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PREPARATION OF DERIVATIVES OF 5-,6-, AND 8-HYDROXY-2-AMINOANTHRACENE

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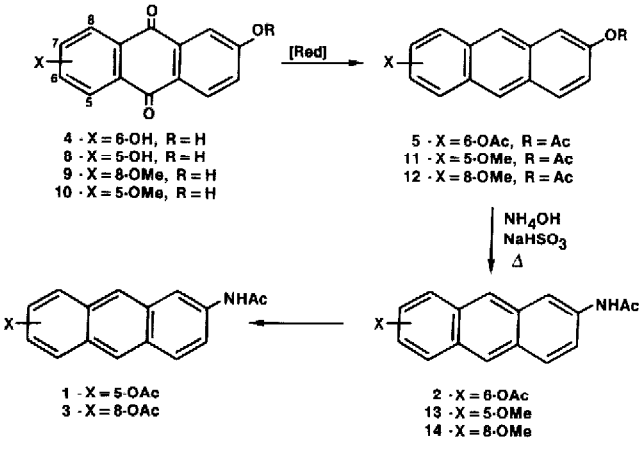
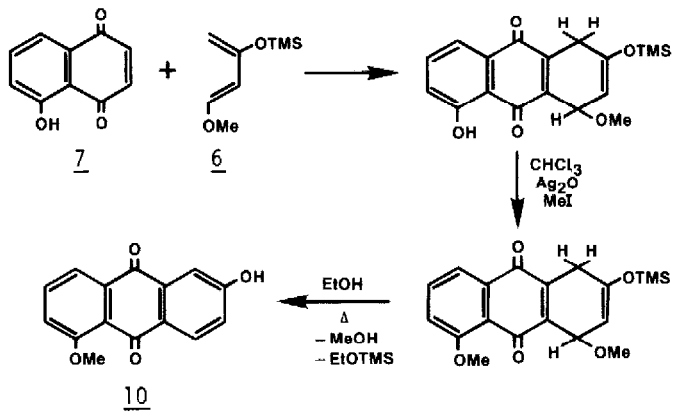
Summary. Three phenolic derivatives of 2-aminoanthracene have been prepared as their diacetyl derivatives by Bucherer-type amination of appropriately substituted anthracenes.

Since many aromatic compounds are metabolized to phenolic products[1] in mammalian systems by oxygenases such as cytochrome P-450, the need for phenols of the potent carcinogen 2-aminoanthracene in carcinogenesis research was evident. We report here the synthesis of the acetylated derivatives[2] of 2-amino-5-hydroxyanthracene 1, 2-amino-6-hydroxyanthracene 2, and 2-amino-8-hydroxyanthracene, 3. The synthetic strategy involved preparation of appropriately substituted dihydroxy- or methoxy-hydroxy-9,10-anthraquinones, reduction of these compounds to the corresponding anthracenes, and amination under Bucherer-type conditions to afford the aminohydroxyanthracene derivatives. For compound 2 the starting dihydroxyanthraquinone was commercially available as anthraflavic acid (2,6-dihydroxy-9,10-anthraquinone) 4. Reduction by the two step method of Clarke and Johnson[3] and acetylation of the product gave 2,6,-diacetoxyanthracene, 5 (42%) mp 263-265.5°C (lit.[3], mp 265-268°C). Heating this symmetrical product in a sealed tube containing concentrated ammonium hydroxide and sodium bisulfite for 1 h at 135°C gave a product that, after acetylation and chromatography, yielded 2-acetylamino-6-acetoxyanthracene 2 mp 257-9°C (dec).[4]



The highly regioselective Diels-Alder reactions between Danishefsky's diene,[5] 6, and both juglone, 7, and 5-methoxy-1,4-naphthoquinone were used to form the 2,5- and 2,8-disubstituted anthraquinones, 8 and 9, respectively.[6] In order to differentially methylate the 5-hydroxyl group of 8 so that later amination would yield only a 2-aminoanthracene product, the Diels-Alder adduct from reaction of 6 and 7 was methylated with CH_3I/Ag_2O in chloroform[7] before homologation in hot ethanol. The overall reaction gave 54% yield of compound 10 mp 278°C (dec).[8]



Reduction of 9 and 10 to the corresponding anthracenes posed the most formidable yield problem in the pathway. Reduction of either the 2-hydroxy-8-methoxyanthraquinone or its acetate using $NaBH_4/BF_3$-Et_2O in diglyme according to Bapat et al.[9] afforded a complex mixture of products containing only a modest amount of the desired anthracene. The method of Traxler[10] led to poor yields of anthracenes that were difficult to isolate. In both instances it appeared that the presence of a hydroxyl group hindered complete reduction because moderate yields of 2,5-dimethoxyanthracene and 2,8-dimethoxyanthracene were obtained when these methods were applied to the respective dimethoxyanthraquinones. The three step reduction of Criswell and Klanderman[11] furnished anthracenes easily isolatable as their acetates in poor yields.

