m), 3.00 (4 H, s), 6.98–7.40 (6 H, m); mass spectrum, *m/e* 392, 394, 396 (M^+). Anal. Calcd for $C_{18}H_{18}Br_2$: C, 54.85; H, 4.60. Found: C, 55.05; H, 4.65.

Bromination of 28a with Bromine. In the Absence of Iron Powder. To a solution of 100 mg (0.424 mmol) of **28a** in 50 mL of carbon tetrachloride was added a solution of 0.41 g (2.54 mmol) of bromine in 10 mL of carbon tetrachloride while stirring with a magnetic stirrer at room temperature. After 4 h, the reaction mixture was poured into a large amount of ice–water. The organic layer was extracted with dichloromethane. The dichloromethane solution was dried over Na_2SO_4 and evaporated in vacuo to leave a residue which was analyzed by liquid chromatography. The pure products, **43a** and **43b**, were not isolated. The structures were determined by NMR.

In the Presence of Iron Powder. To a solution of 100 mg (0.424 mmol) of **28a** and 50 mg of iron powder, in 50 mL of carbon tetrachloride was added a solution of 0.41 g (2.54 mmol) of bromine in 10 mL of carbon tetrachloride while stirring with a magnetic stirrer at room temperature. After the reaction mixture was stirred for 9 h, it was treated as described above to give 86.8 mg (37.2%) of **42**: pale yellow prisms (benzene); mp >300 °C; IR (KBr) 2940, 1580, 1545, 1430, 1360, 1250, 1205, 1020, 705, 780; NMR ($CDCl_3$) δ 2.18 (6 H, s), 2.50–3.20 (8 H, m); mass spectrum, *m/e* 550 (M^+). Anal. Calcd for $C_{18}H_{14}Br_4$: C, 39.31; H, 2.57. Found: C, 38.81; H, 2.12.

Bromination of 16b with Bromine. In the Absence of Iron Powder. To 100 mg (0.29 mmol) of **16b** in 50 mL of carbon tetrachloride was added 0.28 g (1.74 mmol) of bromine in 10 mL of carbon tetrachloride while stirring with a magnetic stirrer at room temperature. After 4 h, the reaction mixture was poured into a large amount of ice–water. The organic layer was extracted with dichloromethane. The dichloromethane solution was dried over Na_2SO_4 and evaporated in vacuo and the residue was chromatographed on silica gel, using petroleum ether for elution. The deep green crystals isolated from the eluate were recrystallized from hexane to give 164.4 mg (85.9%) of **41a**: green prisms (hexane); mp 228–230 °C (lit.[20] mp 228–230 °C). Compound **41b** was also obtained in this manner in 93% yield: deep brown prisms (hexane); mp 165–166 °C (lit.[20] mp 165–166 °C).

In the Presence of Iron Powder. To a solution of 100 mg (0.29 mmol) of **16b** and 50 mg of iron powder in 50 mL of carbon tetrachloride was added a solution of 0.28 g (1.74 mmol) of bromine in 10 mL of carbon tetrachloride while stirring with a magnetic stirrer at room temperature. After the reaction mixture was stirred for 4 h, it was treated as described above to give 110 mg (60%) of **40**: colorless plates (hexane); mp 287–288 °C; IR (KBr) 3040, 2960, 1600, 1425, 1360, 1245, 1040, 980, 870, 720 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (18 H, s), 8.90 (4 H, s); mass sppctrum, *m/e* 630 (M^+). Anal. Calcd for $C_{24}H_{22}Br_4$: C, 45.75; H, 3.52. Found: C, 45.78; H, 3.56.

Registry No. 3d, 14011-00-8; **5b**, 65276-11-1; **6a**, 67691-33-2; **6b**, 76447-56-8; **7a**, 67691-34-3; **7b**, 76447-57-9; **9b**, 76447-58-0; **10**, 76447-59-1; **11d**, 76447-60-4; **11f**, 76447-61-5; **12d**, 76447-62-6; **12f**, 76447-63-7; **13a**, 76447-64-8; **13a′**, 76447-65-9; **13b**, 76447-66-0; **13b′**, 76447-67-1; **13c**, 76447-68-2; **13d**, 76447-69-3; **13e**, 76447-70-6; **13f**, 76447-71-7; **13f′**, 76447-72-8; **13g**, 76447-73-9; **13h**, 76447-74-0; **13i**, 76447-75-1; **13j**, 76447-76-2; **13j′**, 76447-77-3; **13k**, 76466-36-9; **14a**, 76466-29-0; **14b**, 76446-96-3; **14c**, 76446-97-4; **14d**, 76446-98-5; **14e**, 76466-30-3; **14f**, 76446-99-6; **14g**, 76466-31-4; **14h**, 76447-00-2; **14i**, 76447-01-3; **14j**, 76447-02-4; **14k**, 76447-03-5; **15b**, 76447-04-6; **15c**, 76466-32-5; **15d**, 76447-05-7; **15f**, 76447-06-8; **15j**, 76447-07-9; **16a**, 76497-11-5; **16b**, 67691-35-4; **16c**, 76447-78-4; **16d**, 76447-79-5; **16d′**, 76447-80-8; **16e**, 76466-37-0; **16f**, 72523-20-7; **16g**, 76447-81-9; **16h**, 76447-32-0; **16i**, 76447-33-1; **16j**, 76447-34-2; **16j′**, 76497-62-6; **16j″**, 76447-35-3; **16k**, 76447-36-4; **18**, 98-19-1; **22a**, 76447-37-5; **22b**, 76447-38-6; **22c**, 76447-39-7; **22d**, 76466-33-6; **22e**, 76447-40-0; **22f**, 76447-41-1; **22g**, 76447-42-2; **22h**, 76447-43-3; **22i**, 76447-44-4; **22j**, 76447-45-5; **22k**, 76447-46-6; **25**, 98-06-6; **28a**, 51689-61-3; **28b**, 76447-47-7; **28b′**, 76549-93-4; **29**, 76447-48-8; **30**, 76447-49-9; **38**, 76447-50-2; **39**, 76497-10-4; **40**, 76466-34-7; **41a**, 76447-51-3; **41b**, 76466-35-8; **42**, 76447-52-4; **43a**, 76447-53-5; **43b**, 76447-54-6; 5-*tert*-butyl-8,6-dimethyl[2.2]metacyclophane, 76447-55-7; *n*-butylbenzene, 104-51-8; 2,6-di-*tert*-butyl-*p*-cresol, 128-37-0; thiourea, 62-56-6; $ClCH_2OCH_3$, 107-30-2.

