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Improved Synthesis of 5-methylbenz(a)anthracene

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AN IMPROVED SYNTHESIS OF 5-METHYLBENZ(A)ANTHRACENE

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ABSTRACT

A revised synthesis of 5-methylbenz(a)anthracene is reported. It involves only three simple and convenient steps starting from a commercially available compound, and gives a 82% overall yield. Bromination of 5-methylbenz(a)anthracene with N-bromosuccinimide (NBS) in carbon tetrachloride furnishes 5-bromomethylbenz(a)anthracene in a 92% yield. When bromination is carried out using dimethylformamide as the solvent, 7-bromo-5-methylbenz(a)anthracene is formed as the exclusive product.

INTRODUCTION

It has been well established over a period of about sixty years that many polycyclic aromatic hydrocarbons (PAHs) are carcinogens; they are also widespread environmental pollutants (Dipple *et al.*, 1984). PAHs require metabolic activation in order to exert their biological activities, including carcinogenicity (Dipple *et al.*, 1984; Gelboin and Ts'o, 1978). It is not clearly understood why some PAHs are carcinogenic while others arenot carcinogenic.

Methylbenz(a)anthracenes (MBAs) are PAHs that have been found in cigarette smoke and in the environment (Thomas *et al.*, 1978). Among the twelve MBAs, 6-,7-,8-, and 12-MBAs were found to be carcinogenic, but the other isomers are either very weakly carcinogenic or non-carcinogenic (Newman, 1976). Investigation of why these twelve compounds exhibit different carcinogenicity requires syntheses of large quantities of all twelve compounds for detailed metabolic studies.

A simple synthetic procedure for synthesis of 5-MBA was reported by Newman (1950). It involves four steps. The first step is a Friedel-Crafts acylation of 1-methylnaphthalene with phthalic anhydride to give keto-acid *1* in 96% yield. The second step is reduction of the keto-acid to acid *2* (90%) by zinc dust in sodium hydroxide. In the third step, the acid is cyclized by concentrated sulfuric acid. In the fourth step the resulting ketone is reduced by zinc dust to 5-MBA *3*. The over-all yield of this method is 46%.

Newman's method was modified by Fu *et al.*, (1982). The keto-acid *1* was similarly prepared and was cyclized by concentrated sulfuric acid to 5-MBA-7,12-dione. Reduction of the dione by HI in acetic acid gave 5-MBA in a 96% yield. This modified procedure requires only three steps. However, the over-all yield was still low, only 51%. In this report, we describe a modified synthesis of 5-MBA and two of its ring substituted and side-chain-substituted brominated derivatives which also increases the % yield.

METHODS OF INVESTIGATION

Proton NMR spectra were recorded with a Joel WM 100 spectrometer. Mass spectra were obtained on a Finnigan Model 4023 gas chromatograph-mass spectrometer system, via solid probe insertion, by electron impact ionization at 70 ev and anion source temperature of 25 °C.

(*3*) - A Mixture of 2-(1-methyl-4-naphthyl)benzoic acid (*2*) (2.76 g, 10 mmol) and 57% HI (10 ml) in glacial acetic acid (120 ml) was refluxed for 6 hrs. After the resulting solution was poured into a sodium bisulfite solution, the precipitate was collected by filtration and washed with water. Upon purification by silica gel column chromatography and elution with hexane, 5-methylbenz(a)anathracene was obtained as colorless solid (2.6 g, 96%), mp. 156-157 °C (benzene), lit. (Fu *et al.*, 1982) mp. 156-157 °C. This compound was further confirmed by comparison of its mass and NMR data with those of an authentic sample.

(*4*) - A mixture of 5-methylbenz(a)anthracene (605 mg, 250 mmol) and NBS (45 mg, 0.25 mmol) in DMF (15 ml) was heated at reflux for 2 hrs. The precipitate, succinimide, was removed by filtration. Chromatography of the filtrate on silica gel with benzene-hexane (1:1) as eluant afforded 7-bromo-5-methylbenz(a)anthracene (736 mg, 92%), mp. 162-165 °C (Recrystallization from benzene as yellowish needles); mass spectrum: m/z 320 (M^+); NMR (acetone-d_6): 2.72 (s, 3H, CH_3), 7.4-8.3 (m, 8H, $H_{2\text{-}4,6,8\text{-}11}$), 9.04 (d,1H,$H_1$) and 9.0 ppm (s, 1H, H_{12}).

