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# Reversal of the Regioselectivity of Anthrapyrazole Formation. A New Synthesis of *Losoxantrone* (DUP941)

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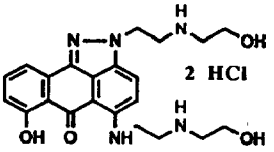
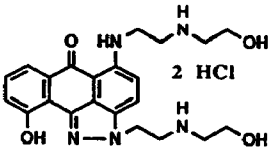
**Abstract:** *Losoxantrone*, a potent anticancer agent, has been efficiently synthesized in a 6 step process from 5-hydroxy-1,4-dichloroanthracene-9,10-dione.

*Losoxantrone* **1** is an anticancer anthrapyrazole compound which is in clinical studies. This agent has produced a good response rate in breast cancer patients, and may cause less cardiotoxicity, hair loss and gastrointestinal disturbance than doxorubicin and mitoxantrone.[1,2] There have been a number of reports on the synthesis of *Losoxantrone*.[3,4,5] All these reported processes, however, required several protection-deprotection procedures and very tedious chromatography separations. Moreover, the inaccessibility of large quantities of 2-[(2-hydrazinoethyl)amino] ethanol, which is a key reagent in previously reported processes, increased the difficulty of producing *losoxantrone* in large scale. Therefore, an efficient synthesis of *losoxantrone* **1** from easily accessible starting materials is necessary for commercial production of this important antineoplastic agent.

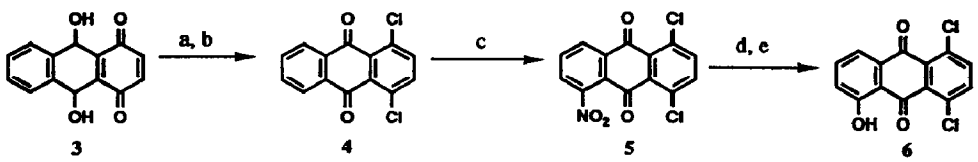



**1**




**2**

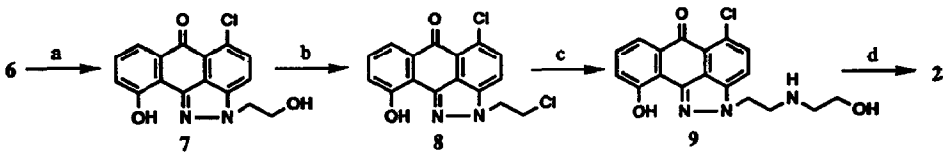
The first synthetic approach to *losoxantrone* began from 5-hydroxy-1,4-dichloroanthracene-9,10-dione **6** and 2-hydroxyethylhydrazine. The anthracene-9,10-dione **6** was synthesized from leucoquinazarin by a modified procedure as outlined in Scheme1.[3]




**3** **4** **5** **6**

(a)$PCl_5$, 77%. (b) pentanol, reflux, 99%. (c) $HNO_3$, $H_2SO_4$, 67%. (d) Fe, HOAc, 70%.
(e) $HO_3SONO$, $H_2SO_4$, 97%.

**Scheme 1**

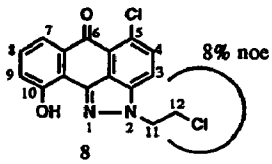


(a) 2-hydroxyethylhydrazine, 50%. (b) $SOCl_2$,90%. (c) ethanolamine, $K_2CO_3$, 80%.
(d) 2-(2-aminoethylamino)-ethanol, Py.; HCl.

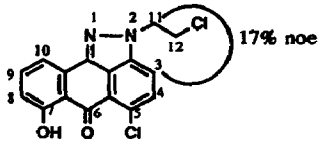
**Scheme 2**

Surprisingly, the reaction of 6 with 2-hydroxyethylhydrazine in a mixted solvent of THF and DMAc (1/1 ratio) provided the undesired 10-hydroxy regioisomer 7 as the major product (80% yield, 4/1 ratio). This isomer 7 can be isolated by crystallization (50%, 97% purity). Due to the poor solubility of 7 in a number of solvents its structure was assigned *via* the soluble derivative 8 (Table1). The nOe between the protons at positions 3 and 11 of 8 verified that the pyrazole ring was on the same side of the molecule as the hydroxyl group. Furthermore, compound 8 was converted into the regioisomer of *Iosoxantrone* (2) as shown in Scheme 2, by reaction of hydroxyethylamine to provide the anthrapyrazole 9 and amination of the anthrapyrazole 9 with 2-(2-aminoethylamino)ethanol.[2a] The regioisomer of *Iosoxantrone* (2) possesses some interesting anticancer activity but it is less potent than *Iosoxantrone*.[2a]

