[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND CORNELL UNIVERSITY]

Carcinogenic Hydrocarbons. I. 15,20-Dimethylcholanthrene[1]

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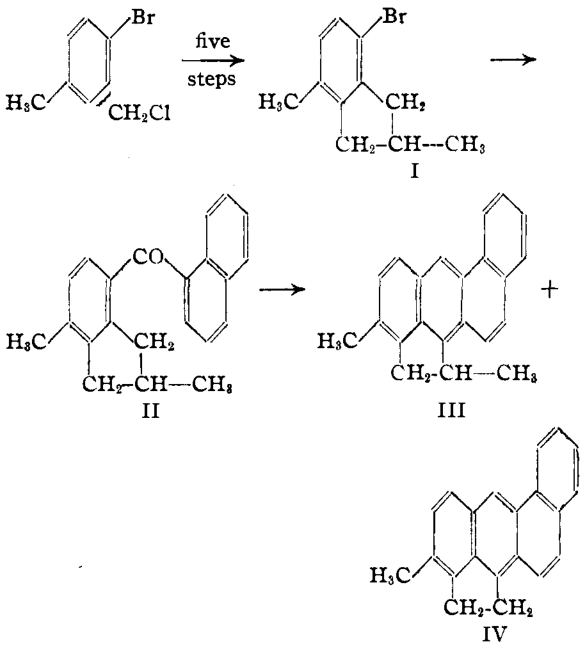
In order to study the effect of optical isomerism on carcinogenic potency, hydrocarbons related to the active carcinogenic agents cholanthrene and methylcholanthrene and possessing also a center of asymmetry are being synthesized and tested biologically. The synthesis of 16,20-dimethylcholanthrene was accomplished by Fieser and Seligman,[2] but Shear has found[3] that the average time of the appearance of tumors following the injection of the hydrocarbon into mice is about seven and one-half months, as compared with about two and one-half months for 20-methylcholanthrene. In view of this surprising increase in the time required for the appearance of tumors as a result of the added methyl group at C_{16}, it seemed desirable to investigate the effect of a methyl group in the alternate position of the five-membered ring, and consequently the synthesis of 15,20-dimethylcholanthrene (III) was undertaken.

The synthesis was accomplished using the general method of the methylcholanthrene synthesis[4] and utilizing in the initial steps a process which has been described by Bachmann, Cook, Hewett and Iball[5] in a paper published since the completion of this part of the present work. The mixture of isomers resulting from the chloromethylation of *p*-bromotoluene[4] was condensed with ethyl methylmalonate and the product was hydrolyzed, decarboxylated, and cyclized to a mixture of dimethylbromohydrindones. On Clemmensen reduction the mixture yielded pure 2,7-dimethyl-4-bromohydrindene (I). From the Grignard reagent of I with α-naphthoyl chloride, the ketone II was obtained, and on pyrolysis it yielded a mixture from which the desired hydrocarbon (III) was separated in an apparently pure condition.

After three crystallizations from propyl alcohol the substance melted at 134–136°, a value which was not changed by another crystallization.



This material was secured in very small yield; the principal part of the hydrocarbon from the pyrolysis was methylcholanthrene (IV), the formation of which involved loss of the methyl group on the carbon adjacent to the point of ring closure. This series of reactions is unsuitable for the production in quantity of either methylcholanthrene or 15,20-dimethylcholanthrene.

Experimental Part[6]

2,7-Dimethyl-4-bromohydrindone.—Since our preparation of 2,7-dimethyl-4-bromohydrindone was anticipated by Bachmann, Cook, Hewett and Iball, the steps leading to this substance may be summarized briefly. From a mixture of 2- and 3-chloromethyl-4-bromotoluenes[3] a mixture of the corresponding diethyl methylbromobenzylmethylmalonic esters was prepared (yield 83.6%, b. p. 168–170° at 1.6 mm.) and from it by hydrolysis with potassium hydroxide and acidification the malonic acid mixture (yield 95%, m. p. 163–165°, dec.) was obtained. The malonic acid mixture was decarboxylated at 170°, giving the propionic acid mixture (yield 98%, m. p. 74–76°) which was converted through the acid chloride to a mixture of hydrindones boiling at 121–142° at 1.5 mm. (yield 95%). The mixture (d^{30}_{30} 1.27) on distillation was separated rather sharply into two fractions of which one, comprising 20% of the total, boiled at 125° (1.5 mm.) and the other at 145° (1.5 mm.). The lower boiling portion ap-

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[1] Originating as a summer problem (1935) in the Converse Memorial Laboratory, Harvard University, this work was completed at the Baker Laboratory, Cornell University, and has been under the supervision of Professor Fieser.—W. F. B.