Lithium Aluminum Hydride Reduction of *peri*-Alkoxy-9,10-anthraquinones

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Received May 5, 1980

The outcome of $LiAlH_4$ reduction of 9,10-anthraquinones is greatly influenced by electronegative substituents in positions peri to the carbonyl groups of the quinone. Reductions of 1,4-, 1,5-, and 1,8-dimethoxyanthraquinones proceed to the anthrone stage. The critical role of the *peri*-methoxy group is evident from the comparison with the reduction of 2,6-dimethoxyanthraquinone and the parent anthraquinone, which give dihydro diols and no anthrone. $LiAlH_4$ reduction of *peri*-diethoxyanthraquinones differs from the reduction of the *peri*-dimethoxy derivatives, and dihydro diols are formed, rather than anthrones. A similar product dependency on the peri substituent is evident from reduction of 1,8- and 1,5-dichloroanthraquinones. The former leads to 4,5-dichloro-9-anthrone, and the latter gives dihydro diol exclusively. These differences are determined by the fate of the intermediate addition products of the quinone and lithium aluminum hydride. Anthrone formation is seen as the result of a carbanionic 1,4-elimination reaction from these *meso*-dihydroanthracene derivatives. Electronic and steric effects of peri substituents on this elimination reaction are discussed.

Reduction of 9,10-anthraquinones may lead to a series of products ranging from anthrahydroquinones to *meso*-dihydroanthracenes and including the intermediate oxidation states of anthrones, 9,10-dihydro-9,10-anthracenediols, and anthracenes. These transformations may be accomplished by several different reducing systems, many of which had found widespread use before the discovery of metal hydride reducing agents. Although the reductive properties of lithium aluminum hydride toward functional groups have been exhaustively documented,[1] use of this reagent for the reduction of 9,10-anthraquinones remains virtually unexplored and has resulted in conflicting reports for its reaction with the parent compound. Reduction of 9,10-anthraquinone with lithium aluminum hydride in ether/benzene resulted in the formation of

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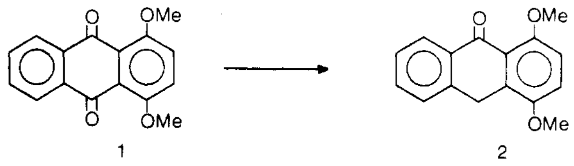
[1] H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Am. Chem. Soc.*, 88, 1458 (1966), and references cited therein.

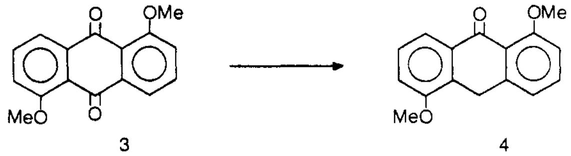
0022-3263/81/1946-1552$01.25/0 © 1981 American Chemical Society

9,10-dihydro-9,10-anthracenediol in 80% yield, obtained as a mixture of cis (75%) and trans (25%) isomers.[2] This largely overlooked report is confirmed by studies of the amount of hydride utilized in the reaction of the quinone with a solution of LiAlH$_4$ in ether, although no product isolation was carried out.[1] Introduction of the quinone with a Soxhlet extractor also gave the dihydro diol;[3,4] an earlier report, wherein anthrahydroquinone was obtained under apparently identical reaction conditions, has never been confirmed.[5] These results are at variance with the conclusion that the reduction of 9,10-anthraquinone with lithium aluminum hydride is not a clean reaction.[6] Yields obtained with this reagent are comparable with, if not superior to, other hydride reducing agents, such as lithium triethylborohydride, 9-borabicyclo[3.3.1]nonane (9-BBN),[6] and sodium borohydride. The latter has been recommended over lithium aluminum hydride for the reduction of 9,10-anthraquinones, although no experimental verification was offered.[7] On the other hand, both these reducing agents were reported to give dihydro diols in nearly quantitative yield (no experimental data).[8] Hydride reductions of substituted anthraquinones have been carried out mainly with sodium borohydride;[7] very few reductions with lithium aluminum hydride have been reported.[8] The renewed interest in the chemistry of 9,10-anthraquinones as potentially useful starting materials prompted us to investigate the synthetic utility of lithium aluminum hydride reductions of *peri*-alkoxy-substituted anthraquinones. The results of this investigation and comparison with chloroanthraquinones are presented in this paper.

