# NOTES

## [G-$^3$H]-7,12-DIMETHYLBENZ[A]ANTHRACENE 5,6-OXIDE*

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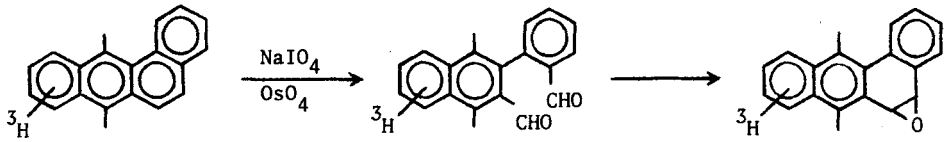
7,12-Dimethylbenz[*a*]anthracene 5,6-oxide* (II) has been detected as a metabolite [1] of the parent hydrocarbon and shown to exhibit mutagenic [2] and carcinogenic [3] activity. Covalent binding of this arene oxide to nucleic acids *in vitro* has also been demonstrated and the structures of the hydrocarbon-guanosine conjugates obtained following degradation to the nucleoside level have been elucidated [4]. However, more conclusive experimental data concerning the role of II in carcinogenesis requires radioactively labelled II.




I IIa

We report now an efficient two step synthesis of the randomly tritiated derivative IIa. The procedure is based on the osmium tetroxide catalyzed oxidation of 7,12-dimethylbenz[*a*]anthracene (DMBA) by sodium periodate reported earlier [5]. This approach is considerably shorter and more convenient than the previously described multistep syntheses of other labelled K-region oxides [6-8].

### EXPERIMENTAL

Materials and Methods: 7,12-DMBA-G-$^3$H was purchased from Amersham/Searle Corporation. The distribution of the tritium label in this compound prepared by exchange in 70% acetic acid in tritiated water catalyzed by platinum has recently been analyzed by $^3$H nmr spectroscopy [9]. Nmr spectra were obtained on a Varian T-60 spectrometer. Radioactivity was counted in a solution of 40 ml Packard Permaflucr per liter toluene on a Packard Tricarb liquid scintillation

*According to IUPAC nomenclature, compound IIa is designated 5,6-dihydro-7,12-dimethyl-5,6-epoxybenz[*a*]anthracene-G-$^3$H.

spectrometer, Model 3330.

3-(Formylphenyl-G-$^3$H)-1,4-dimethyl-2-naphthalene-G-$^3$H-carboxaldehyde (I):

To a solution of DMBA (500 mg) in dimethylformamide (6 ml) was added DMBA-G-$^3$H, 5 mCi (7.4 Ci/mmol)(molar activity = 2.56 mCi/mmol after dilution), in dimethylformamide (4 ml), acetic acid (9 ml), and water (2 ml). To the resulting suspension was added a solution of osmium tetroxide (100 mg) in benzene (0.5 ml). The solution was stirred for 0.5 hr at ambient temperature, then $NaIO_4$ (500 mg) was added in portions over a 3 hr period. A precipitate formed on stirring over-night. An additional 600 mg of $NaIO_4$ was added over the following 8 hr, and the suspension was stirred over-night again (total reaction time ≃ 44 hr). The solution was poured into 300 ml of ice water, made alkaline with sodium carbonate, and the product obtained by filtration. Crude I was dried under vacuum over $P_2O_5$ and purified by chromatography on a Florisil column (2 x 10 cm, 100-200 mesh) eluted with benzene to yield pure I (512 mg, 92%), the nmr spectrum of which was identical with that of authentic unlabelled I [8]. Tlc on silica gel in ethyl acetate-benzene (1:9) gave a single spot ($R_f$ 0.60).

[G-$^3$H]-7,12-Dimethylbenz[a]anthracene 5,6-oxide* (II): To a solution of I (249 mg, 0.86 mmol) in 10 ml of dry benzene under nitrogen was added tris-(dimethylamino)phosphine (0.15 ml, 148 mg). The resulting solution was heated at reflux for 3 hr. The solvent was then removed under vacuum, and the residue was extracted with anhydrous ether. Evaporation of the ether gave the crude product which was triturated with hexane, then chromatographed on a neutral alumina activity grade IV column (2 x 10 cm). Elution with 2% dioxane in benzene gave II (172 mg, 73%); specific activity was 7 μ Ci/mg (1.90 mCi/mmol).

## DISCUSSION

The method described provides a convenient and efficient synthesis of [G-$^3$H]-DMBA 5,6-oxide. The experimental conditions are mild, resulting in minimal net loss of the tritium label. In principal, the method should be applicable to the synthesis of other labelled K-region arene oxides.

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REFERENCES

1. Keysell, G. R., Booth, J., Grover, P. L., Hewer, A., and Sims, P., Biochem. Pharmacol. 22, 2853-2867 (1973).
2. Sims, P., and Grover, P. L., Adv. Cancer Res. 20, 165-274 (1974).
3. Flesher, J. W., Harvey, R. G., and Sydnor, K. L., Int. J. Cancer, in press.
4. Blobstein, S. H., Weinstein, I. B., Grunberger, D., Weisgras, J., and Harvey, R. G., Biochem. 14, 3451-3458 (1975); Jeffrey, A. M., Blobstein, S. H., Weinstein, I. B., and Harvey, R. G., Anal. Biochem. 73, 378-385 (1976); Jeffrey, A. M., Blobstein, S. H., Weinstein, I. B., Beland, F. A., Harvey, R. G., Kasai, H., and Nakanishi, K., Proc. Natl. Acad. Sci. USA, 73, 2311-2315 (1976).
5. Harvey, R. G., Goh, S. H., and Cortez, C., J. Am. Chem. Soc. 97, 3468-3479 (1975).
6. Harvey, R. G., and Fu, P. P., J. Label, Comp. Radiopharm. 12, 259-264 (1976).
7. Yagi, H., Dansette, P., and Jerina, D. M., J. Label. Comp. Radiopharm. 12, 127-132 (1976).
8. Grover, P. L., Forrester, J. A., and Sims, P., Biochem. Pharmacol. 20, 1297-1302 (1971).
9. Al-Rawi, J.M.A., Bloxsidge, J. P., Elvidge, J. A., and Jones, J. R., J. Label. Comp. Radiopharm. 12, 293-306 (1976).

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