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SYNTHESIS OF SPIN-LABELED ANALOGS OF DIHYDROXYAMINOALKYLAMINOANTHRAQUINONE

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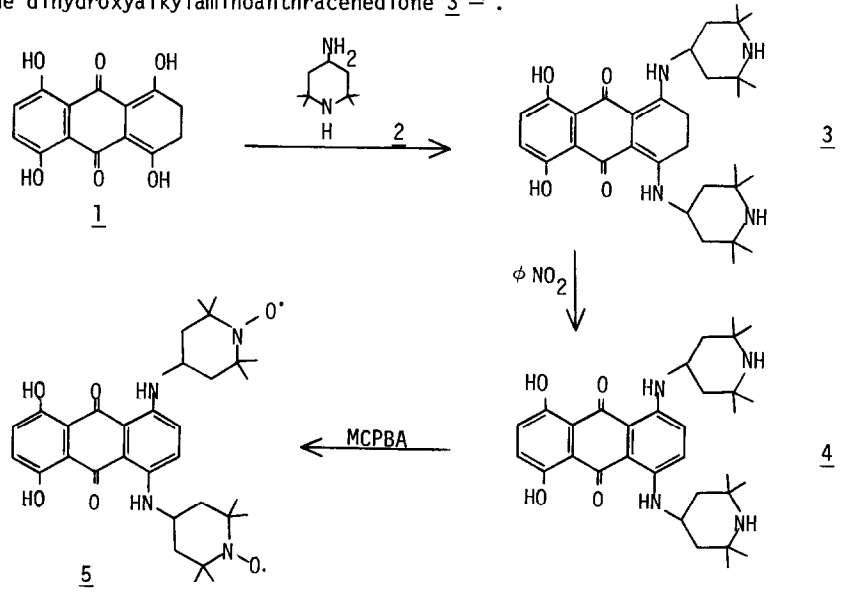
Abstract: Synthesis of spin labeled analogs of antineoplastic dihydroxyaminoalkylaminoanthraquinones is described.

Recently it was discovered that a number of substituted aminoalkylaminoanthraquinones possess outstanding antineoplastic activity in several experimental tumor systems [1,2]. The high activity of this class of compounds stimulated a large number of biological studies including interaction with nucleic acids [3], with chromosome structure and replication [4], antiproliferative activity [5] and effects on radiation therapy [6]. We have been interested in the synthesis of spin-labeled analogs of aminoalkylaminoanthraquinones. The purpose of this study is two fold: Firstly, it was intended to examine whether the nitroxide moiety would improve the antitumor activity of alkylaminoanthraquinones, since a spin labeled analog of thio-TEPA was reported to have more than five times the therapeutic ratio than the parent compound [7]. Secondly, spin-labeled alkylaminoanthraquinones will be a very attractive probe to investigate the binding interactions of this class of compounds with various biological systems.

The method for this synthesis involves the condensation of leuco-quinizarin with an aminoalkyl side chain having a tetra-substituted secondary amino group followed by the oxidation of the secondary amino group to a nitroxide. Reaction of leuco-1,4,5,8-tetrahydroxyanthracene-9,10-dione (1) (Fig. 1) with 2,2,6,6-tetramethyl-4-aminopiperidine (2) in N,N,N'N'-tetramethylenediamine gave the dihydroxyalkylaminoanthracenedione 3 [8].

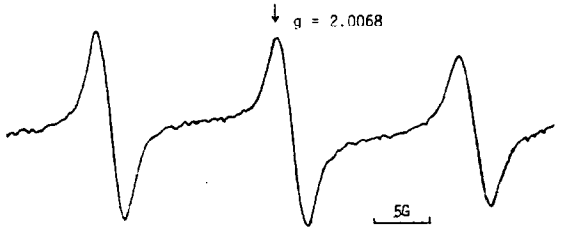
Fig. 1



Oxidation of 3 in the presence of air did not yield the aromatized product 4 in appreciable yield. The oxidation was successfully carried out in the presence of nitrobenzene. The anthraquinone derivative 3 on heating with nitrobenzene at 200-200° for 30 minutes yielded the aromatized product 4, which was purified by crystallization from ethanol, m.p. 286-288° (dec). Uv λ max (MeOH): 240 (ε 46,300) 272 (14,500) 620 (21,400), and 673nm (26,000). NMR ($CDCl_3$ + CD_3COCD_3): 1.2 (s, 12H, CH_3) 1.35 (s, 12H, CH_3, 1.8-2.6 (m, 18H, CH_2 and CH). 2.8-4.4 (bs, 2H, NH), 6.9-7.3 (m, 4H, Ar-H), 10.6 (bs, 1H) and 13.5δ(bs, 1H). Preliminary in vitro screening indicated that compound 4 exhibited activity against L1210 at 3.77 x 10^{-7}M.

Conversion of the sterically hindered secondary amine to the nitroxide was carried out using m-chloroperbenzoic acid. An etherial solution of 4 was oxidized using m-chloroperbenzoic acid at room temperature for two days. The product, after usual workup, was purified by column chromatography on a silica gel column followed by crystallization from ethanol-chloroform to yield 5, m.p. 279-281° (dec). Uv: λ max (MeOH):240 (ε 34,700), 278 (14,500) 570 (sh), 616 (16,800) and 670 nm (22,500)[9]. MS: 578 (M^+) and 580 (M^+ + 2).

Fig. 2



EPR spectrum of 1 x 10^{-4}M solution of spin label 5 in water containing 5% DMF

The ESR spectrum of compound 5 (Fig. 2) gave a three line spectrum characteristic of a nitroxide. A binitroxide could give a three line pattern or a five line pattern of varying peak size, depending on the interaction between the two nitroxides [10]. In compound 5 the radical species are separated by several bonds and there is no appreciable interaction between the two nitroxides, giving rise to a three line spectrum.

Acknowledgement

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References and Notes

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