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IMPROVED SYNTHESIS OF 7,12-DIMETHYLBENZ[a]ANTHRACENE[1)]

Melvin S. Newman* and V. Sankaran[2)]

Department of Chemistry
Ohio State University, Columbus, Ohio 43210, U.S.A.

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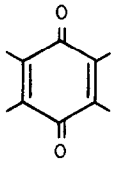
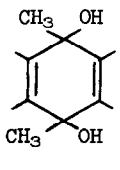
The need for 7,12-dimethylbenz[a]anthracene, 7,12-DMBA, I, and substituted derivatives thereof has increased because of studies designed to attempt to elucidate the mechanism by which I leads to the developement of malignancy in many test systems.[3)] The most frequently used synthesis is that[4)] in which 7,12-benz[a]anthraquinone, II, is reacted with a methylmagnesium halide to produce 7,12-dihydro-7,12-dihydroxy-7,12-dimethylbenz[a]anthracene, III, which is treated with hydriodic acid to yield 7-iodomethyl-12-methylbenz[a]anthracene, IV. Reduction of IV to I is readily accomplished with a variety of reducing agents and replacement of the iodine can lead to 7-substituted methyl compounds. If radioactivity labelled (in the methyl groups) compounds are desired it is important to get the yields as high as possible in each step.

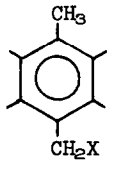
In this report we describe a superior method of converting III to I. On treatment of III[5)] with dry HCl in ethyl acetate almost quantitative conversion to 7-chloromethyl-12-methylbenz[a]anthracene, V, occurs[5,6)]. Reduction of V to I is readily accomplished[4)]. The advantages of this route are two: a, the yields of V (and compounds similar to V with various groups at different positions in the nucleus)[7)] are in general over 90%; and b, the chloromethyl compounds are much more stable than the iodomethyl analogs and can be isolated and purified easily. The chloromethyl compounds are sufficiently reactive that typical reactions, such as reduction and replacement, occur readily to afford high yields of expected products[7)].



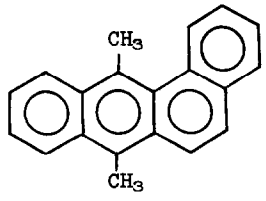
II



III



IV (X=I)
V (X=Cl)



I

We find that better yields (ca 90%) of III[5] are obtained by treatment of II (and other quinones) with methyllithium (2.2 moles per mole of II) than with Grignard reagents.

In a typical experiment dry HCl was passed slowly into a solution at 0° of 2.5 g of III in 20 ml of dry ethyl acetate to saturation. After standing at room temperature overnight the product was crystallized from benzene to yield 2.4 g of V, mp 138-140° (lit[6], mp 139-140°). Similar results have been obtained with monofluorinated, monochlorinated, and monomethoxylated quinones[7].

References

1. This research was supported by grant CA 07394 awarded by the National Cancer Institute, DHEW.

2. Postdoctoral research associates.

3. For a discussion of various hypotheses see "Carcinogenesis," Ed. R. I. Freudenthal and P. W. Jones, Raven Press, New York, 1976, Vol. I, p. 203, and references therein.

4. L. F. Fieser and R. B. Sandin, J. Am. Chem. Soc., 62, 3098 (1940).

5. This diol is mainly cis, see J. W. Cook and R. H. Martin, J. Chem. Soc., 1125 (1940). However, we have shown that trans-III works equally well (unpublished experiments by L. Fikes).

6. J. Pataki, R. Wlos, and Y. Cho, J. Med. Chem., 11, 1083 (1968). R. M. Peck, A. P. O'Connell, and H. J. Creech, ibid., 13, 284 (1970).

7. Unpublished experiments from this laboratory.