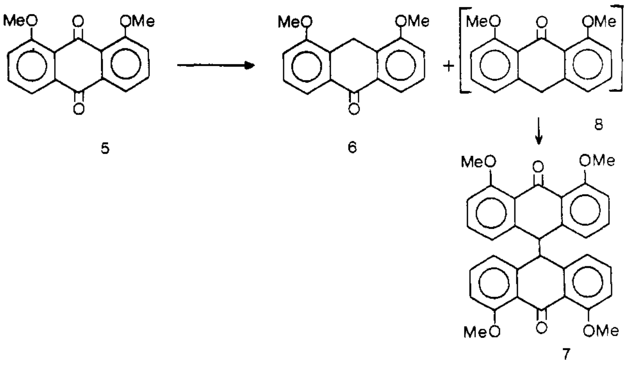
In view of the conflicting statements on the lithium aluminum hydride reduction of 9,10-anthraquinone, we decided to reinvestigate this reaction. We choose tetrahydrofuran (THF) as reaction medium, mainly because of the greater solubility of quinones in this solvent as compared to diethyl ether. Portionwise addition of an excess of LiAlH$_4$ to a solution of 9,10-anthraquinone in THF at room temperature resulted in the formation of 9,10-dihydro-9,10-anthracenediol in 85% yield. Examination of its NMR spectrum, recorded in Me$_2$SO-d_6/D$_2$O,[7] revealed it to be a mixture of cis (60%) and trans (40%) isomers, an assignment qualitatively confirmed by its infrared spectrum. This stereochemical outcome is significantly different from the one found in ether/benzene[2] with lithium aluminum hydride and from the sodium borohydride reduction, which gave nearly exclusively the cis isomer (90%).[7] That no isomerization took place under our conditions was demonstrated when the cis isomer (obtained from sodium borohydride reduction) was recovered unchanged after treatment with excess LiAlH$_4$ in THF at room temperature.



Lithium aluminum hydride reduction of 1,4-dimethoxy-9,10-anthraquinone (1) in THF, under identical reaction conditions, did not result in the anticipated dihydro diol. The reduction product was identified as anthrone 2 on the basis of its mass (*m/e* 254), infrared, and NMR (CDCl$_3$) spectra, which showed it to be present mainly in the tautomeric anthrol form. Additional structure proof was obtained from its facile conversion into the anthrol acetate upon treatment with acetic anhydride/pyridine.



LiAlH$_4$ reduction of 1,5-dimethoxy-9,10-anthraquinone (3) also proceeded to the anthrone oxidation state and gave 4 in good yield. Replacement of a carbonyl group in 1,8-dimethoxy-9,10-anthraquinone (5) by a methylene unit may lead to two isomeric anthrones. Treatment of 5 with LiAlH$_4$ gave a mixture of two products, as evidenced by the presence of two different methoxy signals at δ 4.06 and 3.85 (in approximately 3:1 ratio) in the NMR spectrum (CDCl$_3$) of the crude reduction product. Their separation was achieved by repeated fractional crystallizations from toluene. The major product, obtained as long yellow needles, was identified as anthrone 6.



Its mass spectrum showed a very prominent molecular ion at *m/e* 254; its NMR spectrum displayed a well-resolved doublet of doublets (J = 8 and 2 Hz, respectively) assigned to the 1- and 8-protons. The observed chemical shift position and coupling pattern are characteristic for protons peri to a carbonyl group.[9] The methoxy protons of 6 were found as a single absorption at δ 4.06, and the methylene protons were observed as a singlet at δ 4.18. This is indicative of the presence of the keto form, a conclusion confirmed by the absence of OH absorptions in the infrared spectrum. The second, minor product was obtained as a colorless crystalline material. Its infrared spectrum showed a strong carbonyl absorption at 1650 cm^{-1} and no OH group signal and was virtually identical with that of the major reduction product 6. Its mass spectrum showed a very weak molecular ion at *m/e* 506 and a very intense fragment at *m/e* 253. These data and a combustion analysis are in agreement with a dianthrone structure. The NMR spectrum (CDCl$_3$) did not show characteristic absorptions for protons peri to a carbonyl group, and dianthrone structure 7, derived from dimerization of anthrone 8, was therefore assigned to the minor reduction product. The methoxy groups and the methine protons were observed as sharp singlets, with the proper proton counts, at δ 3.85 and 6.2,

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(2) Y. Lepage, *Ann. Chim. (Paris)*, **13**, 1137 (1959).

(3) E. Boyland and D. Manson, *J. Chem. Soc.*, 1837 (1951).

(4) The yields quoted in ref 1 on the reduction with a Soxhlet extractor are misleading. They were apparently calculated on the total amount of anthraquinone introduced in the Soxhlet apparatus, only part of which was extracted by the solvent (see ref 3). The solvent dependency of these reductions is due to a different extent of extraction from the Soxhlet extractor.

(5) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(6) H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, **45**, 1 (1980).

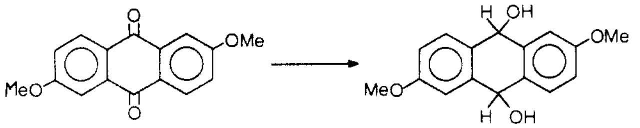
(7) T. R. Criswell and B. H. Klanderman, *J. Org. Chem.*, **39**, 770 (1974).

(8) S. J. Cristol, *Acc. Chem. Res.*, **4**, 393 (1971).