Table 1. $^1H$ and $^{13}C$ NMR Spectroscopic Data of 8 & 16




8

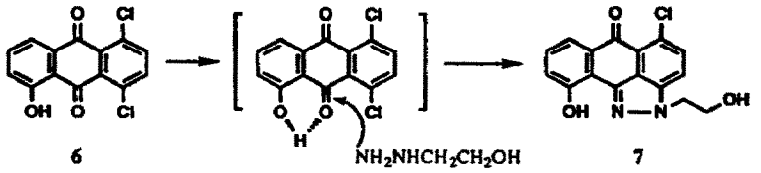



16

| Positions | $^1H$(ppm) | $^{13}C$(ppm) | $^1H$(ppm) | $^{13}C$(ppm) |
|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 |
| 3 | 8.20 | 117.4 | 8.07 | 118.8 |
| 4 | 7.76 | 131.0 | 7.59 | 131.4 |
| 5 | 0 | 127.1 | 0 | 128.5 |
| 6 | 0 | 180.4 | 0 | 187.3 |
| 7 | 7.84 | 119.9 | 0 | 163.8 |
| 8 | 7.48 | 129.1 | 6.90 | 117.9 |
| 9 | 7.37 | 120.6 | 7.57 | 136.8 |
| 10 | 0 | 153.9 | 7.41 | 113.0 |
| 11 | 5.00 | 50.8 | 4.88 | 51.0 |
| 12 | 4.20 | 44.0 | 4.14 | 43.9 |

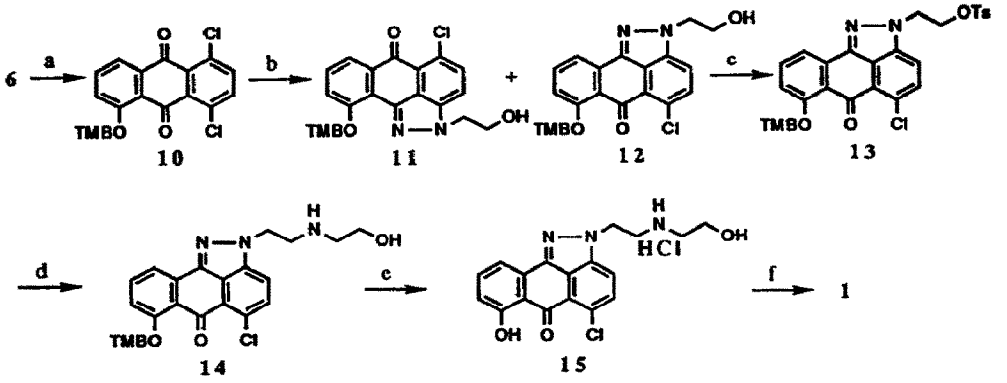
The distribution of products that resulted from reacting 6 with 2-hydroxy-ethylhydrazine was not anticipated. Apparently, the pyrazole ring was formed predominantly on the more hindered side of the anthracene ring to give regioisomer 7. This unusual regioselectivity might arise from neighboring phenolic group participation in which an intramolecular hydrogen bonding rendered the carbonyl group more electron deficient as shown in Scheme 3.

