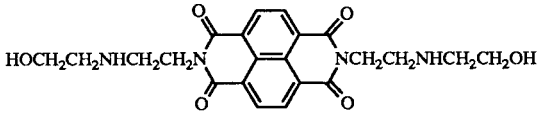

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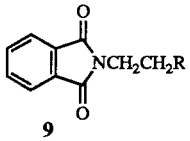
Biological Studies.

The cytotoxicity of the compounds described above, except for **8i** and **8l**, which had poor solubilities, as well as **9a** and **9b** was determined. K562, a human myelogenous leukemia cell line, YAC-1 a mouse lymphoma cell line and HL-60, a human promyelocytic cell line were used at a concentration of 50-100 x 10^3/well. In these experiments the cells were incubated with various concentrations of each compound, at 37° in flat bottomed tissue culture plates in triplicates. After 3-4 days of incubation the number of live cells were determined and compared to that of control using trypan blue exclusion technique. Among various compounds tested only compound **10** had significantly higher



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a, R = C_6H_5
b, R = $N(CH_3)_2$

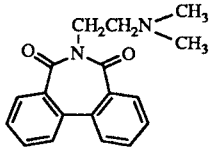

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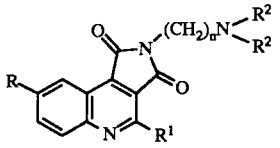
Table I

2-Dialkylaminoalkyl-1,3-dihydropyrrolo[3,4-*c*]quinoline-1,3-diones **8**



No.	R	R^1	R^2	n	Mp °C	Yield %	Formula	Elemental Analysis Calcd. (Found) C%	H%	N%
8a	H	CH_3	CH_3	2	140-142	78	$C_{16}H_{17}N_3O_2$	67.82 (67.78)	6.05 (6.06)	14.83 (14.81)
8b	H	CH_3	CH_3	3	120-123	74	$C_{17}H_{19}N_3O_2$	68.66 (68.64)	6.44 (6.44)	14.13 (14.15)
8c	Br	CH_3	CH_3	2	182-184	71	$C_{16}H_{16}BrN_3O_2$	53.05 (53.10)	4.45 (4.44)	11.60 (11.60)
8d	Br	CH_3	CH_3	3	123-125	76	$C_{17}H_{18}BrN_3O_2$	54.26 (54.18)	4.82 (4.80)	11.16 (11.14)
8e	H	CH_3	C_2H_5	2	152-154	74	$C_{18}N_{21}N_3O_2$	69.43 (69.44)	6.80 (6.82)	13.50 (13.49)
8f	Br	CH_3	C_2H_5	2	100-102	68	$C_{18}H_{20}BrN_3O_2$	55.39 (55.39)	5.16 (5.16)	10.76 (10.77)
8g	H	C_6H_5	CH_3	2	146-147	48	$C_{21}H_{19}N_3O_2$	73.02 (73.10)	5.55 (5.55)	12.17 (12.17)
8h	H	C_6H_5	CH_3	3	118-119	20	$C_{22}H_{21}N_3O_2$	73.51 (73.43)	5.89 (5.88)	11.69 (11.67)
8i	Br	C_6H_5	CH_3	2	189	90	$C_{21}H_{18}BrN_3O_2$	59.44 (59.34)	4.27 (4.27)	9.90 (9.87)
8j	Br	C_6H_5	CH_3	3	114-115	50	$C_{22}H_{20}BrN_3O_2$	60.28 (60.12)	4.59 (4.58)	9.58 (9.59)
8k	H	C_6H_5	C_2H_5	2	141	92	$C_{23}H_{23}N_3O_2$	73.97 (73.89)	6.21 (6.22)	11.25 (11.26)
8l	Br	C_6H_5	C_2H_5	2	122-123	90	$C_{23}H_{22}BrN_3O_2$	61.06 (61.14)	4.90 (4.90)	9.29 (9.28)

activity in abolishing the tumor cells. This compound at a final concentration of 500 μM abolished 90-100% of the tumor cells (HL-60 and K562) after 3 days of culture.

EXPERIMENTAL

The proton magnetic resonance spectra were recorded on Varian LM-360 spectrometer using tetramethylsilane as internal standard (δ scale). Melting points were determined with Fisher-Johns hot stage apparatus.

