Tetrahedron Letters Vol. 22, pp 1093 - 1096 0040-4039/81/0315-1093$02.00/0

SYNTHESIS OF 3-METHYLCHOLANTHRENE

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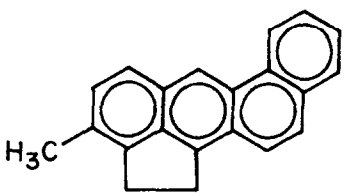
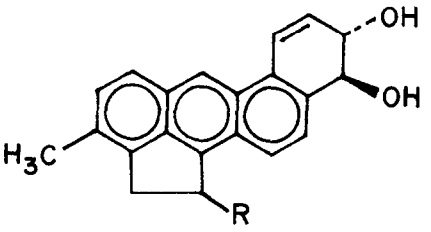
Abstract: A novel synthesis of 3-methylcholanthrene is described which is operationally simpler than the method in current use and is potentially applicable to the synthesis of a wide range of other polycyclic hydrocarbons and their oxidized carcinogenic metabolites.

3-Methylcholanthrene (3-MC) is a highly potent carcinogenic polycyclic hydrocarbon.[1] Recent metabolic studies have led to tentative identification of a dihydrodiol (1a) and/or a dihydrotriol (1b) metabolite as proximate carcinogenic forms of 3-MC.[2]

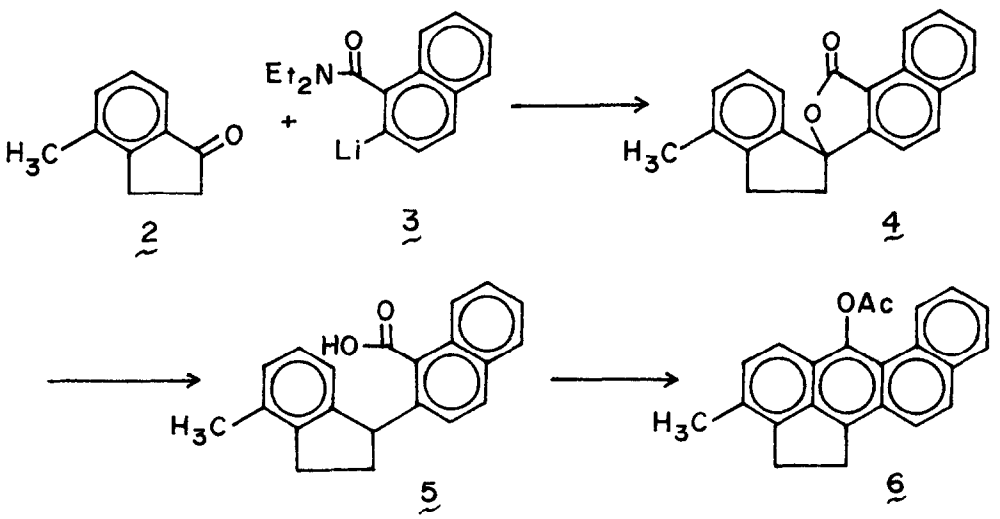


3-MC



1a: R = H; b: R = OH

We now report a novel synthesis of 3-MC which is more convenient than the method in current use[3] and is readily adaptable to the synthesis of 1a,b and other derivatives of 3-MC urgently required for carcinogenesis research. This method involves in the key step condensation of 4-methylindanone (2)[5] with the lithium salt of N,N-diethyl-1-naphthamide (3). Reaction of 2 with 3 at -60°C afforded smoothly the carbonyl addition product which underwent conversion on treatment with acid to the lactone 4. Reductive cleavage of the latter with zinc and alkali gave the free acid 5. Cyclization of 5 took place smoothly on brief treatment with $ZnCl_2$ in acetic acid-acetic anhydride to afford 6-acetoxy-3-MC (6). Reduction of 6 with hydriodic acid in propionic acid[6] provided 3-MC.