(9) J. S. Meek and L. L. Koh, *J. Org. Chem.*, **33**, 2942 (1968).

respectively, confirming the symmetrical structure of the dimerization product. Treatment of **7** with acetic anhydride/pyridine failed to give an acetate. The formation of **6** as the major reduction product of **5** is surprising, because steric effects were expected to favor reduction of the more accessible 10-carbonyl group of the quinone, as was reported for the reduction of **5** with zinc and aqueous ammonia.[10,11]

These results seemed to indicate that the presence of *peri*-methoxy groups in anthraquinones promotes formation of anthrones rather than dihydro diols. To evaluate this point further, we looked into the $LiAlH_4$ reduction of 2,6-dimethoxyanthraquinone (**9**), which lacks such *peri*-methoxy groups. Reduction of **9** under our standard conditions gave dihydro diol **10** in excellent yield, obtained as a mixture of cis (70%) and trans (30%) isomers, as evidenced by its NMR spectrum (Me_2SO-d_6/D_2O), which displayed two peaks at δ 5.41 and 5.7, respectively. No anthrone was detected.

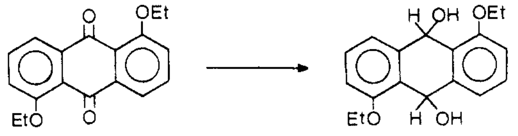


9 10

The product dependency of these reductions on the presence of *peri*-methoxy groups prompted us to investigate the effect of the ethoxy group in positions peri to the carbonyl moieties of 9,10-anthraquinones. To our surprise, lithium aluminum hydride reduction of 1,4-diethoxy-9,10-anthraquinone (**11**) resulted in the exclusive formation of dihydro diol **12**. It will be recalled that, under identical experimental conditions, the 1,4-dimethoxy derivative **1** gave anthrone **2**. Dihydro diol **12** was obtained as the trans isomer, contaminated by a small amount of the cis isomer (~5%). This stereochemical assignment was based on the infrared spectrum of **12**, which displayed a very sharp OH stretching absorption at 3520 cm^{-1}, indicative of a free hydroxyl group. The absence of hydrogen bonding has been used as a diagnostic tool for the trans isomers; the cis isomers are capable of intramolecular hydrogen bonding across the meso positions.[7,8] This sharp peak was also indicative of the absence of hydrogen bonding between an equatorial *meso*-OH and the *peri*-ethoxy group. Our assignment was further confirmed by a strong absorption at 1000 cm^{-1}, a value characteristic for such trans isomers.[7] The NMR spectrum, recorded in Me_2SO-d_6/D_2O, displayed a sharp singlet at δ 6.0, which was assigned to the trans isomer on the basis of the infrared data, and a small absorption at δ 5.91, which represented, therefore, the cis isomer.

11 12

A similar dependency of the reaction product on the nature of the *peri*-alkoxy group was also found in the $LiAlH_4$ reduction of 1,5-diethoxy-9,10-anthraquinone (**13**), which gave dihydro diol **14**, as a mixture of cis and trans isomers in a 3:1 ratio. This assignment was based once again on the infrared spectrum, which showed two distinct absorptions in the OH stretching region, a very sharp peak at 3520 cm^{-1}, and a much broader absorption at 3360 cm^{-1}. The presence of a mixture of isomers was confirmed by absorptions at 1010 (cis) and 980 cm^{-1} (trans). The NMR spectrum (Me_2SO-d_6/D_2O) displayed two sharp singlets, in the indicated ratio, at δ 5.90 (cis) and δ 5.98 (trans). $LiAlH_4$ reduction of 1,8-diethoxy-9,10-anthraquinone (**15**) also proceeded to the dihydro diol stage to give **16**, obtained as a mixture of isomers, as evidenced by its infrared spectrum (broad OH absorption centered at 3390 cm^{-1} and peaks at 1040 and 980 cm^{-1}) and NMR spectrum, recorded in Me_2SO-d_6/D_2O (four singlets at δ 6.61, 6.40, 5.88, and 5.50 in a ratio of 8:3:8:3). Although a stereochemical assignment is made difficult by the nonequivalence of the 9,10-*meso*-protons, we believe the major isomer to be the trans, on the basis of a comparison of chemical shift positions of known pairs of dihydro diols, wherein the trans isomer uniformly absorbs downfield from the cis isomer.[7]



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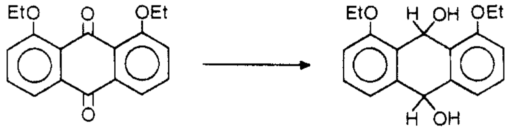
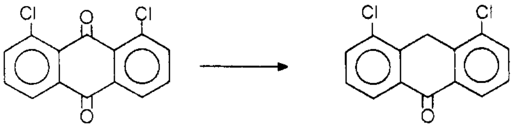


15 16

These results confirmed the critical role of peri interactions in determining the outcome of lithium aluminum hydride reductions of alkoxyanthraquinones. In order to evaluate electronic effects of the peri substituent, we turned to reductions of chloroanthraquinones. Reduction of 1,8-dichloro-9,10-anthraquinone (**17**) under our standard conditions gave anthrone **18**, identified by its NMR spectrum.[9] Treatment of 1,5-dichloro-9,10-anthraquinone (**19**) with $LiAlH_4$ in THF gave dihydro diol **20** in 90% yield. Although a reduction time of 20 days has been reported for this conversion,[12] we found no such unusual sluggishness. Dihydro diol **20** was identified as the trans isomer, based on spectroscopic data and by comparison with a sample obtained from **19** and sodium borohydride.[7]



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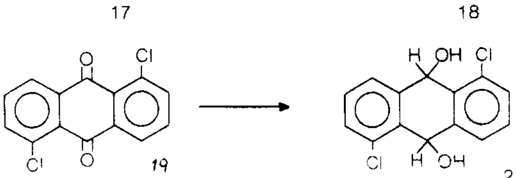

19 20

Reductions of monosubstituted anthraquinones (1-chloro-, 1-methoxy-, and 1-ethoxy-9,10-anthraquinone) proceeded much less cleanly. In each case anthrone formation was observed; their separation from substantial amounts of recovered starting anthraquinone could not be achieved.

