The Synthesis of Heterocyclic Analogs of Bisantrene

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Bisguanylhydrazones of anthracene-9,10-dicarboxaldehyde have demonstrated excellent antitumor activity. Heterocyclic analogs were synthesized in an effort to expand or modify the activity profile.

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Bisguanylhydrazones of anthracene-9,10-dicarboxaldehydes as a class have demonstrated potent anticancer activity [1] and CYABIN™ (bisantrene hydrochloride) [2] is currently in Phase III clinical development. In a synthetic program related to the above, we have converted 9,10-anthracenediones to 9,10-anthracenedicarboxaldehydes [3] and now describe the use of this methodology on several heterocyclic 9,10-anthracenedione equivalents: 4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]*dithiophene-4,8-dione, naphtho[2,3-c*][1,2,5]thiadiazole-4,9-dione, and 1-azaanthraquinone.

Chemistry.

Benzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione [4] (**1**) and 1-azaanthraquinone [5] (**2**) reacted smoothly with trimethylsulfonium ylide in DMSO to produce bis oxiranes **3,4** which were characterized by spectral means and rearranged without further purification with lithium bromide to hydroxymethyl aldehydes **5,6**. Compound **6** is a mixture of positional isomers. In contrast to the above two heterocyclic systems, naphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione [6] (**7**) did not react under the reaction conditions or modifications thereof. Only starting material, or with more drastic conditions, decomposition products were observed. The hydroxymethyl aldehydes **5,6** readily oxidized to the desired bis-aldehydes **8,9** with sulfur trioxide in pyridine.

Discussion.

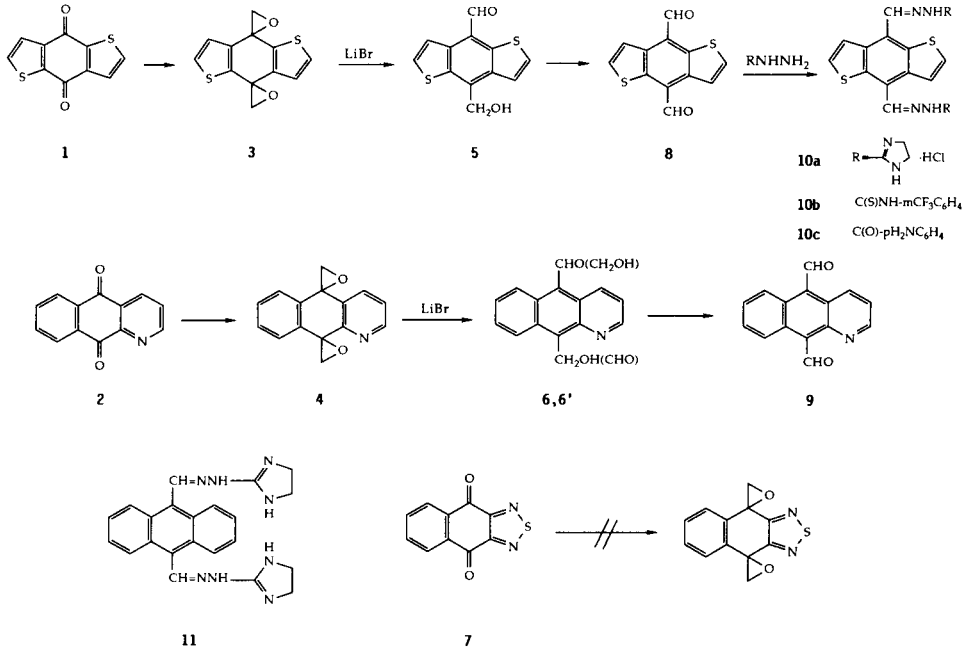
Analogs **10a-c** of CYABIN™ (**11**, bisantrene hydrochloride) were prepared from **8** and only **10a** had marginal activity in comparative testing.

EXPERIMENTAL

All melting points were observed on a Mel Temp Apparatus and are in °C. All new compounds have supportive spectral properties (nmr, ir, M⁺) and/or microanalytical data.

Bis-oxirane of 1-Azaanthraquinone (**4**).

Sodium hydride (50% NaH in oil, 2.55 g, 53 mmoles) was washed 3 x with 100 ml of hexane and 150 ml of dry DMSO was added followed by quinone **2** (5.0 g, 24 mmoles) and the resultant mixture became pinkish



red. The reaction vessel was covered with foil to exclude light. A solution of trimethylsulfonium iodide (10.8 g, 53 mmoles) in 90 ml of dry DMSO was added dropwise with stirring over 20 minutes at room temperature and stirring was continued for an additional hour. The mixture was poured into 400 ml of ice and water and the solid was collected by filtration, washed with 3 x 100 ml of water and dried *in vacuo*. The solid was taken up in 100 ml of dichloromethane filtered and the solvent removed to give 2.7 g (47%) of an off-white solid which melted with decomposition over a broad range. The nmr and other spectral data are consistent with the bis-oxirane structure $C_{15}H_{11}NO_2$ (237.3).

9(10)-Hydroxymethyl-1-azaanthraquinone-10(9)-carboxaldehyde (**6**).

A mixture of bis-oxirane **4**, (2.7, 11 mmoles) and lithium bromide (4.29, 48 mmoles) in 160 ml of acetonitrile was refluxed in the dark for 16 hours. Cooling produced a greenish solid which was collected by filtration, washed with water and air dried. The material was dissolved in chloroform, filtered to remove insolubles by passage through alumina and recovered by *in vacuo* removal of the solvent to give a tan low melting solid (1.6 g, 61%) $C_{15}H_{11}NO_2$.

