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NOVEL SYNTHESIS OF TRANS-TETRAHYDRO DIOL DIACETATES PRECURSORS OF CARCINOGENIC AZA-ARENE DIHYDRO DIOLS AND DIOL EPOXIDES

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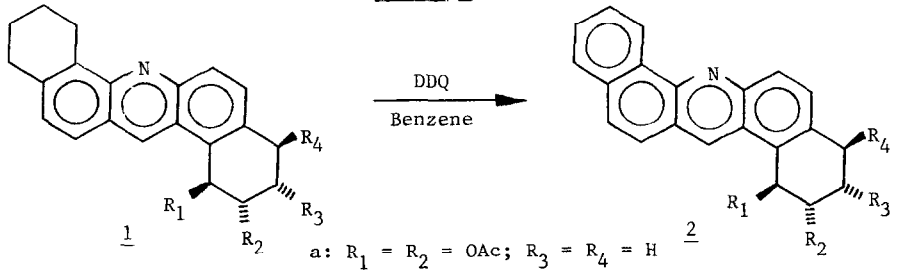
Summary: Selective dehydrogenation of trans-octahydro diol diacetates of dibenz(a,h)acridine by DDQ provides a convenient synthesis of trans-tetrahydro diol diacetates which are the valuable intermediates for the synthesis of proximate and ultimate carcinogens of dibenz(a,h)acridine.

The identification of dihydrodiols and diol epoxides as activated metabolites of benzo(a)pyrene and other arenes[1,2] has stimulated considerable research interest in the analogous derivatives of aza-arenes which are also environmental contaminants[3,4]. The most appropriate intermediates for the synthesis of these metabolites are trans-tetrahydro diol diacetates analogous to 1a and 1b. Although, general approaches for the synthesis of trans-tetrahydro diol diacetates of aza-arenes have recently been developed[5-12], the key problem is the availability of the corresponding tetrahydro aza-arenes which are the potential starting materials of these trans tetrahydro diol diacetates. We have recognized this problem in the synthesis of 1,2,3,4-tetrahydrodibenz(a,h)acridine which could be a useful intermediate for the synthesis of trans-1,2-diacetoxy-1,2,3,4-tetrahydrodibenz(a,h)acridine 2a and trans-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz(a,h)acridine 2b.

We now wish to report a novel approach which requires selective dehydrogenation of trans-1,2-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz(a,h)acridine 1a and trans-3,4-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz(a,h)acridine 1b to the corresponding tetrahydro diol diacetates 2a and 2b by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 1). Trans-octahydro diol diacetates 1a and 1b can conveniently be synthesized from easily available 8,9,10,11-tetrahydro-

Scheme 1



1 2

a: $R_1 = R_2 = OAc$; $R_3 = R_4 = H$

b: $R_1 = R_2 = H$; $R_3 = R_4 = OAc$

dibenz(a,h)acridine[13] using analogous procedures described for the synthesis of similar derivatives of benz(a)acridine[8]. In a typical experiment, 1b (0.6 g) was dissolved in 20 ml of freshly distilled benzene (CaH_2) and then a solution of DDQ (1.2 g) in 40 ml of dry benzene was added. The mixture was refluxed under argon atmosphere for 4 hrs., cooled and poured on to a small column of neutral alumina. The product was eluted with CH_2Cl_2-EtOAc (9 : 1). Distillation of solvent resulted a crystalline solid that was recrystallized from EtOAc to give 260 mg (48%) of 2b, mp[14] 229-230°:nmr (270 MHz, $CDCl_3$) H_3 5.34 (m), H_4 6.27 (d) and H_8 9.49 δ (m) with $J_{3,4}$ = 5.3 Hz. Similarly, selective dehydrogenation of octahydro derivative 1a produced 2a of mp[14] 229-30° (EtOAc): nmr (270 MHz, $CDCl_3$) H_1 6.70 (d), H_2 5.39 (dd) and H_8 9.48 δ (m) with $J_{1,2}$ = 3.0 Hz. We failed to isolate any detectable amounts of products in which 1,2,3,4-tetrahydrobenzo-ring of 1a, 1b, 2a or 2b is aromatized. The strong resistance for the aromatization of 1,2,3,4,-tetrahydrobenzo-ring of 1a and 1b by DDQ is conceivably due to the steric hindrance caused by the substituents present in this ring system. The use of DDQ in selective dehydrogenation of similarly substituted octahydro arenes and aza-arenes is under investigation in our laboratory.

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14. All the intermediates and products gave the expected NMR spectra. When melting points are given, the indicated compound gave expected mass spectra and/or combustion analyses within 0.5% for C, H, and N.

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