acid, and crystallising the material recovered from the organic layer from alcohol. The hydrocarbon dissolves slowly in sulfuric acid without the development of color. The picrate, when prepared from the pure hydrocarbon obtained from the disodium compound, crystallized from alcohol in bright orange needles, m. p. 126–127°.

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 93.34, 92.80; H, 7.06, 7.13. Picrate, calcd. for $C_{20}H_{18}\cdot C_6H_3O_7N_3$: N, 8.62. Found: N, 8.93.

Summary

This paper reports the synthesis of the 1′-methyl and 1′,10-dimethyl derivatives of 1,2-benzanthracene from 1-methyl-7-bromonaphthalene which in turn was prepared synthetically from bromobenzene and succinic anhydride.

1′-Methyl-1,2-benzanthracene and the known 9-isomer are of interest for comparison with the actively carcinogenic 3,4-benzpyrene on the possibility that this hydrocarbon is properly regarded as a 1′,9-disubstituted 1,2-benzanthracene. From a consideration of the problem of the bond structure of 3,4-benzpyrene in the light of recent work by Vollmann, *et al.*, it is concluded that the possibility of a relationship to 4- and 5-disubstituted chrysenes also merits investigation.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

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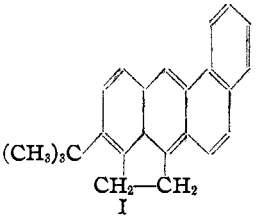
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND THE UNIVERSITY OF CHICAGO]

20-*t*-Butylcholanthrene

BY LOUIS F. FIESER AND DONALD K. SNOW

Among other aspects of the investigation of the relationship between carcinogenic activity and structure, it is of interest to study the variation in activity in a series of homologs related to a given cancer-producing agent of high potency. While the biological tests with the previously described[1] series of 10-alkyl-1,2-benzanthracenes are not yet complete, it has been found that the 10-ethyl homolog produces sarcomas less than half as rapidly as the 10-methyl compound when injected subcutaneously.[2] Bachmann, Cook, *et al.*,[3] have reported interesting results for 5-methyl-, 5-ethyl-, and 5-*n*-propyl-1,2-benzanthracene, all of which exert a carcinogenic action when applied to the skin. The parent hydrocarbon is practically inactive.

In the cholanthrene series the parent hydrocarbon is a highly potent carcinogenic agent and the 20-methyl derivative (sterol numbering system[4]) appears to be even slightly more active than cholanthrene.[3,5] Dr. M. J. Shear has found that 20-ethylcholanthrene (m. p. 179.5–180°, corr.), synthesized in unpublished work by Dr. W. F. Bruce of Cornell University, gives rise to tumors when injected subcutaneously but is much slower in its action than the 20-methyl compound. Tumors were produced in 8 of 16 mice in five months; a total of 11 tumors were obtained in one year, and the rest of the mice died with ulcers. The average time of the appearance of tumors (5 months) is just twice that found for 20-methylcholanthrene.[5]



I

We now report the synthesis of the higher homolog I by a process patterned closely after the first of the two methods developed by one of us with Seligman[6] for the synthesis of 20-methylcholanthrene. Most of the steps proceeded nearly as well as in the simpler case, but the yield in the final pyrolysis was considerably lower. A pure hydrocarbon was isolated without difficulty from the reaction mixture, however, and the analyses clearly indicate that the *t*-butyl group is still present and has not suffered elimination or degradation during the pyrolysis. Biological tests with the compound by Dr. Shear have been in progress for four months (injection technique), and in this time no tumors have been observed.

Experimental Part

Blanc Reaction.—The *p*-bromo-*t*-butylbenzene employed was prepared by brominating *t*-butylbenzene in the

(1) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).
(2) Fieser and Hershberg, *ibid.*, **59**, 2502 (1937).
(3) Bachmann, Cook, Dansi, de Worms, Haslewood, Hewett and Robinson, *Proc. Roy. Soc.* (London), **B123**, 343 (1937).
(4) Fieser and Seligman, THIS JOURNAL, **57**, 1377 (1935).
(5) L. F. Fieser, M. Fieser, Hershberg, Newman, Seligman and Shear, *Am. J. Cancer*, **29**, 260 (1937).
(6) Fieser and Seligman, THIS JOURNAL, **57**, 942 (1935).

presence of iodine catalyst according to Tchitchibabine, Elgasine and Lengold;[7] yield 63%; b. p. 228–236°. The chloromethylation proceeds more slowly than with *p*-bromotoluene[6] and, since no polysubstitution was observed in trial experiments, the reaction was conducted at a higher temperature, more catalyst was used, and a full molecular equivalent of trioxymethylene was employed.