1-Aza-anthraquinone-9,10-biscarboxaldehyde (**9**).

Solid **6** (1.6 g, 6.8 mmoles) was added to a stirring mixture of triethylamine (14 ml) and DMSO (20 ml). A solution of 4.8 g sulfur trioxide-pyridine in 25 ml of DMSO was added and the resultant product stirred at room temperature for 2 hours, then poured onto 200 ml ice and water. The yellowish solid was collected by filtration, washed with water and dried to give 1.1 g of solid. The nmr indicated the presence of some starting material (CH_2OH). The above procedure was repeated with 2 hours additional oxidation to give 0.91 g of a tan solid on which no starting material could be seen in the nmr. The solid was chromatographed on a short silica column eluting with acetonitrile. The 550 mg of tan solid was recrystallized from methanol 16 ml to yield 362 mg (23%) of a tan solid, mp 208-212° dec.

Anal. Calcd. for $C_{15}H_9NO_2$ (235.2): C, 76.5; H, 3.86; N, 5.96. Found: C, 76.4; H, 4.07; N, 5.69.

8-Hydroxymethylbenzo[1,2-*b*:4,5-*b'*]dithiophene-4-carboxaldehyde (**5**).

Benzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (22.0 g, 0.1 mole) was added to sodium hydride (10.4 g of 50% in oil washed with 3 x 100 ml of hexane) in 200 ml of DMSO and stirred for 1 hour in subdued light. To this was added dropwise over 30 minutes a solution of trimethylsulfonium iodide (44 g, 0.21 mole) in 200 ml of DMSO. Stirring at room temperature was continued for 1.5 hours after which the mixture was poured into 2 l of ice and water. The solid was collected, washed with water and dried. The solid (19.8 g) was dissolved in chloroform (500 ml), filtered to remove insolubles and recovered by *in vacuo* removal of the solvent to give 16.1 g of crude **3** which was characterized by spectral methods and used without further purification.

Crude **3** (20 g, 0.81 mole) was dissolved in 500 ml of acetonitrile containing 50 g of lithium bromide. The resultant was heated in low light overnight and poured into 2 l of ice and water. The solid was collected, washed with water, dissolved in 500 ml of chloroform and dried over anhydrous sodium sulfate. After filtration, the volume of chloroform was reduced to ~150 ml by boiling on a steam bath and hexane was added to incipient cloudiness. Cooling gave 11.6 g (72%) of an orange solid, mp 168-171°. Two additional recrystallizations gave microanalytical material.

Anal. Calcd. for $C_{12}H_8O_2S_2$ (248.3): C, 58.0; H, 3.25; S, 25.8. Found: C, 58.3; H, 3.46; S, 25.5.

Benzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dicarboxaldehyde (**8**).

Compound **5** (14.4 g, 0.058 mole) in 150 ml of DMSO and 40 ml of triethylamine was oxidized with sulfur trioxide pyridine, complex (60 g) in 180 ml of DMSO as for **9** to give a solid which was chromatographed on silica gel and recrystallized from methanol/water to give 7.7 g (54%) of an orange solid, mp 283-285°.

Anal. Calcd. for $C_{12}H_6O_2S_2$ (246.3): C, 58.5; H, 2.64; S, 26.0. Found: C, 58.2; H, 2.66; S, 26.4.

Benzo[1,2-*b*:5-*b'*]dithiophene-4,8-dicarboxaldehyde Bis(2-imidazolin-2-ylhydrazone) Dihydrochloride (**10a**).

A solution of **8** (0.9 g, 3.6 mmoles) and 1.3 g of 2-hydrazino-2-imidazoline dihydrochloride (7.4 mmoles) was refluxed in 10 ml of 1-propanol for 1 hour. Cooling in an ice bath yielded 0.21 g (12%) of **10a** as a yellow solid, mp 347-349°.

Anal. Calcd. for $C_{18}H_{18}N_8S_2 \cdot 2HCl$ (483.4): C, 44.7; H, 4.17; N, 23.2; S, 13.3; Cl, 14.8. Found: C, 44.7; N, 4.25; N, 22.9; S, 12.9; Cl, 15.1.

Benzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dicarboxaldehyde Bis[3-thio-4-(α,α,α-trifluoro-*m*-tolyl)]semicarbazone (**10b**).

A solution of **8** (0.3 g, 1.2 mmoles) and thiosemicarbazide (0.6 g, 2.5 mmoles) in 5 ml of 1-propanol was treated as for **10a** to yield 390 mg (46%) of an orange solid, mp 288-291° dec. One additional recrystallization from 1-propanol gave the analytic material.

Anal. Calcd. for $C_{28}H_{18}F_6N_6S_4$ (680.7): C, 49.4; H, 2.67; N, 12.3; S, 18.8; F*, 16.7. Found: C, 49.6; H, 3.02; N, 11.9; S, 18.4; F*, 16.0. (F microanalytical determination was performed only once).

4,8-Bis-*p*-aminobenzoylhydrazinylidenemethylbenzo[1,2-*b*:4,5-*b'*]dithiophene (**10c**).

A solution of **8** (0.9 g, 3.7 mmoles) and *p*-aminobenzoylhydrazine (1.1 g, 7.4 mmoles) in 15 ml of 1-propanol was treated as for **10a** to yield **10c** (1.5 g, 79%) of a yellow powder, mp 258-262° dec.

Anal. Calcd. for $C_{26}H_{20}N_6O_2S_2$ (512.6): C, 60.9; H, 3.93; N, 16.4; S, 12.5. Found: C, 60.8; H, 4.04; N, 16.0; S, 12.7.

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