**Elimination of the hydrogen bonding by addition of different bases to the reaction medium failed to reverse the regioselectivity.**




**Scheme 3**

**In a further effort to eliminate the undesired intramolecular hydrogen bonding, the protection of the phenolic group was studied. A number of different protecting groups have been studied resulting in the choice of trimethylbenzyl chloride. Other protecting agents either gave poor yields or did not survive the conditions of hydrazine required in the next step. Reaction of 6 with trimethylbenzyl chloride[3] in the presence of cesium carbonate afforded the protected dichloro anthracene 10 in 98% yield. Condensation of 10 with 2-hydroxyethylhydrazine in the presence of diisopropylethylamine generated a mixture of the 7-trimethylbenzoxyanthrapyrazole 12 and 10-trimethylbenzoxyanthrapyrazole 11 in 85% yield and 4/1 ratio. The reaction took place predominantly from the less hindered side of the anthracene ring and produced the desired regioisomer 12 as the major product. The structure was confirmed by a strong nOe between the protons designated H3 and H11 in compound 16. Since separation of 12 from 11 was extremely difficult and required costly preparative HPLC, an effective regiospecific preparation became of critical important for the success of this synthetic route.**




(a) trimethylbenzyl chloride, $Cs_2CO_3$, 98%. (b) 2-hydroxyethylhydrazine, $(i\text{-}Pr)_2NEt$, 85%.
(c) TsCl, Py., 83% isomer recovery. (d) ethanolamine, $K_2CO_3$, 91%. (e) HCl, 100%.
(f) 2-(2-aminoethylamino)-ethanol, Py.; HCl, 55%.

**Scheme 4**

After a number of studies it was discovered that 12 undergoes tosylation at a different rate than 11. When the mixture of 11 and 12 was reacted with tosyl chloride in methylene chloride in the presence of pyridine, 12 was completely converted into the tosylated product 13 while most of 11 remained. The pure 13 was obtained by crystallization from a mixed solvent of methylene chloride and methanol with 83% isomer recovery. This success provided an easily accessible route to pure 13 which is amenable to commercial preparations. Replacement of the tosylate with 2-hydroxyethylamine in the presence of potassium carbonate proceeded smoothly and afforded the desired compound 14 in 91% yield. The trimethylbenzyl protecting group was removed by treatment with HCl to give 15 in quantitative yield.[3] Nucleophilic replacement of the chloride in compound 15 with 2-(2-aminoethylamino)ethanol[3] provided *Iosoxantrone* 1 in 55% yield (Scheme4).

This new synthetic route provided *Iosoxantrone* in six steps and 28% overall yield from commercially available material 6. The key step in the synthesis is the regiospecific preparation of tosylate 13 in high yield (83%). This success coupled with other steps has provided a chromatography-free commercial process for manufacture of *Iosoxantrone*.

**Acknowledgment**

The structural assignments[6] of 8 and 16 were made with the assistance of NMR spectroscopy carried out by Dr. Greg Nemeth and Mr. Tom Scholz.

**References and Notes**

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6. 8: mp. 178-80$^0$C; $^1$H NMR (300 MHz, DMSO) δ 4.20 (2H, t, J = 4.8 Hz), 5.0 (2H, t, J = 4.8 Hz), 7.37 (1H, dd, J = 8.0 & 1.5 Hz), 7.48 (1H, t, J = 7.8 Hz), 7.76 (1H, d, J = 7.9 Hz), 7.84 (1H, dd, J = 8.0 & 1.5 Hz), 8.20 (1H, d, J = 7.9 Hz), 10.06 (1H, s); $^{13}$C NMR (75 MHz, DMSO) δ 43.96, 50.75, 117.05, 117.39, 119.88, 120.57, 120.65, 123.15, 127.15, 129.12, 131.04, 133.89, 136.94, 137.66, 153.92, 180.46. 16: mp. 210-12$^0$C; $^1$H NMR (300 MHz, DMSO) δ 4.14 (2H, t, J = 4.8 Hz), 4.88 (2H, t, J = 4.8 Hz), 6.89 (1H, d, J = 8.1 Hz), 7.41 (1H, d, J = 7.7 Hz), 7.57 (1H, t, J = 8.0 Hz), 7.59 (1H, d, J = 8.8 Hz), 8.07 (1H, d, J = 8.8 Hz), 13.05 (1H, s); $^{13}$C NMR (75 MHz, DMSO) δ 43.87, 51.04, 112.99, 116.47, 117.88, 118.75, 120.03, 122.66, 128.50, 130.94, 131.40, 136.78, 137.41, 138.15, 163.84, 187.21.

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