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The Synthesis of 5-Hydroxymethyl-, 5-Acetoxymethyl-, and 5-Methylmercapto-7,12-dimethylbenz[*a*]anthracenes, and of 5,7,12-Trimethylbenz[*a*]anthracene†

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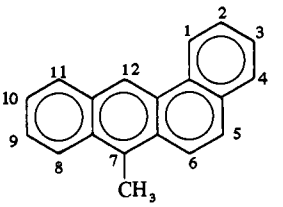
Received September 11, 1971

The evidence for assuming that the 5 position of 7-methylbenz[*a*]anthracene and 7,12-dimethylbenz[*a*]-anthracene is important in the metabolism by which these hydrocarbons induce the formation of cancer is presented. The syntheses of 5-hydroxymethyl-7,12-dimethylbenz[*a*]anthracene (**5**), 5-acetoxymethyl-7,12-dimethylbenz[*a*]anthracene (**6**), 5,7,12-trimethylbenz[*a*]anthracene (**7**), and 5-methylmercapto-7,12-dimethylbenz[*a*]anthracene (**8**) are described. Since none of these compounds is carcinogenic, they probably do not enter into the carcinogenic metabolic pathway by which 7,12-dimethylbenz[*a*]anthracene produces cancer.

Some years ago a cooperative program designed to find out more about the carcinogenic activity of 7-methylbenz[*a*]anthracene (**1**) was started by our group at Ohio State University and Drs. J. A. and E. C. Miller at the University of Wisconsin. 7-Methylbenz[*a*]anthracene (**1**) was selected because, in the laboratories of several investigators, each of whom had studied all of the monomethyl derivatives of benz[*a*]anthracene, **1** proved to be by far the most active carcinogen.[1-4] The hypothesis was proposed that **1** was the most active of all of the monomethylbenz[*a*]anthracenes because of the presence of a 7-Me group, the position in the parent aromatic hydrocarbon most easily attacked by chemical reagents.[5] It was reasoned that when a benz[*a*]anthracene is unsubstituted at the 7 position, the host is able to deactivate the compound by means of reactions which take place at that position. However, when the 7 position is blocked by Me, the compound cannot thus be deactivated. Hence, more compound may be available for reaction at another position in such a way that cancer results.‡

As one approach to find out at which position(s) metabolism leading to cancer occurred, we undertook to synthesize the 11 monofluoro-7-methylbenz[*a*]anthracenes. We reasoned that F at a position not involved in carcinogenic metabolism might not greatly affect the carcinogenic activity of **1**. However, if F were placed at such a critical position, then activity would be greatly diminished.[6,7] Furthermore, since 7,12-dimethylbenz[*a*]anthracene (**2**) is a more active carcinogen than **1**, the synthesis of monofluoro derivatives of **2** was also deemed desirable.

The explanation as to why **2** is more active than **1** is difficult to give solely in terms of our original hypothesis. Since 12-methylbenz[*a*]anthracene is carcinogenic without having a blocking group at 7 (as are 6-methyl- and 8-methylbenz[*a*]anthracenes) it may be argued that since the 12-Me group is situated at one of the meso positions of the anthracene portion of benz[*a*]anthracene somehow it helps to block the detoxifying metabolism and hence allow the compound to be present long enough for the carcinogenic process to occur. To the extent that 12-methylbenz[*a*]anthracene is carcinogenic whereas the parent hydrocarbon is not, the greater activity of **2** than **1** is explained. A further explanation for the greater activity of **2** as compared to **1** may have a steric origin. The presence of a Me group at 12 causes the molecule **2** to be more sterically crowded than **1**. Since this is undoubtedly a significant factor§ **2** is probably more reactive toward both chemical and biological reagents than **1** and the cancer-initiating reaction may be favored. This steric factor may be used to account for the carcinogenic activity of 12-methylbenz[*a*]anthracene by assuming that its cancer-producing metabolism is favored relative to the deactivation metabolism.



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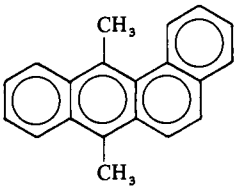

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We have prepared all of the monofluoro-7-methylbenz[*a*]-anthracenes[9-14,#] except the 11- and 12-F compounds**,†† and submitted samples for testing.‡‡ Of these, only 5-

†This work was supported by Grant CA-07394 of the National Institutes of Health.

