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STEREOSELECTIVE SYNTHESIS OF 1,8- AND 1,5-DIKETO-TRANS-SYN-TRANS-PERHYDROANTHRACENES

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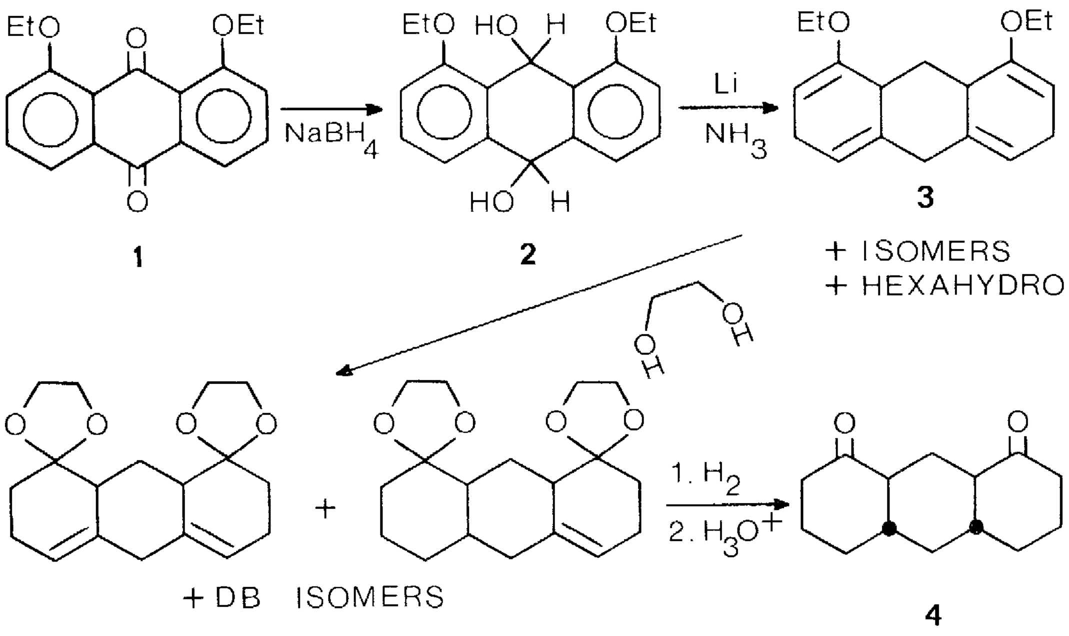
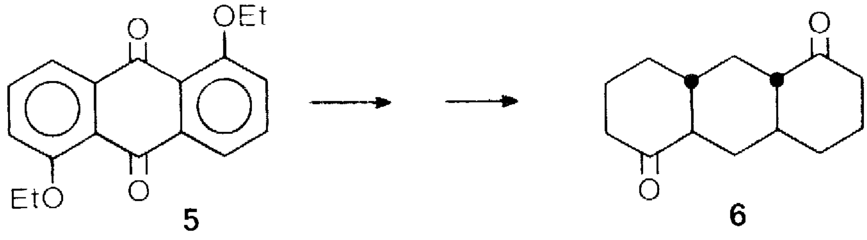
Abstract: A stereoselective conversion of 1,8- and 1,5-diethoxy-9,10-anthraquinone to 1,8- and 1,5-diketo-trans-syn-trans-perhydroanthracenes by successive sodium borohydride, metal-ammonia, and catalytic reductions is described.

Much current research deals with the development of annelating reagents and methodology of construction for fused carbocyclic ring systems from more simple starting materials.[1] Complementary to this task is the need to synthesize properly functionalized alicyclic polycondensed systems of well defined stereochemistry from readily available starting materials by non-annelative synthetic methods. Incorporation of a carbonyl group by the latter strategy is highly desirable, because this functionality plays a pivotal role in many annelation sequences, and may lead therefore to a successful combination of the two methodologies. Additionally, we felt that creation of bifunctionality in such polycyclic systems would enhance the scope and versatility of further ring annelations. These objectives were realized by the stereoselective formation of aliphatic linearly annelated tricyclic diketones from dialkoxy-9,10-anthraquinones. In this paper we report on this transformation starting with 1,8- and 1,5-dialkoxy-9,10-anthraquinones, two of the most accessible anthraquinone derivatives, and readily prepared from inexpensive commercially available materials. The use of these peri-alkoxy quinones offers considerable advantage over other alkoxy derivatives. Indeed, their transformation into alicyclic ketones, outlined below, creates two centers for epimerization at two different ring junctions of the tricyclic systems; furthermore, they lead to a structural type of ketone, for which very few conventional annelation methods are available.[1]