[2] Fieser and Seligman, This Journal, **57**, 1377 (1935).

[3] Shear, *Am. J. Cancer*, **28**, 334 (1936).

[4] Fieser and Seligman, This Journal, **57**, 942 (1935).

[5] Bachmann, Cook, Hewett and Iball, *J. Chem. Soc.*, 60 (1936).

[6] Semimicroanalyses by E. L. Martin and R. G. Larsen; microanalyses by W. F. Bruce.

pears to be the 2,7-dimethyl-4-bromohydrindone (b. p. 115–117° at 0.15 mm.) of Bachmann, Cook, Hewett and Iball, for like theirs it failed to crystallize. The higher boiling portion solidified and after four crystallizations from petroleum ether the 2,4-dimethyl-7-bromohydrindone melted at 81°.

Anal. Calcd. for $C_{11}H_{11}OBr$: C, 55.23; H, 4.64. Found: C, 55.25; H, 4.76.

2,7-Dimethyl-4-bromohydrindene (I).—The mixture of hydrindones was reduced by the Clemmensen method according to the technique of Fieser and Seligman. From 27 g. of hydrindone mixture 22 g. (87%) of 2,7-dimethyl-4-bromohydrindene was obtained. The substance is a colorless mobile liquid with a kerosene-like odor boiling at 104–106° (2.5 mm.).

Anal. Calcd. for $C_{11}H_{13}Br$: C, 58.66; H, 5.82. Found: C, 58.77; H, 6.14.

4-(α-Naphthoyl)-2,7-dimethylhydrindene (II).—The ketone was prepared by allowing the Grignard reagent prepared from the hydrindene to react with α-naphthoyl chloride according to the procedure of Fieser and Seligman.[8] It was advantageous in the preparation of the Grignard reagent to add a few drops of ethyl bromide to the ethereal solution of the hydrindene rather than to the initial portion only. From 10 g. of the hydrindene 4.3 g. (48%) of a light yellow oil boiling at 200° (1 mm.) was secured. Upon four crystallizations from petroleum ether rosets melting at 80–81° separated.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.9; H, 6.7. Found: C, 87.4; H, 6.6.

In addition 3.0 g. of a hydrocarbon, presumably **2,4-dimethylhydrindene,** boiling at 105–106° (25 mm.) was isolated.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.64. Found: C, 89.8; H, 9.7.

15,20-Dimethylcholanthrene.—For pyrolysis 2.5 g. of the ketone was heated for one-half hour at 405–410°. A light yellow fraction boiling at 200–210° (0.5 mm.) and weighing 0.6 g. (23.5%) was secured. This material readily formed a dark purple picrate which after three crystallizations from benzene melted at 179–180° and weighed 0.4 g. This material was washed with warm dilute ammonia to remove picric acid, leaving 0.3 g. of a pale yellow solid. This was crystallized from benzene and petroleum ether and yielded 0.25 g. of yellow solid melting at 163–165°. This was dissolved in anhydrous benzene and passed twice through a tower containing activated alumina, by which a considerable amount of dark colored material was removed. The product melting at 169–171° was sublimed in a small molecular still, by which more dark colored material was left behind, and was again crystallized from benzene and petroleum ether. The solution deposited 0.06 g. of light yellow silky needles melting sharply at 174–175° (177.5–178.5°, corr.). A mixed melting point with methylcholanthrene (177–178°, corr.) showed no depression.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.6; H. 6.4. Calcd. for $C_{21}H_{16}$: C, 93.98; H, 6.02. Found: C, 93.9; H, 6.4.

From the Elbs condensation there was obtained, in addition to this fraction, 1.1 g. of a dark red very viscous oil boiling from 240–250° at 0.5 mm. This portion formed very little picrate and failed to crystallize from petroleum ether.

From the mother liquor after the first crystallization of the picrate a second crop of crystals (0.15 g.) was secured. After three recrystallizations, the substance melted fairly sharply at 173–174°. The picric acid was removed by warm alcoholic ammonia, and the residue was purified by microsublimation. The product melted at 120–122°, and the mixed melting point with methylcholanthrene was 117–120°. After three crystallizations from propyl alcohol, the substance melted at 134–136°, mixed melting point with methylcholanthrene 120–126°. Purification involved a large loss of material since the product was more soluble than the impurity, methylcholanthrene.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.43. Found: C, 93.49; H, 6.42.

Summary

The synthesis of 15,20-dimethylcholanthrene has been accomplished by the method of Fieser and Seligman, but the yield is very low because the pyrolysis results in loss of the methyl group adjacent to the point of ring closure, giving 20-methylcholanthrene as the chief product, and 15,20-dimethylcholanthrene in smaller amount.

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