‡Of the other monomethyl derivatives, only the 6, 8, and 12 isomers have appreciable activity. The activity of the 6- and 8-Me isomers may be explained on the basis of our hypothesis because Me groups in the peri positions adjacent to 7 would be expected to have a steric effect (see text) which would delay metabolic deactivation at the 7 positions. The activity of the 12-Me isomer is harder to explain. Probably the main reason is related to a different kind of steric effect: an effect on the whole molecule which has a much higher ground state energy due to the molecular overcrowding caused by the 12-Me group.

§See Frisch, *et al.*,[8] for a discussion of the principle involved.

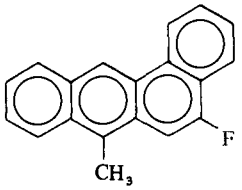
#4-F-7-methyl,[9] 9-F and 10-F-7-methyl,[10] 3-F- and 6-F-7-methyl,[11] 2-F-7-methyl,[12] and 8-F-7-methyl.[14]

**The synthesis of 12-fluoro-7-methylbenz[*a*]anthracene has been reported by Blum, *et al.*,[15] but to our knowledge no biological testing has been divulged. Dr. E. D. Bergmann (private communication) stated that he was to prepare 11-fluoro-7-methylbenz[*a*]anthracene.

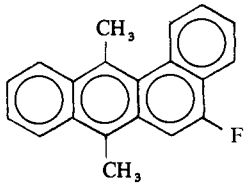
††Dr. James A. Miller has informed me that he is preparing a paper which will summarize the carcinogenic activity of a large number of halogenated (mainly fluorinated) benz[*a*]anthracenes.

‡‡All comments concerning carcinogenic activity (or lack of it) obviously pertain only to cancer induced by the techniques used by the Millers, and where pertinent, C. Huggins and coworkers.

fluoro-7-methylbenz[*a*]anthracene (3) was completely inactive.[16,17] In addition the 4-fluoro-, 5-fluoro-, and 8-fluoro-7,12-dimethylbenz[*a*]anthracenes were tested. Of these only the 5-F derivative (4) was inactive.§§,##



3



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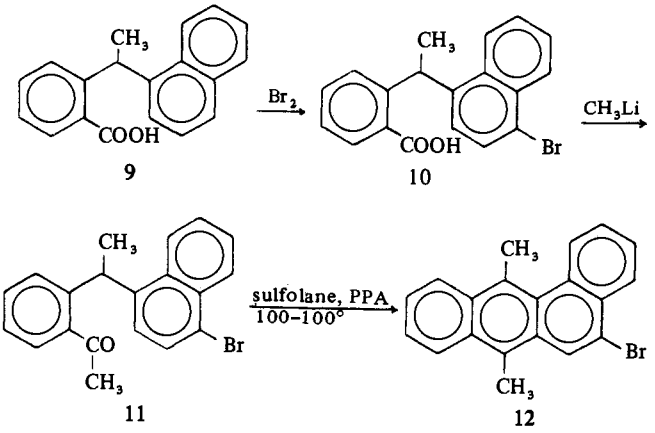
Thus, if one accepts the hypothesis advanced,[6,7] position 5 seems to be the spot at which the carcinogenic metabolism in both **1** and **2** occurs. In the hope of gaining further insight into the carcinogenic process at position 5, we have started a program to synthesize a number of 5-substituted 7,12-dimethyl- and 7-methylbenz[*a*]anthracenes. The idea is that if a 5-substituted derivative is found which acts more rapidly than does **1** or **2** this substituent is probably involved in the carcinogenic metabolic pathway.

In this paper we report the synthesis of 5-hydroxymethyl-7,12-dimethylbenz[*a*]anthracene (**5**), 5-acetoxymethyl-7,12-dimethylbenz[*a*]anthracene (**6**), 5,7,12-trimethylbenz[*a*]anthracene (**7**), and 5-methylmercapto-7,12-dimethylbenz[*a*]anthracene (**8**). Since all of these compounds have been shown to be noncarcinogenic,§§ they are probably not metabolites in the path by which **2** produces cancer.‡‡

Compounds **5-8** were synthesized from 5-bromo-7,12-dimethylbenz[*a*]anthracene (**12**) by methods described in the Experimental Section. The key compound **12** was prepared as illustrated in Scheme I.