A procedure entailing overreduction and back oxidation was the most consistent and convenient.[12] A diglyme solution of 9 or 10 was treated with 5-fold excess of the $NaBH_4/BF_3$-Et_2O reagent.[8] After 20 h stirring at room temperature, acidic work-up[9] and acetylation gave a crude mixture of the desired anthracene and its 9,10-dihydro congener.[13] Treatment of the crude products with excess chloranil in refluxing xylene[14] gave 11 (58%) mp 138-140[4] and 12 (70%) mp 115-117.[4]

Compounds 11 and 12 were converted to 2-acetylamino-5-methoxyanthracene 13 mp 182.5-184°C and 2-acetylamino-8-methoxyanthracene[4] 14 mp 187-189°C in 27% and 32% yields respectively. To our knowledge there have appeared no reports that have applied the Bucherer reaction to the preparation of aminoanthracenes from their hydroxy counterparts. Although application of this technique to quinolines and other hetercyclic systems has occurred,[15] extension of the reaction

from naphthalenes to anthracenes has not been described.[16] In this instance particular care was necessary to avoid destruction of product.[17]

Conversion of 13 and 14 to the desired compounds 1 and 3 was accomplished by demethylation using HBr in acetic acid followed by acetylation in Ac_2O/NaOAc. This treatment gave 1 mp 166-170°C (dec) in 45% yield[18] and 3 mp 226-8°C[18] (dec) in 48% yield.

In summary, the use of (1) diene-quinone reactions to fix isomer positions, (2) the relatively mild $NaBH_4$-BF_3-Et_2O reagent for the anthraquinone-to-anthracene reduction, and (3) the Bucherer reaction to introduce the amino function has led to the regioselective preparation of a number of aminohydroxyanthracene derivatives.

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References and notes

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3. R. L. Clarke and W. S. Johnson, J. Am. Chem. Soc., 81, 5706 (1959).

4. New compound. The IR, UV, PMR, and high resolution mass spectra were consistent with those expected.

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6. R. K. Boeckman, Jr., T. M. Dolak, and K. O. Culos, J. Am. Chem. Soc., 100, 7908 (1978).

7. The general procedure may be found in J. F. Garden and R. H. Thomson, J. Chem. Soc., 2483, (1957). The toluene was removed from the reaction solution in vacuo and the remainder treated with the methylating agent overnight.

8. Acetylation of 10 with Ac_2O/NaOAc gave 11 mp 173-174.5°C. The IR, NMR, and high resolution mass spectrum were consistent with those expected for the postulated structure.

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12. The presence of the peri-hydroxyl group appeared to promote formation of the 9,10-dihydroanthracenes. We have obtained similar results with hydroxybenz[a]anthracene-7,12-diones. W. B. Manning, G. M. Muschik, and J. E. Tomaszewski, J. Org. Chem.,44, 1661 (1979).

13. The proton NMR spectra exhibited broad singlets at about 4 ppm δ. This is expected for protons "doubly benzylic," as are the protons in the 9,10-dihydro product.
14. For a review of dehydrogenation of polycyclic aromatic compounds, see P. P. Fu and R. G. Harvey, Chem. Rev., 78, 317 (1978).
15. V. G. Pesin, A. M. Khaletskii, and I. A. Lotsmanenko, Zh. Obshch. Khim., 33, 1746 (1963).
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17. In a typical experiment 150 mg of 10 or 11, 150 mg of $NaHSO_3$, and 6 ml concentrated NH_4OH were sealed in a pyrex tube (15 x 175 mm) and heated in a 140°C oil bath for 1 h. After cooling and opening of the reaction vessel, the contents were filtered and the filtered solid acetylated with Ac_2O/NaOAc. Chromatography on Silicar (Mallinkrodt) using benzene as eluting solvent afforded the pure product.
18. New compound. The IR, UV, and high resolution mass spectra were in agreement with those expected.

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