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(10) G. F. Attree and A. G. Perkin, *J. Chem. Soc.*, 144 (1931).

(11) We were unable to confirm this observation. In our hands reduction of **4** with zinc–aqueous ammonia gave 1,8-dimethoxyanthracene [mp 198 °C: D. W. Cameron and P. E. Schütz, *J. Chem. Soc. C*, 2121 (1967)], together with small amounts of 1,8-dimethoxy-9,10-dihydroanthracene, as evidenced by the NMR and mass spectra.

(12) S. J. Cristol, W. Barasch, and C. H. Tieman, *J. Am. Chem. Soc.*, 77, 583 (1955).

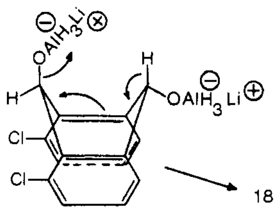
Discussion

Our results indicate that lithium aluminum hydride reduction of 9,10-anthraquinones is a far more complex reaction than generally believed on the basis of the behavior of the parent compound and its simple derivatives. The presence of electronegative substituents in positions peri to the carbonyl groups of the quinone plays a decisive role in $LiAlH_4$ reductions, as is most clearly seen by comparing the methoxy- and ethoxyanthraquinone series. Introduction of methoxy groups in peri locations invariably results in the formation of anthrones, a reaction pathway not observed previously in hydride reductions. Incorporation of methoxy groups away from the carbonyl moieties, as in 2,6-dimethoxyanthraquinone (**9**), has no special effect, however, and leads to the dihydro diol stage (**10**), as was the case for the parent compound. Introduction of two ethoxy groups on the other hand, in any combination of peri locations, totally inhibits anthrone formation, and dihydro diols are formed exclusively. A more subtle competition is at hand in *peri*-dichloroanthraquinones. Anthrone formation is observed for 1,8-dichloroanthraquinone, whereas dihydro diol **20** is the only product obtained from $LiAlH_4$ reduction of 1,5-dichloroanthraquinone.

The observed product dependency on the peri substituents is the result of their electronic and steric interactions. These effects, although undoubtedly operative in the starting anthraquinone, exert their decisive influence on the primary addition products of the quinones and lithium aluminum hydride. The central ring in such 9,10-dihydroanthracene-9,10-bis(lithium oxyaluminum hydride) derivatives is in a boat form, wherein steric interactions between equatorial positions and neighboring peri groups are very pronounced.[8] The outcome of $LiAlH_4$ reductions of anthraquinones is thus determined by the fate of these alkoxyaluminum hydrides. Their conversion into anthrones,[13] before aqueous workup, requires elimination of one alkoxyaluminum hydride moiety, a process reminiscent of elimination reactions in $LiAlH_4$ reductions of amides.[14] This leads to lithium anthroxyaluminum hydrides, which in the nonprotic reaction medium are essentially inert to further reduction. Their hydrolysis during workup gives the tautomeric anthrones. When such elimination reactions are not possible, for electronic or steric reasons, traditional isolation procedures will, of course, give dihydro diols.

The tendency of many *meso*-dihydroanthracenes, including 9,10-dihydro-9,10-anthracenediols, toward elimination is well-known. Syn and anti eliminations of trans isomers as well as eliminations from cis isomers are possible, and these have been studied extensively in a search for 1,4 conjugate elimination reactions.[8] Kinetic data, deuterium exchange, and isomerization reactions strongly support carbanionic intermediates for base-promoted eliminations. Attack of base on axial meso protons is favored for steric and electronic reasons.[8] In the case at hand, such attack is clearly hindered by the presence of negatively charged alkoxyaluminum hydride moieties on the meso positions and is, in fact, not possible for the intermediates obtained from $LiAlH_4$ reductions of anthraquinones lacking electronegative peri substituents. This was confirmed by the absence of isomerization of *cis*-9,10-dihydro-9,10-anthracenediol upon treatment with $LiAlH_4$ (see above).

The reduction behavior of dichloroanthraquinones permits an evaluation of the electronic effect of the peri substituent on these 1,4-elimination reactions. The formation of anthrone **18** from 1,8-dichloroanthraquinone requires proton abstraction from the 10-position (away from the chlorine atoms) in the intermediate addition product **21**. Although this preference for the 10-proton may be sterically controlled (9-proton is in an equatorial position for the favored conformation of the trans isomer **21**), a comparison with the intermediate **22**, obtained from $LiAlH_4$ reduction of 1,5-dichloroanthraquinone (**19**), strongly points to an electronic effect in favor of base attack at the 10-proton in **21**. As pointed out earlier, reduction of **19** did not result in anthrone formation but gave *trans*-1,5-dichloro-9,10-dihydro-9,10-anthracenediol (**20**). In *trans*-**22** one meso proton must therefore be axial and sterically accessible to base attack. However, both meso protons are in the immediate vicinity of a *peri*-chloro substituent, a structural feature that inhibits proton abstraction. This electronic effect is most likely the result of repulsion between the electronegative substituent and the incoming base. A similar preference for base attack on meso-substituted 1,8-dichloro-9,10-dihydroanthracenes has been reported.[12] The effective base in our system is most likely lithium aluminum hydride, present in large excess; however, an intramolecular proton abstraction by the intermediate alkoxyaluminum hydrides is sterically possible in trans isomers (e.g., **21**) and cannot be ruled out.