(*5*) - To a solution of 5-methylbenz(a)anthracene (605 mg, 250 mmol) in 20 ml of CCl_4 was added NBS (45 mg, 0.25 mmol) and benzoyl peroxide (10 mg). The resulting heterogeneous solution was refluxed under nitrogen for 2 hrs. Workup and column chromatography as described above followed by recrystallization with benzene afforded 5-bromomethylbenz(a)anthracene as colorless needle (704 mg, 88%), mp. 164-166 °C; mass spectrum: m/z 320 (M^+); NMR (acetone-d_6): 4.8 (s, 2H, CH_2), 7.3-8.5 (m, 8H, $H_{2\text{-}4,6,8\text{-}11}$), 8.4 (s, 1H, H_7), 9.02 (d, 1H, H_7), 9.02 (d, 1H, H_1) and 9.38 ppm (s, 1H, H_{12}).

RESULTS AND DISCUSSION

The modified method for the synthesis of 5-MBA requires only three simple steps (Fig. 1). The first two steps, synthesis of *1* and *2*, are the same as those reported by Newman. The novelty is in the last step. The acid *2* can be simultaneously cyclized and reduced to 5-MBA by HI in glacial acetic acid under reflux for 6 hours. The yield is 96%. The over-all yield of these three steps is 82%, which is much higher than the 46% yield reported by Newman, and the 51% yield reported by Fu *et al.* The 5-MBA synthesized is very pure, and can be used for biological study just after one recrystallization from benzene. The simplicity and the much higher overall yield of this improved synthesis compared to the other two known methods are ascribed to avoidance of concentrated sulfuric acid as the cyclization reagent.

Bromination of 5-MBA by NBS in dimethylformamide affords 7-bromo-5-MBA (*4*) in 92% yield. The structural assignment was based on analysis of its mass spectrum, which shows the molecular ions at m/z 320 and 322, and its proton NMR data which indicates that the resonance assigned for the proton at carbon-7 is missing. Based on perturbation molecular orbital theoretical calculation, the 7-position is the most reactive position of 5-MBA in an electrophilic aromatic substitution reaction (Dewar, 1969). Thus, the formation of 7-bromo-5-MBA is not only consistant with these calculations, but also confirms that bromination using NBS is dimethyl formamide is *via* an ionic mechanism. On the other hand, bromination of 5-MBA *via* a free radical mechanism is expected to take place at the side chain methyl group, and bromination using NBS in carbon tetrachloride is known to proceed by a free radical mechanism. Indeed, bromination of 5-MBA by

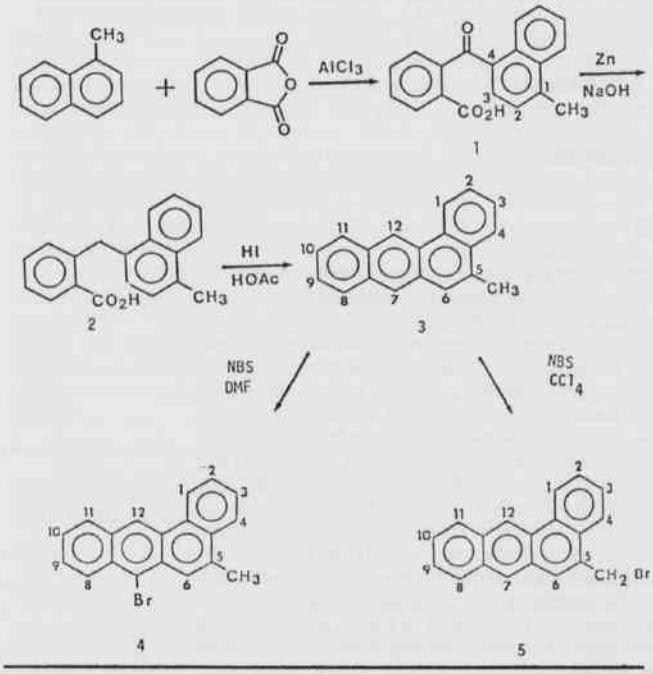

Figure 1. Synthetic scheme for 5-methylbenz(a)anthracene and its derivatives

this reagent provide 5-bromomethylbenz(a)anthracene (*5*) as the sole product, without the detection of 7-bromo-5-MBA. The structure of (*5*) was also assigned from its mass spectrum which had the molecular ions at m/z 320 and by analysis of its proton NMR data. These two bromo compounds are important intermediates for the synthesis of other 5-MBA derivatives which are useful for biological studies.

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