Scheme I



9 10 11 12

Bromination of *o*-(α-methyl-α-1-naphthyl)toluic acid (**9**)[18] produced *o*-[α-methyl-α-(4-bromo-1-naphthyl)toluic acid (**10**) in 92% yield. The evidence for this assignment of structure is discussed later. Treatment of **10** with MeLi (prepd from MeI) afforded pure **11** in 61% yield. Cyclization of **11** in polyphosphoric acid yielded **12** in 83% yield. The transformations of **12** to **5**, **6**, **7**, and **8** are described in the Experimental Section.

The fact that **9** brominates at the 4 position in the naphthyl group was established by preparing **7** by an alternate route (see Experimental Section) starting from 1-bromo-4-methylnaphthalene and showing that the 2 samples of **7** were identical. The structure of 1-bromo-4-methylnaphthalene was confirmed by preparing *o*-(4-methyl-1-naphthoyl)-benzoic acid (**15**)[19] from the Grignard reagent and phthalic anhydride. This keto acid (**15**) was converted into **7** as described in the Experimental Section.

§§ Unpublished results by E. C. Miller and J. A. Miller.

##Unpublished results by C. B. Huggins and coworkers at the Ben May Laboratory for Cancer Research, University of Chicago.

Experimental Section***

o-(α-1-Naphthylethyl)benzoic acid (**9**)[18] was prepd in 90% yield by adding a slurry of 77 g of Zn dust (activated by prior treatment with 3 g of $CuSO_4$ in 160 ml of H_2O contg 10 ml of concd NH_4OH) to a mixt of 65 g of 3-methyl-3-(1-naphthyl)phthalide,[19] 60 g of KOH, 150 ml of H_2O, and 500 ml of 95% EtOH. The stirred mixt was refluxed for 38 hr and concd by allowing 550 ml of solvent to dist at the end. Recrystn of the acidic fraction of the reaction products from MeOH yielded 58.8 g (90%) of **9**,[18] mp 166.5–168.5°. The requisite phthalide was prepd by adding the Grignard reagent (from 76 g of Mg and 460 g of MeI in 1 l. of Et_2O) to a vigorously stirred refluxing suspension (prepd by adding 2 l. of dry Et_2O to 354 g of organic acid in 1800 ml of PhH) of *o*-(1-naphthoyl)-benzoic acid.[20] After being held at reflux for 2.5 hr, 1 l. of solvent was distd and the mixt was treated with dil HCl. The neutral fraction of the reaction products was crystd from EtOH–PhH to yield 214 g (63%) of 3-methyl-3-(1-naphthyl)phthalide,[18] mp 150–154°.

***o*-(α-[4-Bromo-1-naphthyl]ethyl)benzoic Acid (10).** A soln of 11.8 ml (35.4 g, 0.22 mole) of Br_2 in 150 ml of $CHCl_3$ was added slowly during 4.5 hr to a refluxing soln of 60.9 g (0.22 mole) of **9** in 500 ml of dry $CHCl_3$ with protection from light at all times. After a 2-hr induction period the mixt was held at reflux for 7 hr after the addition of Br_2 was completed. After standing at room temp for 12 hr, filtration yielded 45.5 g of **10**, mp 204–208.5°. *Anal.* ($C_{19}H_{15}BrO_2$) C, H, Br, N. The filtrate, after being washed with Na_2SO_3, was concd to yield a further 26.2 g, mp 196–206.5° (total yield 92%). Product of either purity could be used in the next step without noticeable difference in yield.

***o*-(α-[4-Bromo-1-naphthyl]ethyl)acetophenone (11).** A soln of 13.0 g of **10** in 400 ml of Et_2O and 80 ml of PhH was treated dropwise with stirring with 125 ml of 0.87 *M* ethereal MeLi (from MeI†††) during 2.5 hr. After 4 hr, the neutral portion of the reaction products in PhH was passed through a short column of neutral alumina. Crystn from hexane contg a small amt of PhH yielded 9.9 g (77%) of **11** as large colorless crystals, mp 100.5–103.5°, suitable for further work. The analytical sample, mp 103.0–104.5°, was obtd by one recrystn from hexane. *Anal.* ($C_{20}H_{17}BrO$) C, H, Br, N.