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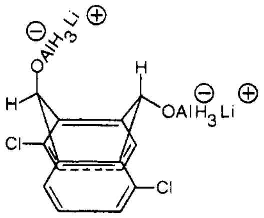

22

A more complex situation is at hand in *peri*-dialkoxy-9,10-anthraquinones. The formation of anthrones is indicative of the activating effect of a *peri*-methoxy group compared to hydrogen. Base attack at the meso position flanked by the electronegative substituent is not hindered, as was the case for the dichloro derivatives (compare 1,5-dichloro- and 1,5-dimethoxyanthraquinone). The formation of anthrone **6** as the major reduction product from 1,8-dimethoxyanthraquinone, which formally represents reduction of the most crowded carbonyl, may be seen as the result of preferential proton abstraction at C-10 in the intermediate addition product **23**. As illustrated for the trans isomer, H-10 occupies the axial position in the most stable conformation (**23a**); its removal is favored for electronic and steric reasons. The formation of dianthrone **7**,[15] derived from anthrone **8**, would require an axial hy-

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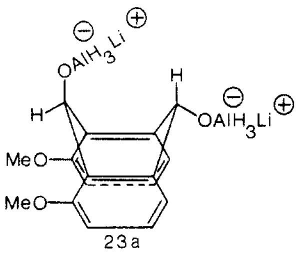
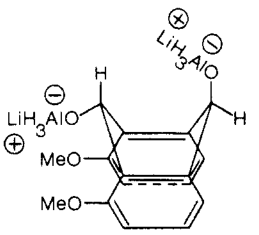
(13) It was suggested by a reviewer that formation of anthrones could be the result of an elimination reaction during workup. This would, of course, not provide more insight into the product dependency on the peri substituent, and it appears unlikely based on a comparison with $NaBH_4$ reduction of dialkoxyanthraquinones, which involves a similar aqueous workup. These reductions gave dihydro diols exclusively for the *peri*-diethoxy as well as for the *peri*-dimethoxy derivatives (N. Shyamasundar and P. Caluwe, *J. Org. Chem.*, **46**, 809 (1981)). At the suggestion of the reviewer we have carried out reduction of **5** with $LiAlD_4$ followed by aqueous workup. Mass spectral investigation of the resulting crude anthrone was indicative of the incorporation of one deuterium atom (*m/e* 255). This peak was accompanied by a smaller but significant peak at *m/e* 254, originating from nondeuterated anthrone, resulting from exchange during workup. $LiAlD_4$ reduction of **15** gave dihydro diol with incorporation of two deuterium atoms at the 9,10-positions, as revealed by the absence of absorptions due to meso protons in the NMR spectrum (Me_2SO-d_6/D_2O).

(14) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, New York, 1972, p 79.

(15) Formation of dianthrone **7** via dimerization of anthrone **8** was also observed in the acid-catalyzed[7] dehydration of 1,8-dimethoxy-9,10-dihydro-9,10-anthracenediol and is thus of no special mechanistic significance for the $LiAlH_4$ reduction of **5**.



23a



23b

drogen on C-9 (conformation **23b** for the trans isomer). This conformation is accessible from **23a** via ring inversion, which brings the 9-oxyaluminum hydride moiety into an equatorial position. Although bulky groups generally prefer an axial orientation, especially in the case of peri-substituted derivatives,[8] it is conceivable that intramolecular association of the lithium oxyaluminum hydride moiety on C-9 with the peri oxygen atoms could stabilize this conformation. The alternative would be equatorial proton abstraction from C-9 in **23a**, a process that may be facilitated by stabilization of the carbanion by complexation of its lithium counterion with the *peri*-methoxy groups. Similar considerations apply also to proton abstraction from a *cis*-*meso*-bis(oxyaluminum hydride) intermediate. We are at present in no position to differentiate between these alternatives.

The isolation of dihydro diols from $LiAlH_4$ reduction of *peri*-diethoxyanthraquinones indicates that no 1,4-elimination reactions take place in the intermediate alkoxyaluminum hydrides, most likely for steric reasons. Since *cis*-9,10-dihydro-9,10-anthracenediols are more stable than the trans isomers,[8] it was important to ascertain the stereochemistry of dihydro diols **12**, **14**, and **16**, and thus of the corresponding bis(alkoxyaluminum hydride) intermediates. Our results (see above) leave no doubt that an unfavorable configuration (cis) of the intermediates is not the determining factor in preventing 1,4-elimination reactions. Although steric hindrance to base attack at axial meso protons could still play a role in some members of this series, this effect cannot be the dominant factor in the 1,8-diethoxy derivative. Indeed, in the trans isomer, one meso proton must be axial, and this is most likely to be the 10-proton. The alternative conformation would be of much higher energy, because it would force the 9-oxyaluminum hydride moiety into an equatorial position, creating strong steric interaction with the two *peri*-ethoxy groups (stabilization of this conformation by intramolecular complexation appears unlikely on steric grounds). Base attack at the exposed axial 10-proton would be expected to be independent of the nature of the alkoxy groups on C-1 and C-8, and one would therefore anticipate no major differences in the behavior of the 1,8-dimethoxy and 1,8-diethoxy derivatives, clearly in contradiction with the experimental results. It appears more likely that the increased bulk of *peri*-ethoxy groups as compared with methoxy groups, manifests itself at the transition state leading to the expulsion of an oxyaluminum hydride moiety from the meso 9-position. This steric interference with the attainment of the transition state for removal of the leaving group could also be operative in the other isomeric diethoxy derivatives, although in these cases a distinction between this effect and steric hindrance to proton abstraction is not possible. The reduction of 1,4,5,8-tetramethoxyanthraquinone is reported to give 1,4,5,8-tetramethoxy-9,10-dihydro-9,10-anthracenediol, of undetermined stereochemistry.[16] The absence of anthrone formation in this system is most likely the result of similar unfavorable steric interactions. It has been reported that peri-substituted dihydro diols with bulky meso substituents are also resistant to base-promoted elimination reactions; the inertness of such dihydro diols was seen as the result of prohibitive steric hindrance at the final anthrone stage.[8]