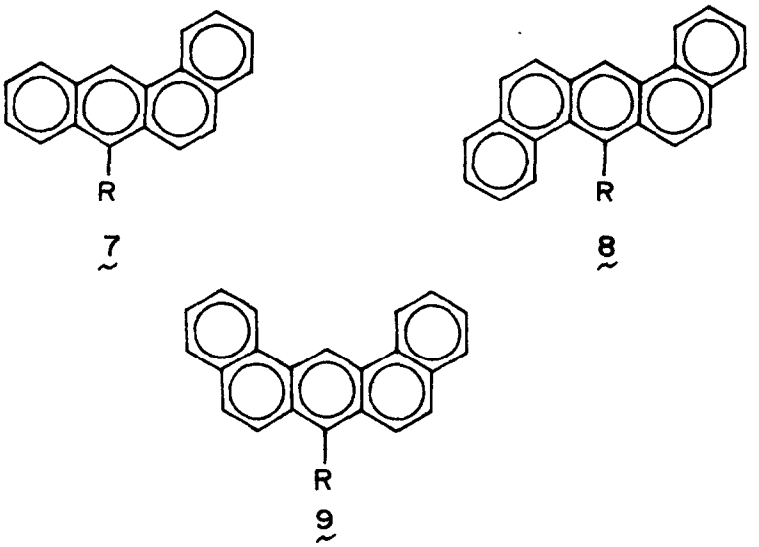


2 3 4 5 6

In a typical experiment, a solution of sec-butyllithium (22.4 mmol) was added to a solution of N,N-diethyl-1-naphthamide (4.5 g, 20 mmol) and N,N,N',N'-tetramethylethylenediamine (2.5 g, 21.5 mmol) in diethyl ether (150 ml) under argon at -60°C. After 1 hr, to this solution was added dropwise a solution of 2 (2.6 g, 22 mmol) in freshly distilled tetrahydrofuran (30 ml). The cooling was removed, and the mixture was stirred overnight. The crude product was taken up in CH_2Cl_2, methanesulfonic acid (1 ml) was added, and the solution was refluxed briefly. Workup afforded the lactone 4 (1.7 g, 30%), mp 217°C (toulene).[7] A solution of 4 (3.5 g, 12 mmol) in pyridine (50 ml) was added to 20 g of activated zinc dust[8] suspended in a solution of KOH (5 g) in 20 ml of water and 50 ml of methanol. The mixture was stirred at reflux for 2.5 hr and worked up to afford the reduced acid 5 (3.2 g, 91%), mp 218-219°C. To a solution of 5 (1.0 g, 3.3 mmol) in glacial acetic acid (20 ml) and acetic anhydride (8 ml) was added $ZnCl_2$ (60 mg), and the mixture was stirred at reflux for 20 min. Recrystallization of the product from dimethylformamide gave 6 (1.0 g, 90%). Reduction of 6 (100 mg) with HI and a slight excess of hypophosphorus acid in refluxing propionic acid[6] gave 3-MC (76 mg, 93%), mp 179-180°C (cyclohexane) (lit.[4] 178.5-179.5°C).

This synthetic approach to 3-MC is operationally simpler than the prior method[3] and potentially more general in its applicability. The starting compounds 2 and 3 are conveniently obtainable by straightforward synthesis from readily available compounds. This contrasts with the older synthetic approach which entails pyrolysis in sealed tubes and mixtures of isomeric intermediates. Yields, which were not optimized, were > 90% in all steps except the first. In other studies conducted in this laboratory this method has been employed with appropriate modification to synthesize benz[a]anthracene (7 : R = H), dibenz[a,h]anthracene (8 : R =

H), dibenz[a,i]anthracene (9: R = H), and their monomethyl derivatives (7-9: R = CH_3) in good overall yields.[9] Synthesis of 9-methoxy-3-MC, the potential precursor of 1a,b,[10] is currently in progress. Full details of these latter experiments will be reported in due course.



Acknowledgement . This research was supported by grants CA 11968 and CA 09183 and research contract CP 033385 from the National Cancer Institute, DHEW. NMR spectra were taken on a HX 270 Bruker spectrometer funded by the University of Chicago Cancer Research Center grant CA 14599.

References and Footnotes

1. International Agency for Research on Cancer: "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds", World Health Organization: Geneva, Switzerland, 1973; Vol. 3.

2. H.W.S. King, M. R. Osborne, and P. Brookes, Int. J. Cancer, 20, 564 (1977); D. R. Thakker, W. Levin, A. W. Wood, A. H. Conney, T. A. Stoming, and D. M. Jerina, J. Am. Chem. Soc., 100, 645 (1978); C. Malaveille, H. Bartsch, H. Marquardt, S. Baker, B. Tierney, A. Hewer, P. L. Grover, and P. Sims, Biochem. Biophys. Res. Commun., 85, 1568 (1978).

3. Prior to these studies, 3-MC derivatives were obtainable only through the Fieser synthesis[4] involving Elbs reaction in a sealed tube at $\sim$400°C. The need for an alternative synthetic approach to 3-MC was emphasized recently by M. S. Newman and V. K. Khanna, J. Org. Chem., 45, 4507 (1980), who cite

failure of the Elbs synthesis in the cases of 10- and 11-methoxy-3-MC and 11- and 12-fluoro-3-MC.

4. L. F. Fieser and A. M. Seligman, J. Am. Chem. Soc., 58, 2482 (1936); ibid., 57, 228, 942 (1935).

5. 4-Methyl-1-indanone (2) was prepared through a sequence involving initial alkylation of diethylmalonate with 2-bromomethyltoluene, decarboxylation of the resulting 2-(2-methylbenzyl)malonic acid at 200°C to 2-methylphenylpropionic acid, and cyclization of the latter in liquid HF to 2. The salt 3 was prepared essentially according to the method of P. Beak and R. A. Brown, J. Org. Chem., 42, 1823 (1977).

6. This method differs from the method recently reported by M. Konieczny and R. G. Harvey, J. Org. Chem., 44, 4813 (1979), in the use of hypophosphorus acid which serves to inhibit formation of iodinated side-products through reduction of the iodine formed. Reaction was conducted by addition of 2 ml of 56% HI solution and 0.5 ml of 50% H_3PO_2 solution to 6 (100 mg) dissolved in hot propionic acid, and the mixture was refluxed for 10 min. Workup is somewhat simpler for reactions with hypophosphorus acid than for those using red phosphorus.

7. All new compounds gave satisfactory microanalysis and exhibited NMR spectra consistent with the assigned structures.

8. Zinc was activated by consecutive treatment with 10% HCl, H_2O, 5% cuprammonium sulfate solution, and H_2O.

9. Starting compounds employed in place of 2 in these reactions were benzaldehyde, 1- and 2-naphthaldehyde, acetophenone, and 1- and 2-acetylnaphthalene, respectively.

10. K. B. Sukumaran and R. G. Harvey, J. Am. Chem. Soc., 101, 1353 (1979); ibid., J. Org. Chem., 45, 4407 (1980).

(Received in USA 11 December 1980)