Known procedures [7] were adopted for the preparation of quinoline-3,4-dicarboxylic acids **6** and the corresponding anhydrides **7**.

4-Methyl-2-[2-dimethylaminoethyl]-1,3-dihydropyrrolo[3,4-*c*]-quinoline-1,3-dione (**8a**).

To a stirred solution of 2-methylquinoline-3,4-dicarboxylic anhydride (0.64 g, 3 mmoles) in toluene (50 ml) *N,N*-dimethylethylenediamine (0.32 g, 3.6 mmoles) was added dropwise. The mixture was stirred at room temperature for 60 minutes and was refluxed, while connected to a Dean-Stark trap, for 2 hours. At this time a clear solution was obtained. The solvent was removed under vacuum and the residue was recrystallized from a mixture of toluene and hexane; ^{1}H nmr (deuteriochloroform): 2.31 (s, 6H), 2.50 (t, 2H), 3.02 (s, 3H), 3.85 (t, 2H), 7.6-8.85 (m, 4H).

8-Bromo-4-phenyl-2-[2-dimethylaminoethyl]-1,3-dihydropyrrolo-[3,4-*c*]quinoline-1,3-dione (**8i**).

This compound was prepared in a similar manner as described for **8a** from 6-bromo-2-phenylquinoline-3,4-dicarboxylic anhydride (1.06 g, 3 mmoles) and *N,N*-dimethylethylenediamine (0.32 g, 3.6 mmoles) to give 1.25 g of solid which was recrystallized from toluene-hexane; ^{1}H nmr (deuteriochloroform): 2.2 (s, 6H), 2.5 (t, 2H), 3.8 (t, 2H), 7.1-9.0 (m, 8H).

The other compounds in this series were prepared according to the above procedure.

For the physical data of compounds **8a-l** see Table I.

N-2-Phenethylphthalimide (**9a**).

To a refluxing mixture of phthalic acid (1.66 g, 10 mmoles) and 2-phenethylamine, (1.21 g, 10 mmoles) in tetrahydrofuran (25 ml), dicyclohexylcarbodiimide (2.06 g, 10 mmoles) was added. The mixture was stirred and refluxed for 2 hours. After cooling, the dicyclohexylurea which formed was then separated. After evaporating the solvent the residue was recrystallized from ethanol to give 1.96 g (78%) of small crystals, mp 131-133° (lit **8**, mp 131-132°). When the reaction was conducted with two equivalent of dicyclohexylcarbodiimide, the yield was increased to 86%; ^{1}H nmr (trifluoroacetic acid): 3.35 (t, 2H), 4.11 (t, 2H), 7.21-8.21 (m, 9H).

N-2-Dimethylaminoethylphthalimide (**9b**).

This compound was prepared from phthalic acid and *N,N*-dimethylethylenediamine as described for **9a**. Using one equivalent mole of dicyclohexylcarbodiimide, a pure compound in 91% yield was obtained; ^{1}H nmr (trifluoroacetic acid): 2.32-2.93 (d, 6H), 3.48 (t, 2H), 4.03 (t, 2H), 7.69 (s, 4H). The hydrochloride had mp 217-218° (lit **1**, mp 217-218°).

6-[2-Dimethylaminoethyl]-1*H*-dibenz[*c,e*]azepine-5,7-dione hydrochloride (**10**).

N,N-Dimethylethylenediamine (0.97 g, 11 mmoles) was added to a stirred solution of diphenic acid (2.42 g, 10 mmoles) in anhydrous tetrahydrofuran (40 ml). A gummy substance was immediately, formed. To the mixture 1,3-dicyclohexylcarbodiimide (4.18 g, 20 mmoles) was added and refluxed for two hours. Upon heating, and right before refluxing, all the gum was dissolved and a greenish solution containing insoluble dicyclohexylurea was obtained. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and the foamy solid residue (2.5 g, 85%), was converted to the hydrochloride salt by the addition of 10 equivalent moles of hydrochloric acid in methanol. The compound was separated and washed with ether. It was left over phosphorus pentoxide and under high vacuum (0.05 torr) overnight, upon which, a hygroscopic solid was obtained; ^{1}H nmr (dimethyl sulfoxide-d_6): 2.5 (s, 6H), 2.5-3.5 (m, 4H), 6.8-8.2 (m, 8H).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$ (294.36): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.54; H, 6.14; N, 9.55.

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