Experimental Section

General Methods. NMR spectra were recorded with a Varian A-60 spectrometer using Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were obtained on Nujol mulls on a Perkin-Elmer 137 and 621 spectrophotometer. All melting points are uncorrected.[17] Microanalyses were done by Micro-Analysis, Inc. Alkoxyanthraquinones were prepared by alkylation of hydroxyanthraquinones with alkyl iodides in the presence of silver oxide.[11]

General Procedure for $LiAlH_4$ Reduction of Anthraquinones. $LiAlH_4$ (1.5 g) was added portionwise with stirring to a solution of the anthraquinone (0.01 M) in 100–150 mL of anhydrous tetrahydrofuran. After the addition was completed (5 min), the mixture was stirred under $CaCl_2$ protection at room temperature for 15 h. Excess $LiAlH_4$ was destroyed by the addition of ethyl acetate. The reaction mixture was poured into ice–water, and the product was isolated in the traditional way (ether extraction). The crude products obtained after removal of the solvent (rotary evaporator) were recrystallized from ethanol in the case of anthrones; the dihydro diols could not be recrystallized without decomposition,[2] and the crude reaction products were therefore dissolved in benzene at room temperature and precipitated with petroleum ether. The resulting products gave satisfactory NMR spectra and showed no residual carbonyl peaks in the infrared spectrum.

1,4-Dimethoxyanthrone (2). Recrystallization of the crude reduction product from ethanol gave **2** in 70% yield: mp 130–132 °C (lit.[18] mp 140–141, lit.[7] mp 127–170 °C); IR 3400–3300, 1615 cm^{-1}; NMR ($CDCl_3$) δ 10.41 (s, 9-OH), 8.91–7.41 (very complex, aromatic protons), 6.48 (s, H-2 and H-3), 3.98 (distorted s, OCH_3), 3.88 (s, methylene); mass spectrum, *m*/*e* 254. The acetate was readily obtained with acetic anhydride/pyridine; mp 122–124 °C (lit.[18] mp 125–126 °C).

1,5-Dimethoxyanthrone (4). Recrystallization of the crude reduction product from ethanol gave **4** in 65% yield: mp 238–240 °C (lit.[10] mp 181–182 °C); IR 3400–3300, 1650 (weak), 1620 cm^{-1} (indicative of a mixture anthrone–anthrol); NMR ($CDCl_3$) δ 10.16 (s, 9-OH), 8.83 (s, H-10), 8.26–6.5 (very complex, remaining aromatic protons), 4.1 and 4.05 (s, OCH_3, methylene protons of the anthrone form are overlapping with the methoxy signal; in Me_2SO-d_6 they were observed at δ 3.98); mass spectrum, *m*/*e* 254. The acetate was readily obtained upon treatment with acetic anhydride/pyridine; mp 160–162 °C (lit.[10] mp 169–171 °C).

4,5-Dimethoxy-9-anthrone (6). The crude reaction product (80%) obtained from $LiAlH_4$ reduction of **5** was dissolved in the minimum amount of boiling toluene, and the solution was left at room temperature until no new crystals appeared. The yellow needles were collected and recrystallized once again under identical conditions to give pure **6**: mp 244–245 °C (lit.[18] mp 234–236 °C); IR CO at 1650 cm^{-1}; NMR ($CDCl_3$) δ 8.21 (dd, 2, H-1 and H-8), 7.75–7.16 (m, 4, remaining aromatic protons), 4.18 (s, 2, methylene), 4.06 (s, 6, OCH_3); mass spectrum, *m*/*e* 254.

The combined filtrates were concentrated until cloudiness appeared. Toluene was added, and the clear solution was brought to room temperature. The crystalline material was recrystallized as before to give analytically pure **7**: mp 299–301 °C; IR 1650 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.0–7.16 (m, 12, aromatic protons), 6.2 (s, 2, methine protons), 3.85 (s, 12, OCH_3); mass spectrum, *m*/*e* 506 (very weak), 253 (very intense). Anal. Calcd for $C_{32}H_{26}O_6$: C, 75.87; H, 5.17. Found: C, 76.00; H, 5.14.

2,6-Dimethoxy-9,10-dihydro-9,10-anthracenediol (10): 90% yield: mp 192–195 °C; IR OH centered at 3200 cm^{-1}, 1600, 1020,

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(16) Y. Lepage, *Bull. Chim. Soc. Fr.*, 1759 (1961).

(17) There is frequently a large disparity of the melting points between published reports for 9,10-dihydro-9,10-anthracenediols and for anthrones; see ref 7 for an illustrative list of examples.

(18) K. Zahn and H. Koch, *Ber. Dtsch. Chem. Ges.*, 71, 172 (1938).

975 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 7.78–6.93 (aromatic protons, 6), 5.7 and 5.41 (H-9 and H-10, 2, indicative of a trans–cis mixture in a ratio of 30:70), 3.85 (s, 6, OCH_3).