A mixture of 304 g. of *p*-bromo-*t*-butylbenzene, 43 g. of trioxymethylene, and 200 g. of zinc chloride which had been freshly fused with 3 g. of aluminum chloride, was stirred vigorously (Hershberg wire stirrer) and treated with dry hydrogen chloride at 60–70° for eighteen to twenty hours. On extracting with ether and fractionating the combined reaction product from three runs, there was obtained 340 g. of unchanged *p*-bromo-*t*-butylbenzene and 486 g. (69%, based on material consumed) of a mixture of **2- and 3-chloromethyl-4-bromo-*t*-butylbenzene**, b. p. 120–140° at 5 mm. In early attempts to separate the constituents of this mixture about half of the product was found to distil up to 130° (6 mm.) and the remainder at 130–145° (6 mm.), but when various fractions were put through the remaining steps of the synthesis it became apparent that but little separation had been accomplished.

The Arylpropionic Acids.—The condensation of 300 g. of the mixture of chloromethyl derivatives with 600 g. of ethyl malonate and 44 g. of sodium by the procedure of Fieser and Seligman[6] gave 360 g. (81.5%) of a viscous liquid, b. p. 190–200° at 6 mm., consisting of a mixture of the bromo-*t*-butylbenzylmalonic esters. The product was hydrolyzed with barium hydroxide as described[6] and the malonic acid mixture was decarboxylated without purification. Vacuum distillation gave 132 g. (50%) of colorless crystalline solid melting at 132–134° and consisting of a mixture of **β-(2-bromo-5-*t*-butylphenyl)-** and **β-(5-bromo-2-*t*-butylphenyl)-propionic acids.**

Anal. Calcd. for $C_{13}H_{17}O_2Br$: C, 54.73; H, 6.02. Found: C, 54.77; H, 6.00.

In other experiments using high- and low-boiling fractions of the product from the Blanc reaction, samples of acid melting, after recrystallization, at 151–152° and 138–139° were obtained.

Cyclization and Reduction.—Cyclization of the arylpropionic acid mixture through the acid chloride by the process described[6] seemed to proceed less readily than with the product from *p*-bromotoluene. The use of highly purified thionyl chloride and fresh aluminum chloride is essential, but even under the most satisfactory conditions the yield of hydrindone mixture was distinctly less than in the parallel case.[6] From 108 g. of the acid mixture there was obtained after distillation 75 g. (74%) of **4-bromo-7-*t*-butyl- and 7-bromo-4-*t*-butyl-hydrindone-1** as a crystalline solid. A recrystallized sample formed hexagonal plates, m. p. 69.3–70.3°.

Anal. Calcd. for $C_{13}H_{15}OBr$: C, 58.42; H, 5.66, Found: C, 58.43; H, 5.51.

Reduction of the above product (75 g.) with amalgamated zinc in the presence of alcohol[6] gave 50 g. (70%) of **4-bromo-7-*t*-butylhydrindene**, b. p. 149–150° at 6 mm.

Grignard Reaction and Pyrolysis.—To the solution of Grignard reagent from 20 g. of 4-bromo-7-*t*-butylhydrindene a solution of 13 g. of α-naphthonitrile was added, and after refluxing the mixture to complete the reaction the complex was decomposed with dilute acid and the ketimine hydrochloride was hydrolyzed by refluxing for one hour. Vacuum distillation of the extracted product gave 12 g. (46%) of a very viscous reddish oil consisting of crude 4-(α-naphthoyl)-7-*t*-butylhydrindene. On pyrolyzing this material at 390–400° for fifteen minutes and distilling the product in vacuum an oil was obtained. Crystals were obtained on adding ligroin to a rather concentrated solution of the oil in benzene, and in all 0.9 g. (8%) of crystalline **20-*t*-butylcholanthrene** was collected in a nearly pure condition. On further crystallization from benzene–ligroin the hydrocarbon formed pale yellow opalescent plates, m. p. 204–205°, corr.

Anal. Calcd. for $C_{24}H_{22}$: C, 92.85; H, 7.15. Found: C, 92.75; H, 7.34.

The picrate forms purplish-brown needles from benzene–ligroin, m. p. 149–150°.

Anal. Calcd. for $C_{24}H_{22}\cdot C_6H_3O_7N_3$: N, 7.79. Found: N, 7.98.

Summary

20-*t*-Butylcholanthrene has been synthesized from *p*-bromo-*t*-butylbenzene by application of a general method previously described.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

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(7) Tchitchibabine, Elgasine and Lengold, *Bull. soc. chim.*, [4] **43**, 238 (1928).