5-Bromo-7,12-dimethylbenz[*a*]anthracene (12). A soln of 9.5 g of **11** in 80 ml of hot sulfolane [$(CH_2)_4SO_2$] was added in 1 portion to 300 g of well-stirred polyphosphoric acid at 100–110°. After 1 hr the mixt was cooled and treated with ice. The product was extd with PhH and the dried PhH soln was passed through a short column of neutral alumina. The crude product obtained by removal of solvent was recrystd from EtOH–cyclohexane to yield 7.5 g (83%) of yellow elongated prisms of **12**, mp 99.5–102.5°. Material of this quality was used for further reactions. Two recrystns from EtOH–PhH yielded the analytical sample, mp 102.4–103.8°, with little loss. *Anal.* ($C_{20}H_{15}Br$) C, H, Br. The 2,4,5,7-tetranitrofluorenone 1:1 complex[21] formed in black elongated prisms, mp 235–237° dec. *Anal.* ($C_{33}H_{19}BrNO_4$) C, H, Br, N.

5-Hydroxymethyl-7,12-dimethylbenz[*a*]anthracene (5). The Grignard reagent was prepd from 11.0 g of **12**, 5 ml of $(BrCH_2)_2$,[22] and 3.6 g of sublimed Mg (generously donated by the Dow Chemical Co.) in 20 ml of PhH and 150 ml of Et_2O and was poured on a slurry of Dry Ice and Et_2O. The acid portion of the product was recrystd from THF–EtOH to yield 8.4 g of 5-carboxy-7,12-dimethylbenz[*a*]-anthracene (**13**), mp 269–272°. The Me ester, mp 104.0–105.5° from cyclohexane, was obtd by treatment of **13** with CH_2N_2.

The acid **13** was also prepd from **12**: by treatment with $Cu_2(CN)_2$ as described[23] to yield 5-cyano-7,12-dimethylbenz[*a*]-anthracene (**14**), mp 178.0–178.7°, followed by hydrolysis of **14**, with a soln of KOH in ethoxyethanol at 140–150° for 45 hr; and by carbonation of the Li reagent prepd by treatment of **12** with BuLi.

A mixt of 3.5 g of **13**, 20 ml of THF, and 30 ml of $SOCl_2$ was stirred and heated until a soln was obtd. A soln of the product in THF was added dropwise to a stirred soln of LAH in 20 ml of THF

***Where analyses are indicated only by symbols of the elements analytical results by the Galbraith Laboratories, Inc., Knoxville, Tenn., were within ±0.4% of the theoretical. The nmr and ir spectra of all compounds were consistent with the proposed structures.

†††Better yields of methyl ketones have always been obtained here when MeLi is prepd from MeI rather than MeBr.

at −30°. After hydrolysis, a soln of the crude alcohol in CH_2Cl_2 was passed through a column of Florisil and the product was crystd from hexane–CH_2Cl_2 to give 2.3 g (70%) of **5**, mp 140–142°. Recrystn yielded the analytical sample, mp 142.2–143.0°, with little loss. *Anal.* ($C_{21}H_{18}O$) C, H.

5-Acetoxymethyl-7,12-dimethylbenz[*a*]anthracene (6). By treatment of **5** with Ac_2O in pyridine and recrystn of the product from hexane–CH_2Cl_2 there was obtained **6**, mp 136.0–137.5°, in high yield. *Anal.* ($C_{23}H_{20}O_2$) C, H.

5,7,12-Trimethylbenz[*a*]anthracene (7). A soln of 0.3 ml of PBr_3 in 10 ml of THF was added slowly to a soln of 0.10 g of **5** in 7 ml of THF. After 2 hr, the mixt was poured on ice and a THF soln of the crude product was treated with LAH in THF. The product thus obtd was purified by chromatography and crystn from hexane to yield **7**, mp 128.0–129.5°, in 32% yield. A better product, mp 129–130°, was obtd by ring closure of **18** as described above for the synthesis of **12**. *Anal.* ($C_{21}H_{18}$) C, H. The 1:1 TENF complex of **7**, black elongated prisms, mp 238–239° dec., was prepd. *Anal.* ($C_{34}H_{22}N_4O_9$) C, H, N.