1,4-Diethoxy-9,10-dihydro-9,10-anthracenediol (12): 90% yield: mp 112–114 °C; IR 3520 (s), 1000 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 7.86–7.38 (aromatic protons, 4), 7.08 (s, 2, H-2 and H-3), 6.0 and 5.91 (s, 2, H-9 and H-10), 4.2 (q, 4, methylene protons), 1.41 (t, 6, methyl).

1,5-Diethoxy-9,10-dihydro-9,10-anthracenediol (14): 90% yield; mp 211–215 °C; IR 3520 (s), 3360 (br), 1580, 1010, 980 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 7.58–6.98 (aromatic protons, 6), 5.98 and 5.90 (H-9 and H-10, 2, in a 1:3 ratio), 4.5–3.83 (2 overlapping q, 4, methylene protons), 1.6–1.21 (2 overlapping t, 6, methyl protons).

1,8-Diethoxy-9,10-dihydro-9,10-anthracenediol (16): 90% yield; mp 228–230 °C; IR OH centered at 3390 cm^{-1}, 1590, 1040, 980 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 7.55–6.91 (aromatic protons, 6), 6.61, 6.40, 5.88, 5.50 (H-9 and H-10, 2, in a ratio of 8:3:8:3), 4.46–3.93 (2 overlapping q, 4, methylene protons), 1.38 (t, 6, methyl protons).

4,5-Dichloro-9-anthrone (18): 75% yield; mp 188–190 °C (lit.[19] mp 198 °C); NMR ($CDCl_3$) δ 8.30 (dd, 2, H-1 and H-8), 7.83–7.3 (m, 4, remaining aromatic protons), 4.21 (s, 2, methylene protons). These values are in agreement with published NMR data.[9]

1,5-Dichloro-9,10-dihydro-9,10-anthracenediol (20) was obtained in 90% yield: mp 215–216 °C (lit.[7] mp 215–220 °C); IR OH centered at 3200, 980 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 7.83–7.5 (aromatic protons, 6), 5.90 (s, 2, H-9 and H-10).

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Registry No. 1, 6119-74-0; 2, 50259-94-4; 2 acetate, 76403-00-4; 3, 6448-90-4; 4, 76403-01-5; 4 acetate, 76403-02-6; 5, 6407-55-2; 6, 76403-03-7; 7, 76403-04-8; 9, 963-96-2; *cis*-10, 76403-05-9; *trans*-10, 76403-06-0; 11, 75829-97-9; *trans*-12, 76403-07-1; 13, 22924-22-7; *cis*-14, 76403-08-2; *trans*-14, 76403-09-3; 15, 16294-26-1; *cis*-16, 76403-10-6; *trans*-16, 76403-11-7; 17, 82-43-9; 18, 63605-29-8; 19, 82-46-2; 20, 41187-73-9; 1,8-dimethoxyanthracene, 16294-34-1.

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[19] E. B. Barnett, J. W. Cook, and M. A. Matthews, *Recl. Trav. Chim. Pays-Bas*, 45, 68 (1926).

Synthesis of 2-Azetidinones from Serinehydroxamates: Approaches to the Synthesis of 3-Aminonocardicinic Acid

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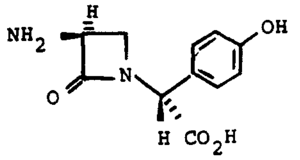
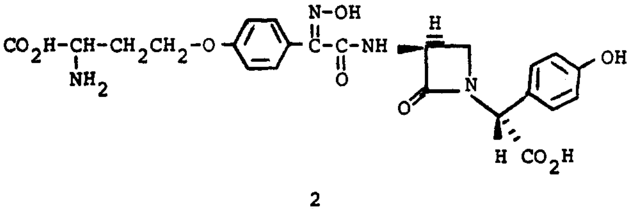
Protected forms of 3-aminonocardicinic acid (3-ANA, 1) have been synthesized in a short and efficient manner from L-serine. The serine derived *O*-benzyl hydroxamate 4 was cyclized to the 1-(benzyloxy)-2-azetidinone 5 with $Ph_3P/CCl_4/Et_3N$. N–O reduction gave the N-unsubstituted 2-azetidinone 6. While conventional methods proved unsatisfactory for the N-alkylations of 6, both phase-transfer-catalyzed alkylation and rhodium acetate catalyzed carbenoid insertion provided 3-ANA derivatives in good yield. Other alkylation methods and studies related to deprotection of the 3-ANA derivatives are also described.

3-Aminonocardicinic acid (3-ANA, 1) has been utilized as the key intermediate in the synthesis of nocardicin A (2),[1] a member of the nocardicin family of unusual monocyclic β-lactam antibiotics. Previous approaches to the synthesis of 3-ANA have used now-classical methods for the formation of the 2-azetidinone nucleus, including ketene–imine cycloaddition[2] and cyclization of β-halo amides.[3] Our approach to 3-ANA (Scheme I) relies on the efficient preparation of the N-unsubstituted β-lactam 6 from readily available, chiral starting materials, followed by subsequent alkylation of the β-lactam nitrogen.



1, 3-ANA



2

We chose as our starting material *N*-(*tert*-butoxycarbonyl)-L-serine (3). As previously reported,[4] compound 3 was directly coupled with *O*-benzylhydroxylamine in the presence of a carbodiimide. The product, 4, was cyclized to 5 with $Ph_3P/CCl_4/Et_3N$. Sequential reduction of 5 with H_2–Pd/C and $TiCl_3$[5] gave 3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (6) in 67% overall yield from 3.

A review of the literature revealed that alkylation of N-unsubstituted β-lactams on nitrogen is not consistently efficient.[6] Strong bases (NaH, $NaNH_2$, *n*-BuLi, and

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[5] Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* 1979, *45*, 410–415.

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