Conversion of alkoxy substituted aromatic compounds to cyclic enones by alkali metal-ammonia reduction has found widespread use in steroid chemistry,[2] but remains virtually unexplored in other alkoxy substituted fused aromatic systems[3] and to our knowledge Birch reduction of peri-alkoxyanthracenes has not been reported. The facile reduction of the central ring of anthracene by alkali metals is however well documented.[3] This led us to conclude that fully aromatic peri-alkoxyanthracenes, not readily available in large quantities, were not required for the conversion of the alkoxy substituted rings to cyclic enones, but could be substituted in our synthetic scheme by their 9,10-dihydro derivatives. The first task at hand was therefore the conversion of peri-alkoxyanthraquinones to derivatives suitable for metal-ammonia reduction. This was readily accomplished by sodium borohydride reduction of the quinones to give peri-alkoxy 9,10-dihydroanthracenediols (e.g. 2), a reaction discussed in detail elsewhere.[4] These dihydrodiols may be used directly in the metal-ammonia reduction, because benzylic alcohol groups are readily eliminated under these reaction conditions to give the required peri-dialkoxy 9,10-dihydroanthracenes.[5]





Thus, reduction of 2[6] with lithium (30 eq.) in anhydrous ammonia and tetrahydrofuran with t-butyl alcohol as added proton source[7] effected elimination of the alcohol groups and reduction of the aromatic moieties. Traditional work-up gave an oily product, virtually free from unreacted aromatic products. Its infrared spectrum displayed pronounced absorptions at 1710 and 1665 cm^{-1}, indicative of the presence of the anticipated tetrahydro derivative 3 (m/e 272), but also showed a peak at m/e 274 of nearly equal intensity; further over-reduction was indicated by a peak at m/e 276. A substantial amount of hydrogenolysis of the ethoxy group was evidenced by peaks at m/e 228 and m/e 230. The ^1H NMR ($CDCl_3$) showed vinyl ether and vinyl protons centered at δ 5.58 and 4.60, but was of little further diagnostic value, in view of the complexity of the crude reaction product revealed in the mass spectrum. The absorption at δ 5.58 is indicative of the presence of the trisubstituted vinyl ether moiety; tetrasubstituted vinyl ethers may also be present, but this could not be ascertained due to the unreliable ratio of the different vinyl protons as a result of over-reduction. Despite numerous attempts, we were not successful in separating the crude reaction mixture. Traditional unmasking of the vinyl ether functionalities led to an equally complex mixture of products, and was not further pursued.

The complexity of the crude reaction product would be greatly reduced if the degree of unsaturation resulting from Birch reduction of the dihydrodiols could be equalized. We accomplished this by ketalization (BF_3-etherate, THF, ethylene glycol) of the vinyl ethers present in the crude reaction product, followed by catalytic hydrogenation (Pd/C, ethyl acetate) of the carbon-carbon double bonds. The resulting mixture of saturated mono- and diketals (mass spectrum) could not be purified and was therefore hydrolyzed (10% HCl, ethyl acetate, R.T.) as received. Traditional work-up gave an oily product, from which diketone 4 was precipitated by trituration with ethyl acetate. Final recrystallization from ethyl acetate gave highly crystalline, analytically pure 4, mp 206-207°, obtained in 10-15% overall yield based on the starting ethoxyanthraquinone. [Anal. Calcd for $C_{14}H_{20}O_2$: C,76.33; H, 9.15. Found: C, 76.52; H, 9.32. Infrared (Nujol) : CO at 1710 cm^{-1}. Mass spectrum: m/e 220] The ^1H NMR ($CDCl_3$) showed a very complex pattern, containing a large number of peaks between δ 4.16 and δ 1.66 and was largely uninformative. The stereochemistry of the ring junctions in 4 was determined by conversion of the diketone into perhydroanthracene, whose five possible isomers have been adequately characterized.[8] This transformation (thioketalization, Raney nickel desulfurization) was carried out under reaction conditions that did not lead to epimerization in closely analogous systems.[9] The crystalline product thus obtained gave an infrared spectrum identical to the published one for the trans-syn-trans isomer.[8] The trans-syn-trans stereochemistry of 4 was further confirmed by its proton decoupled ^{13}C NMR spectrum ($CDCl_3$ or C_6D_6), which displayed the expected number of eight lines. It was also noted that a small amount (1-2%) of another isomer, also showing an eight line spectrum, was present. Its identity has not yet been established.

Conversion of 1,5-diethoxy-9,10-anthraquinone 5 to 1,5-diketoperhydroanthracene 6 was carried out by the same strategy and showed the same complexities as those outlined earlier for the 1,8 derivative. Hydrolysis of the crude mixture of ketals gave the desired ketone 6, which was however contaminated by a significant amount of α,β -unsaturated ketones (ir, mass spectrum), which could not be removed by conventional separation techniques. The crude ketone mixture was therefore reduced (Li-ammonia, t-butyl alcohol), and the reaction product reoxidized with Jones reagent. Recrystallization from ethyl acetate gave analytically pure 6, mp 226-227° [Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.46; H, 9.10]. Its stereochemistry was established as trans-syn-trans, on the basis of its conversion to trans-syn-trans and was confirmed by the expected number of seven lines, observed in its proton decoupled ^{13}C NMR spectrum ($CDCl_3$). No other isomers could be detected.

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References and Notes:

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5. These dihydroanthracenes may be isolated in nearly quantitative yield when the reduction is carried out in the presence of ethanol (see Ref. 4).
6. The methoxy derivatives are essentially inert, due to their very low solubility.
7. These reaction conditions are essentially those reported for difficult to reduce aromatic systems (Ref. 2, p. 203).
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