In an alternate synthesis of **7**, the Grignard reagent from 1-bromo-4-methylnaphthalene (Aldrich Co.) was added to phthalic anhydride to yield *o*-(4-methyl-1-naphthoyl)benzoic acid (**15**), mp 171.5–173.0°, in 61% yield essentially as described for the preparation of *o*-(1-naphthoyl)benzoic acid.[19,20] *Anal.* ($C_{19}H_{14}O_3$) C, H. Treatment of **15** with MeMgBr essentially as described for the synthesis of 3-methyl-3-(1-naphthyl)phthalide[18] yielded 3-methyl-3-(4-methyl-1-naphthyl)phthalide (**16**), mp 147–149°, in 57% yield as colorless platelets from EtOH–PhH. *Anal.* ($C_{21}H_{16}O_2$) C, H. Reduction of **16** as for **9** above yielded 87% of *o*-(2-[4-methyl-1-naphthyl]ethyl)benzoic acid (**17**), mp 189–192° [*Anal.* ($C_{20}H_{18}O_2$) C, H], which was converted into *o*-(2-[4-methyl-1-naphthyl]ethyl)-acetophenone (**18**), mp 110–111.5°, in 70% yield as described in 11 above. *Anal.* ($C_{21}H_{20}O$) C, H. By treatment with PPA at 110° for 35 min, **18** was converted to **7**, identical with the sample of **7** prepd as described above. The TENF derivs were also identical.

5-Methylmercapto-7,12-dimethylbenz[*a*]anthracene (8). A soln of 1.0 ml of $SOCl_2$ in 20 ml of $CHCl_3$ was added during 15 min to a stirred mixt of 1.0 g of **5** in 50 ml of $CHCl_3$. After a further 30 min, the mixt was treated with ice and the crude chloromethyl compd, isolated rapidly and dissolved in 20 ml of dry THF, was added to a suspension of $NaSCH_3$ in THF at −10° prepd with NaH. After several hours at −10° and overnight at room temp, the crude product was chromatogd on Florisil using hexane–PhH (5:1) to yield 0.76 g (69%) of **8** as pale yellow prisms, mp 104.5–106.0°, from hexane–CH_2Cl_2. *Anal.* ($C_{22}H_{20}S$) C, H, S. The TENF complex (1:1) of **8** melted at 167–169° and formed black elongated prisms. *Anal.* ($C_{35}H_{24}N_4O_9S$) C, H, N, S.

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Notes

Preparation and Antimicrobial Properties of the D and L Forms of 3-Amino-3,4-dihydro-1-hydroxycarbostyril†

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Received July 24, 1971

Even though a large amount of work has been previously reported on the interesting biological activities displayed by both the natural and synthetic hydroxamic acids,[1-3] no study has appeared on the structure-activity relationships of enantiomeric hydroxamate compounds. Interest in such a study stems from our previous work on the unusual chemical and microbiological properties of racemic 3-amino-3,4-dihydro-1-hydroxycarbostyril.[4,5] As an extension of this work, we now report the preparation of the title compounds and a comparative study of the stereochemical effects on their inhibitory activities.

The D- and L-3-amino-3,4-dihydro-1-hydroxycarbostyrils, III and IV, were obtained by catalytic hydrogenation of the corresponding D and L forms of the *o*-nitrophenylalanine hydrochloride salts, I and II, under acidic conditions[4] as depicted in the accompanying reactions. Since the reductive cyclization of I and II proceeds with retention of stereochemical configuration about the α-symmetric C atoms, the resulting enantiomers of the cyclic hydroxamic acid, III and IV, respectively, are configurationally equiv at the 3 position in the carbostyril ring system. Consequently, the requisite starting materials, I and II, were obtained by resolution of racemic *o*-nitrophenylalanine as its *N*-Ac derivative with brucine under the conditions described in the Experimental Section. The provisional assignment of the D and L

†The support of this work by research grants (R-285 and R-286) from The Robert A. Welch Foundation of Houston, Texas, is gratefully acknowledged.

‡Taken in part from the M.S. Thesis of D. R. Smith, Abilene Christian College, Abilene, Texas, May 1971.